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DOCTORAL SCHOOL
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EFFECTIVENESS OF DIFFERENT INTENSIVE TREATMENT STRATEGIES FOR EARLY RHEUMATOID ARTHRITIS

Veerle Stouten

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“Two roads diverged in a wood, and I,
I took the one less travelled by,
And that has made all the difference.”

The road not taken, by Robert Frost

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Veerle

CONTENT

ABBREVIATIONS

ACPA	Anti-Citrullinated Protein Antibody
ACR	American College of Reumatology
AE	Adverse Event
AEs	Adverse Events
ANOVA	ANalysis Of VAriance
Anti-CCP	Anti-Cyclic Citrullinated Peptide
bDMARD	biological Disease-Modifying Antirheumatic Drug
BeSt	BehandelStrategieën in Reumatoïde Arthritis
BL	BaseLine
CAMERA	Computer-Assisted Management in Early Rheumatoid Arthritis
CareRA	Care in Early Rheumatoid Arthritis
CATCH	Canadian Early Arthritis Cohort
CDAI	Clinical Disease Activity Index
CDI	Charlson-Deyo Index
CI	Confidence Interval
COBRA	Combinatietherapie Bij Reumatoïde Artritis
CRP	C-Reactive Protein
csDMARDs	conventional synthetic Disease Modifying Anti-Rheumatic Drugs
CVD	CardioVascular Disease
DAS	Disease Activity Score
DAS28	DAS based on 28 joints
DAS44	DAS based on 44 joints
DMARD	Disease-Modifying Antirheumatic Drug
e-CRF	electronic Case Report Form
ERAS	Early RA Study
ESR	Erythrocyte Sedimentation Rate

EudraCT	European union drug regulating authorities Clinical Trials Database
EULAR	European League Against Rheumatism
FCI	Functional Comorbidity Index
FWRO	Fund for Scientific Research in Rheumatology
GC	GlucoCorticoid
GEE	Generalized Estimating Equation
GLMM	Generalized Linear Mixed Models
HAQ	Health Assessment Questionnaire
HLA	Human Leucocyte Antigen
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IQR	Inter Quartile Range
IWT	Instituut voor innovatie door Wetenschap en Techniek
JAK	JAnus Kinase
LDA	Low Disease Activity
LEF	LEFlunomide
LMM	Linear Mixed Models
MCID	Minimal Clinical Important Difference
MCS	Mental Component Summary
MHC	Major Histocompatibility Complex
MTX	MethoTreXate
NEO-RACo	New Finnish RA Combination therapy
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PCS	Physical Component Summary
PGA	Patient's Global Assessment
PhGA	Physician's Global Assessment;
RA	Rheumatoid Arthritis

RCGP	Royal College of General Practitioners Research and Surveillance database
RCT	Randomized Controlled Trial
RDCI	Rheumatic Diseases Comorbidity Index
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SDAI	Simplified Disease Activity Index
SDD	Smallest Detectable Difference
SE	Standard Error
SF36	Short Form 36 questionnaire
SJC	Swollen Joint Count
SPSS	Statistical Package for the Social Sciences
SSZ	SulphaSalaZine
SvdH	Sharp van der Heijde
T2T	Treat-to-Target
TICORA	Tight Control for Rheumatoid Arthritis
TJC	Tender Joint Count
tREACH	the Treatment in the Rotterdam Early Arthritis study
TSU	Tight Step Up
VAS	Visual Analogue Scale

GENERAL INTRODUCTION

GENERAL INTRODUCTION

What is Rheumatoid arthritis?

1. Epidemiology and pathogenesis

Rheumatoid Arthritis (RA) is an autoimmune-induced, chronic, inflammatory joint disease with a worldwide prevalence of approximately 5 per 1000 adults. In Western countries, RA was shown to have a prevalence in the range of 0.5-1.0% in Caucasian individuals. Women are 2 to 3 times more affected by RA than men and the peak age of RA onset is in the sixth decade [1,2].

The exact cause of RA is still unknown, although several risk factors are known to contribute to the development of this disease, including genetics and environmental factors, besides female sex. The strong genetic component has been demonstrated in twin studies in which the heritability of RA was estimated to be around 60% [3]. Certain class II human leukocyte antigen (HLA) loci, which encode the major histocompatibility complex (MHC) molecules, are very strongly associated with RA. These MHC molecules are expressed on the surface of antigen presenting cells, which activate the T-cells of the immune system. MHC molecules may contain the "shared epitope" which is a short amino acid motif commonly encoded by the HLA-antigen D related locus and most closely associated with development of RA [4]. There are also many other gene loci linked to the risk to develop RA, with weaker associations [5]. However, also non-coding factors may play an important role in susceptibility. Environmental risk factors include smoking, periodontitis and characteristics of the microbiome of the gut, mouth and lungs, as well as viral infections [6–11]. Current tobacco smokers with a 20-pack-year history were shown to have a double risk of RA compared with non-smokers [12]. Current smoking status was also associated with increased RA disease activity [13].

Generally, the pathogenesis of RA begins years before signs and symptoms occur. During this pre-RA stage, typical autoantibodies develop. The most important autoantibodies in RA detection and diagnosis are Anti-Citrullinated Peptide-Antibodies (ACPA) and rheumatoid factor (RF). ACPAs targets citrullinated proteins (autoantigens), while RF is an antibody to IgG. The immune complexes formed by these autoantibodies may activate complement, and thereafter enhance

inflammatory responses [6]. The presence of ACPAs, but also RF, is traditionally associated with a more severe disease course and therefore not only used by clinicians as a diagnostic but also as a prognostic marker. Remarkably, not all patients diagnosed with RA seem to be seropositive for these autoantibodies, with one third being seronegative for ACPAs and RF [14,15]. Although this seronegative form is associated with a better long term prognosis, it should not be seen as a mild form of RA [16].

Further in the development, T cells, B cells, and monocytes start to infiltrate the synovial membrane in multiple joints. The lining of the synovium becomes hyperplastic due to expansion of synovial fibroblast-like and macrophage-like cells. This "pannus" of expanded synovial membrane, invades the periarticular bone resulting in bony erosions and produces enzymes leading to cartilage degradation [17].

2. Clinical presentation

RA is characterized by inflammation of multiple, generally peripheral joints with a symmetric distribution. Patients with RA typically present with painful and swollen joints of the hands and feet, often accompanied with nocturnal pain and morning stiffness in the joints. RA is a systemic disease, and may also lead to extra-articular manifestations in eyes, lungs, heart and other organs [18]. Severe RA can induce rheumatoid nodules and vasculitis, although these extra-articular manifestations are less commonly observed nowadays. Patients diagnosed with RA may be affected by multiple comorbidities and may have an increased mortality rate [19–21]. Cardiovascular disease is highly prevalent in RA. This comorbidity is influenced by chronic inflammation and is the primary cause of death in patients with RA. Other prevalent comorbidities include respiratory diseases, depression and malignancies [22]. However, with current treatment strategies, no excess mortality was observed in individuals with RA compared with the general population [23].

If insufficiently treated, this inflammatory process can lead to impaired physical functioning, work productivity and quality of life which is only reversible in the early phase of the disease. However, at later stages irreversible joint damage can occur through degradation of cartilage and destruction of articular and periarticular bone. RA used to be a disease leading to joint deformations in 80% of patients and to work

incapacity in 44% of patients within 15 years after diagnosis [24,25]. Such severe evolution of the disease is nowadays rarely seen due to early diagnosis and improved treatment.

3. Diagnosis and clinical assessment

There are no diagnostic criteria for RA, but classification criteria have been developed, which are being used in practice by rheumatologists as guidance to diagnose RA [26]. These consist of clinical manifestations and serological assays including autoantibodies and levels of acute-phase reactants. The most recent classification criteria of RA of 2010 require presence of synovitis in at least one joint, and achievement of at least 6 out of 10 points from a scoring system with four domains: number and site of involved joints (range 0-5), presence of autoantibodies ACPA and or RF (range 0-3), symptom duration ≥6 weeks (range 0-1) and elevated acute-phase reactants (range 0-1). These criteria have a sensitivity of 82% and specificity of 61% for RA [27].

Clinical follow-up of patients with RA is focused on inflammation as the hallmark of RA. Tender and swollen joint counts and evaluation of acute phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are essential. However, also patient reported outcomes are important, which include in daily clinical practice often an assessment by patients of their global health, pain and fatigue on a visual analogue scale (VAS) of 0 to 100. Likewise, physicians tend to evaluate the disease activity of their patients based on an evaluation of their global health on a VAS scale. Additionally physical function is an important outcome, which can be evaluated for instance with the health assessment questionnaire (HAQ) [28,29].

In order to evaluate disease control, the disease activity has to be assessed and quantified. Due to heterogeneous manifestations of RA, it is difficult to base disease activity on a single measure. Therefore, several disease aspects have been grouped into composite scores to have a more reliable and complete view on disease activity. Each type of score is calculated with a formula including, and in some cases also weighting of several clinical assessments. One of the most commonly used scores is the Disease Activity Score in 28 joints (DAS28) including the ESR or CRP level, and the patient's assessment of global health. More recently developed scores include the

Simplified Disease Activity Index (SDAI), which additionally contains the physician's assessment of disease activity and the Clinical Disease Activity Index (CDAI) with also the physician's assessment added but without C-reactive protein. These scores are associated with progression of joint damage and functional impairment [30,31]. For these indices, specific cut-offs have been specified to define several disease activity states in order to help guide treatment (table 1; [18]).

Table 1: Disease activity measures used for RA; [18]

Scoring system	Formula	Disease activity states			
		Remission	Low disease activity	Moderate disease activity	High disease activity
SDAI	SJC28 + TJC28 + PGA + EGA + CRP	≤3.3	>3.3–11	>11–26	>26
CDAI	SJC28 + TJC28 + PGA + EGA	≤2.8	>2.8–10	>10–22	>22
DAS	Complex formula including the Ritchie index, SJC44, ESR and GH	≤1.6	>1.6–2.4	>2.4–3.7	>3.7
DAS28	Complex formula including the TJC28, SJC28, ESR (or CRP) and GH	≤2.6	>2.6–3.2	>3.2–5.1	>5.1

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein (in SDAI in mg per dl); DAS, Disease Activity Score; DAS28, DAS using 28-joint counts; EGA, Evaluator Global Assessment (on a 0–10 cm scale); ESR, erythrocyte sedimentation rate; GH, global health (that is, patient global assessment); PGA, patient global assessment (on a 0–10-cm scale); RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; SJC, swollen joint count (the number indicates the number of joints taken into account); TJC, tender joint count (the number indicates the number of joints taken into account).

RA can be considered as a syndrome characterized by the typical complex of signs and symptoms described above. At the basis of RA lie several different genetic and environmental risk factors, leading to different cellular and subcellular pathophysiological pathways, all converging to a comparable dysregulation of the immune system. This hypothesis might explain why some patients with RA have a different disease course or react differently to a specific treatment than others.

How to manage rheumatoid arthritis?

1. The arsenal of pharmacological treatments for RA

Since RA is an incurable chronic disease which, if left untreated, may lead to high levels of pain, discomfort and disability as well as to serious joint damage, it is vital to pursue a good disease control. For this purpose, treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs) is essential. Such immune modulating drugs can inhibit progression of joint damage and prevent irreversible disability. DMARDs can be grouped into two main categories of synthetic or biologic DMARDs.

Synthetic DMARDs are small chemical molecules, administered orally, consisting of conventional synthetic and targeted synthetic DMARDs. The most commonly used conventional synthetic DMARDs are methotrexate (MTX), Sulphasalazine (SSZ), Leflunomide (LEF) and Hydroxychloroquine (HCQ). These compounds suppress the immune system, but their modes of action are still mostly unknown. Some of these drugs have been used in clinical practice for more than 50 years and have proven their effectiveness with an acceptable safety profile. The more recently developed targeted synthetic DMARDs are designed to target a specific molecule in the intracellular inflammatory signal transmission, such as the Janus Kinase (JAK) enzymes, which also show good potential for patients with RA.

Methotrexate is the most important among the csDMARDs and has a key role in the management of RA. It has been used for more than 50 years in treatment of RA and its attributes in terms of efficacy and safety are increasingly demonstrated [32,33]. It has a good overall efficacy for signs and symptoms, while inhibiting joint damage and improving functional ability. Its adverse effects are well known and many of them, such as hair loss, hepatotoxicity and stomatitis, can be prevented by using folate as prophylaxis. Therefore, MTX has an acceptable and manageable safety profile [34]. Additionally, this medicine has a large range of up-titratable doses, options for oral or parenteral administration and a currently unrivalled cost-effectiveness [33]. However, it should be noted that MTX is a relatively slow acting anti-rheumatic drug. Based on findings of several combination therapy studies with MTX monotherapy arms, it takes generally 6 months before MTX reaches its full therapeutic potential [35–38]. Nevertheless, based on prescribing practices in the US from 2009 to 2014, it seems that MTX is underutilized in the treatment of RA with inadequate duration before evaluation of efficacy and suboptimal dosing [39].

Biologic DMARDs are biotechnologically engineered monoclonal antibodies or receptor constructs, administered parenterally. These drugs act on a molecular target within one of the pathways of inflammation or autoimmunity with a high specificity. The largest group of biologics consists of TNF inhibitors, which target TNF alpha, a key cytokine in the pathophysiology of RA. These include etanercept, infliximab, adalimumab, golimumab, and certolizumab. The other groups consist of biologics with different modes of action, targeting other parts of the inflammation cascade, including abatacept, rituximab, tocilizumab and sarilumab. Abatacept inhibits T-cell activation by interfering with the co-stimulation by antigen presenting

cells. Rituximab lowers the amount of CD20 positive B-lymfocytes and tocilizumab/sarilumab inhibit IL-6 signalling by targeting its receptor. These types of drugs generally reach their therapeutic efficacy more rapidly than conventional synthetic DMARDs and are effective also in patients not sufficiently responding to conventional synthetic DMARDs. However, biologic DMARDs are costly, which should be taken into account when choosing rationally a therapy with the right agent at the right dose and at the lowest cost to the individual and society according to WHO reports [40]. Nowadays, with the advent of biosimilars for biologic originator DMARDs, costs for these drugs have considerably decreased. In some countries, prices of bDMARDs have decreased by more than 50% in comparison with the originators [41].

Glucocorticoids are also commonly used in the treatment of RA and can be considered DMARDs as they possess disease modifying activity since they can prevent progression of joint damage [18,42–44]. Their prolonged use is not recommended due to their association with several adverse effects [45]. In 2007, a EULAR taskforce identified based on a literature review the following main adverse effects of GCs: cardiovascular diseases, infections, gastro- intestinal diseases, psychological disorders, endocrine pathologies, dermatological issues, musculoskeletal disorders (including osteoporosis) and ophthalmological diseases [45]. However, GCs can rapidly attenuate the over-active immune system and suppress inflammation [46]. Therefore, GCs are useful to bridge the time needed by csDMARDs to reach their maximum anti-inflammatory effect [33].

Symptomatic treatment of RA entails non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics. These drugs do not interfere with the underlying pathophysiological mechanisms of RA and can consequently not prevent joint damage but can partly relieve swelling and remaining pain. They are used in the very early phase of disease, before initiation of a DMARD or as additional symptomatic therapy later on.

2. Treatment strategies for RA

The outcomes for patients with RA have dramatically improved over the past two decades. This is not only due to the development of advanced therapy, as described above, but foremost also due to new therapeutic strategies based on traditional

DMARDs. It became apparent that prompt initiation of intensive treatment with optimized medication schedules, in a treat to target approach resulted in much improved clinical outcomes [47–51].

Firstly, it is recommended to treat every newly diagnosed patient with RA as soon as possible with a DMARD, since a longer delay between onset of symptoms and treatment initiation influences treatment outcome. If treatment is initiated within 12 weeks after symptom onset, a better outcome can be expected [52–54].

Secondly, the treatment strategy should be intensive. MTX is considered the anchor drug for treatment of RA. It has been intensively investigated whether combining MTX with other csDMARDs or with more rapidly acting anti-rheumatic drugs such as biologics or glucocorticoids, would be more effective than plain MTX monotherapy. The COBRA (Combinatietherapie Bij Reumatoïde Artritis) trial was one of the hallmark studies in early RA to shed light on this matter. This study demonstrated that a combination of MTX, SSZ and a tapering down scheme of oral prednisolone started at 60mg/day was superior over SSZ monotherapy [51]. However, since SSZ monotherapy was chosen as comparator it remained unclear whether MTX monotherapy was less effective than a combination of DMARDs with a tapering down scheme of glucocorticoids. In the BeSt (Dutch acronym for 'Behandel-Strategieën' or 'treatment strategies') trial, initial DMARD combinations including either a prednisone scheme or infliximab resulted in earlier clinical improvement and less radiographic damage after 1 year than initial MTX monotherapies [55,56]. Also other trials demonstrated that early intensive treatment strategies with csDMARDs, especially when combined with oral glucocorticoids or biologics, were superior to DMARD monotherapy [37,48,49,55,57–61].

Thirdly, the treatment strategy should involve a treat-to-target approach, including frequent measuring of disease activity and adapting treatment as long as the pre-set goal of treatment has not been achieved [36,48,62]. Application of the treat-to-target principle should take patients' clinical characteristics into consideration and patients should be involved in treatment decisions and planning [63]. Systematically adapting therapy in case the treatment target was not reached, proved to lead to better clinical outcomes compared to routine care in a randomized controlled setting within the TICORA and CAMERA trial [36,64]. The currently recommended treatment goal is defined as remission, which is a state of no or minimal disease activity, or at

least low disease activity. Achievement of remission in patients with early RA can lead to normalization of physical function and prevention of occurrence or progression of joint damage [65,66].

The window of opportunity theory states that intensive treatment should be initiated as soon as possible after diagnosis of RA, to achieve remission rapidly, to prevent progression of joint damage and to increase chances of sustained remission [67,68]. This period in which patients are more responsive to RA therapy seems to be limited to the first 12 weeks after symptom onset [69,70]. Moreover, to benefit maximally from the window of opportunity, any sign of disease activity after treatment initiation should be controlled as soon as possible by adjusting treatment regularly [48,71]. In case patients are insufficiently responding to initial treatment, it is possible to switch or add another csDMARD like LEF or to initiate a biologic or targeted synthetic DMARD.

Rapid remission induction can be achieved by combining MTX with fast acting agents like GCs or biologics. In the BeSt trial, a combination strategy of MTX with infliximab showed similar efficacy as initial combination of MTX, SSZ and a GC remission induction scheme [56]. The use of bDMARDs for initial remission induction is however restricted in practice by economic constraints incorporated in reimbursement criteria and guidelines. Combinations of MTX with costly biologics were superior compared to MTX monotherapy in several RCTs mostly without a treat to target approach, with remission rates ranging between 20-60% [37,72–79]. However, also combinations of MTX with the cheaper GCs showed remission rates ranging between 30-70% [51,56,80–84].

Nevertheless, some questions remained unanswered regarding the optimal initial therapy for patients with early RA. The COBRA and BeSt trial showed that MTX and SSZ combined with a GC remission induction scheme starting at 60mg/day prednisone was superior compared to SSZ or MTX monotherapy [51,55]. The efficacy, safety and cost- effectiveness of the COBRA therapy have been confirmed in the short and long term [43,51,85]. However, the added benefit of SSZ in this schedule and of the initial high dose of prednisolone remained unclear. Furthermore, rheumatologists indicated that they often did not intend to prescribe COBRA schemes due to their concerns regarding the complexity of the schedule, the high initial dose of prednisolone, inclusion of SSZ and the low dosage of MTX of 7.5

mg/week in the original scheme. [86–88]. Moreover, it was unknown which maintenance therapy would lead to sustained effectiveness after achieving a sufficient treatment response with a combination of csDMARDs. In such case it is recommended to step down to csDMARD monotherapy [89]. However, no conclusive data exist as to which drug to stop preferentially after reaching disease control with a combination of csDMARDs.

In order to define an optimal, effective treatment regimen for patients with early RA, the Care in early RA (CareRA) trial was performed by the rheumatology department of University Hospitals Leuven. This trial served as the backbone of my PhD. The overall objective of CareRA was to compare the effectiveness of different intensive treatment regimens based on the 'combinatietherapie bij reumatoïde artritis' (COBRA) scheme in patients with RA during the first 2 years of their disease. Before randomisation, patients were allocated to a high-risk or low-risk group using a stratification scheme based on presence of classical predictors for radiographic damage. The tested schemes consisted of a combination or a monotherapy of csDMARDs, with or without a tapering scheme of GCs. The results after 4 months and 1 year indicated that MTX monotherapy associated with a short moderately dosed tapering scheme of glucocorticoids, named the COBRA-Slim scheme, was as effective as other regimens with multiple csDMARDs and glucocorticoids in patients of the high-risk group. Moreover, this COBRA-Slim regimen resulted in fewer treatment-related side effects, thereby yielding the best risk-benefit balance. Additionally, this COBRA-Slim regimen seemed more effective than MTX monotherapy without glucocorticoids in patients of the low-risk group, with a similar safety profile [90–92]. However, the long-term effectiveness of these treatment regimens, as well as their practical applicability remains to be further explored.

3. Adherence to treat-to-target principle

The treat-to-target approach is currently the most efficient strategy to control disease activity, but its implementation in daily clinical practice remains challenging. It depends on the commitment of both physicians and patients to the treat-to-target treatment recommendations. However, current treatment strategies with a treat-to-target approach can be perceived as complex to both patients and physicians, with multiple drugs, simultaneous oral and parenteral intake, daily and weekly administration times, adverse effects and dose adaptations. Additionally, their

management can be labour intensive with frequent visits to the rheumatologist and regular assessments of disease activity. Therefore, a treat-to-target approach may be liable to suboptimal adherence in daily clinical practice [93].

In order to improve outcomes of treatment and achieve the pre-set goal, the physician's adherence to treat-to-target (T2T) guidelines is critical. Physician adherence is defined as the extent to which the treating healthcare professional, usually the rheumatologist, adheres to evidence-based clinical guidelines or treatment recommendations or to a treatment protocol. Several studies have reported on the rate of physicians' adherence which ranged from 42% to 79% [94–97]. Within the BeSt study with its 10-year follow-up data, the average protocol adherence was 79%, and declined from 100% at baseline to around 60% of the visits in the final 2 years of follow up [95]. The chances for non-adherence were higher if rheumatologists thought the DAS under- or overestimated the actual disease activity, or if they disagreed with the required treatment or if they were dissatisfied with the level of disease suppression. In the COBRA-light trial, 67% of the study population required a treatment adaptation, which was predefined per protocol as initiation of etanercept, although only 62% of those patients were actually prescribed etanercept since rheumatologists often didn't adhere to the study protocol [98,99]. However, it is difficult to compare these adherence rates across studies since there were differences in how adherence was assessed, in the type of protocol or guideline used and in the treatment approach. Only few studies reported on the relation between physician adherence and treatment outcome with a strategy in a T2T setting [94,100,101]. A study by Wabe et al. in an Australian early arthritis cohort demonstrated that increased adherence to T2T was associated with improved disease activity and functionality on the long term. Another study by Wabe et al. in a treatment naïve early RA cohort treated initially with a combination of MTX, SSZ and hydroxychloroquine showed that failure to escalate the dose when indicated, occurred more often in patients not achieving remission after 3 years [100].

It is still unclear how adherent physicians were to a T2T approach in patients with early RA treated with intensive remission induction schemes in the CareRA trial. It can be expected that greater physician adherence to these intensive COBRA-like strategies can improve clinical outcomes, but whether this holds true is not yet known.

4. Comorbidities in early RA

As previously indicated, RA is associated with a high prevalence of comorbidities. The COMORA study evaluated the prevalence of comorbidities in a large sample of patients with RA from 17 different countries on 5 different continents and demonstrated a high prevalence of comorbidities and their risk factors [22]. Even at disease onset, there is substantial comorbidity among patients with early RA, as shown in large inception cohorts in Sweden and the UK [102,103]. In other cohorts in UK and France, the prevalence of comorbidities was demonstrated to be higher in patients with RA than in the general population, especially the occurrence of arterial hypertension [103–105].

Having comorbidities can negatively affect disease outcomes of RA, including worse physical functioning, lower control of disease activity and decreased health related quality of life [103,106–111]. The interaction between comorbidity and physical function has been shown to be independent of disease activity in established RA [106]. In an observational cohort of RA patients of the CORRONA registry, patients with reported comorbidities had less improvement over time in CDAI and modified HAQ with also lower CDAI remission rates [112]. Presence of comorbidities in patients with RA may also lead to an increased mortality, more hospitalizations and medical costs [113,114].

Response to treatment can also be negatively affected by the presence of comorbidities. In a prospective cohort of patients with established RA, the effect of multimorbidity status on treatment outcomes at 1 year after initiation of any DMARD was investigated. Having multiple comorbidities led to significantly lower percentages of patients achieving remission or low disease activity and to worse CDAI and modified HAQ scores [115]. In other cohort studies, comorbidities affected the retention rate and efficacy of biologic DMARDs [116–119].

The above evidence indicates the importance of comorbidities within the management of RA due to their potential prognostic value and their potential influence on treatment decisions because of fear of side effects. Therefore, comorbidities should be recognized and taken into account in the management of RA patients, but also when analyzing treatment responses in clinical studies. When investigating the impact of comorbidity, one can quantify the presence of

comorbidities by a simple count of all comorbidities. However, not every comorbid condition has the same impact on the outcome of interest. This has been solved by using different approaches, including selecting only specific, relevant conditions, and providing weights for each condition according to their relative impact. Several comorbidity index scores have been developed this way, usually taking into account the impact of comorbidities on 'hard' outcomes such as mortality or being hospitalized. The Charlson-Deyo index (CDI) among others has been based on this methodology. However, for RA there are also other outcomes of interest, such as functional ability, quality of life, work disability, and medical costs. The Functional Comorbidity Index (FCI) has been developed to predict physical function taking into account the sum of 18 comorbidities. More recently, a comorbidity index for use specifically in RA has been created, by selecting and weighting 11 comorbidities based on their impact on mortality, hospitalization, work disability, functional disability and medical costs [113]. This index is called the Rheumatic Diseases Comorbidity Index and has been validated to predict both death and physical disability in RA, by comparing its predictive ability to several other existing indices including the CDI and FCI [120]. In a recent study, the explanatory value of these three commonly used indices was compared for functionality, quality of life, utility and health resource utilization with all indices performing comparably well [121]. These comorbidity indexes can be useful to investigate the impact of comorbidity status on treatment responses, since they are able to predict important RA outcomes.

Comorbidities are prevalent, even in early RA, and are assumed to have a negative impact on treatment response. However, it is not known whether this still holds true on the long term when patients are treated intensively according to the latest recommendations for management of RA.

OVERALL OBJECTIVE AND RESEARCH QUESTIONS

The overall objective of this thesis is to evaluate the long-term effectiveness of intensive treatment strategies in early RA, based on the pragmatic RCT CareRA. The hypothesis, based on the previously published results from the CareRA trial, is that newly diagnosed patients with RA would benefit most also on the long-term from a treatment strategy consisting of MTX monotherapy with a short moderately dosed tapering scheme of glucocorticoids, called COBRA-Slim. Therefore, it will be investigated whether this strategy is sufficiently efficacious, has a good safety profile, leads to a stable long-term response and is well applicable, within a pragmatic research setting.

The following research questions (RQ) will be addressed and each will be described as a separate (sub)chapter in this thesis:

- RQ1: How effective is COBRA-Slim to treat early RA in the long term, in comparison to combination treatments with csDMARDs and a tapering scheme of glucocorticoids?

- RQ2: Could these treatment strategies be further refined to increase their applicability for daily clinical practice?

    - RQ2a: Which maintenance therapy is effective after achieving a sufficient clinical response with an initial combination of MTX and LEF?

    - RQ2b: To what extent do rheumatologists adhere to the treat-to-target approach in patients treated with these treatment strategies and what is the impact of treat-to-target adherence on treatment outcomes?

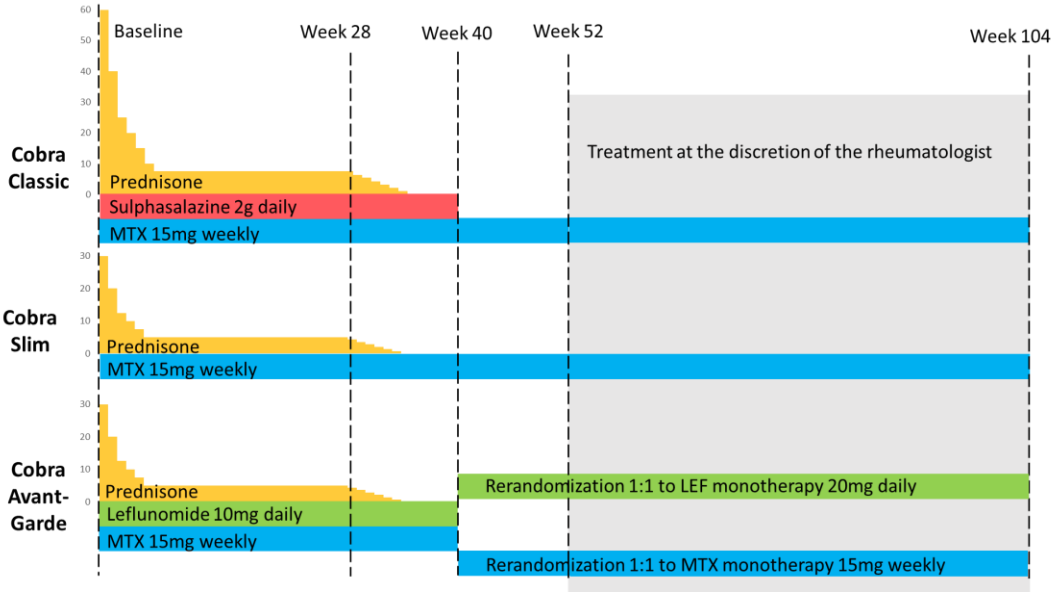
- RQ 3: What is the prevalence of comorbidities in early RA and to what extent do they influence long-term outcomes under intensive treatment?

Overall methodology: the CareRA study

This PhD research project is based on data of the 2-year CareRA RCT and the 3-year observational CareRA plus follow-up study. CareRA is a prospective, multicenter, pragmatic RCT. Investigators from 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium conducted this trial. Included patients were diagnosed with RA less than 1 year ago, were naïve to and had no contraindications for csDMARDs or glucocorticoids. Before randomisation, patients were allocated to a high-risk or low-risk group using a stratification scheme based on presence of classical predictors for radiographic damage. Subsequently, high-risk patients were randomized to one of three possible intensive treatment regimens, including different DMARD combinations with a high or moderate initial dosed GC remission induction scheme (figure 1). On the other hand, low-risk patients were randomized to an intensive approach including DMARD monotherapy and GC remission induction scheme or to a conservative step up approach of DMARD monotherapy without initial GC. The primary aim of CareRA was to compare the effectiveness of the different intensive treatment regimens.

Prednisone was tapered over the first six weeks to 7.5 mg in COBRA-Classic and over 5 weeks to 5 mg in the other regimens, continued to week 28 and then tapered until discontinuation at week 34. In COBRA-Classic and COBRA-Avant-Garde the combined csDMARD therapy was tapered to monotherapy at week 40, in patients achieving low disease activity. The objective was to bring all patients as soon as possible to at least a state of low disease activity using predefined treatment adaptation schemes in case this target was not reached. Remission was defined as a DAS28-CRP score of less than 2.6. During the first year, from week 8 onwards, treatment had to be adapted following predefined steps in case low disease activity (DAS28-CRP≤3.2) was not achieved. As a first step, the MTX dose was adjusted to 20 mg weekly in all arms. As a second step, the dose of the other DMARD was adapted in the COBRA-Classic and COBRA-Avant-Garde arm. In COBRA-Slim and Tight Step Up the second step consisted of initiating leflunomide 10mg daily. During the second year of the trial and in the 3-year observational follow-up CareRA plus study, treatment was at the discretion of the rheumatologist. Further application of the treat-to-target principle was recommended.

High-risk patients (75% of total population) randomized into 3 treatment schemes:



Low-risk patients (25% of total population) randomized into 2 treatment schemes:

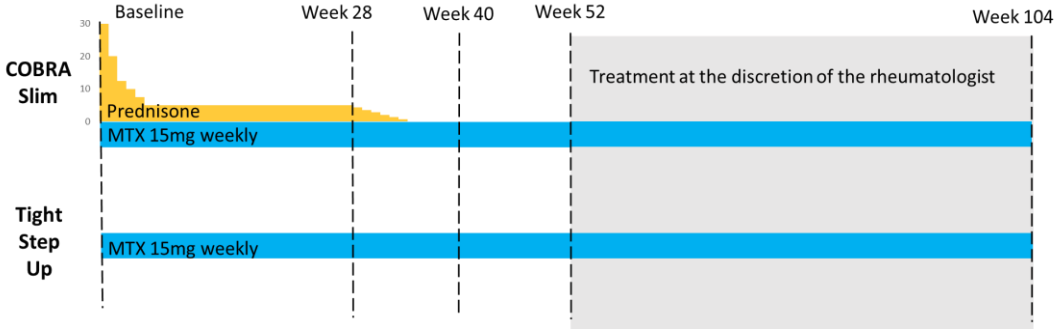


Figure 1: treatment regimens of the CareRA trial

Previous results of the CareRA study

The results after 4 months and 1 year indicated that methotrexate (MTX) monotherapy associated with a short moderately dosed tapering scheme of glucocorticoids, named the COBRA-Slim scheme, was as effective as other regimens with multiple csDMARDs and glucocorticoids. Moreover, this COBRA-Slim regimen resulted in fewer treatment-related side effects, thereby yielding the best risk-benefit balance [90,91]. Additionally, this COBRA-Slim regimen seemed more effective than MTX monotherapy without glucocorticoids, with a similar safety profile [92]. However, the long-term effectiveness of these treatment regimens, as well as their practical applicability remains to be further explored.

OUTLINE OF THE PHD THESIS

This PhD thesis is a compilation of research articles published or to be published in international, peer-reviewed journals.

GENERAL INTRODUCTION

What is rheumatoid arthritis?

How to manage rheumatoid arthritis?

OVERALL OBJECTIVE AND RESEARCH QUESTIONS

CHAPTER 1: Effectiveness of different treatment regimens for early RA in the long term

CHAPTER 1.1: presents the 2-year outcomes of the treatment schemes of the CareRA trial

CHAPTER 1.2: presents the 5-year outcomes of the observational follow-up CareRA plus study

CHAPTER 2: Refinement of the practical applicability of an optimal treatment strategy for early RA

CHAPTER 2.1: presents the results of the comparison of maintenance therapy of MTX or LEF after rerandomization in the COBRA Avant-garde arm of the CareRA trial

CHAPTER 2.2: presents the findings of investigation of the adherence to the treat-to-target principle in the CareRA trial

CHAPTER 3: Prevalence of comorbidities and their influence on outcomes of RA treatment in CareRA

GENERAL DISCUSSION:

includes per chapter a summary of the key findings and their importance for early RA management, a reflection about methodological considerations, implications for clinical practice and future research, and ends with an overall conclusion

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CHAPTER 1

Effectiveness of different treatment regimens for early RA in the long term

CHAPTER 1.1

Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: two-year results of CareRA

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ABSTRACT

Objectives

To investigate whether methotrexate should be combined with an additional disease-modifying antirheumatic drug (DMARD) and bridging glucocorticoids as initial treatment for patients with early rheumatoid arthritis (RA) to induce an effective long-term response.

Methods

CareRA is a two-year investigator-initiated pragmatic multicentre randomised trial. Early RA patients, naïve to DMARDs and glucocorticoids were stratified based on prognostic factors. High-risk patients were randomised to COBRA-Classic (n=98): methotrexate, sulfasalazine, prednisone step-down from 60mg; COBRA-Slim (n=98): methotrexate, prednisone step-down from 30mg; COBRA-Avant-Garde (n=93): methotrexate, leflunomide, prednisone step-down from 30mg. Low-risk patients were randomised to COBRA-Slim (n=43); or Tight Step Up (TSU) (n=47): methotrexate without prednisone. Clinical/radiological outcomes at year 2, sustainability of response, safety and treatment adaptations were assessed. Clinical trials NCT01172639.

Results

In the high-risk group 71/98 (72%) patients achieved a DAS28-CRP<2.6 with COBRA-Slim compared to 64/98 (65%) with COBRA-Classic and 69/93 (74%) with COBRA-Avant-Garde (p=1.00). Other clinical/radiological outcomes and sustainability of response were similar. COBRA-Slim treatment resulted in less therapy-related adverse events compared to COBRA-Classic (p=0.02) or COBRA-Avant-Garde (p=0.005). In the low-risk group, 29/43 (67%) patients on COBRA-Slim and 34/47 (72%) on TSU achieved a DAS28-CRP<2.6 (p=1.00). On COBRA-Slim, low-risk patients had lower longitudinal DAS28-CRP scores over 2 years, a lower need for glucocorticoid injections and a comparable safety profile compared to TSU.

Conclusion

All regimens combining DMARDs with glucocorticoids were effective for patients with early RA up to 2 years. The COBRA-Slim regimen, methotrexate monotherapy with glucocorticoid bridging, provided the best balance between efficacy and safety, irrespective of patients' prognosis.

INTRODUCTION

Current guidelines to treat rheumatoid arthritis (RA) recommend starting as soon as possible with an intensive therapeutic strategy including rapid treatment adaptations until remission or at least low disease activity is achieved. (1-5) The conventional synthetic disease-modifying antirheumatic drug (csDMARD) methotrexate (MTX) is considered the anchor drug for initial RA treatment. Adding glucocorticoids temporarily can facilitate rapid remission induction by bridging the time needed for MTX to reach its full therapeutic potential. Whether MTX should initially be combined with an additional csDMARD or glucocorticoids to induce remission in all patients with early RA is still under debate and the effectiveness, safety and feasibility of such treatment strategies needs further study. In the 'Care in early RA' (CareRA) trial, efficacy of all different csDMARD combinations and glucocorticoid bridging schemes in patients with recent onset RA was high after 1 year, without differences between treatment arms. Moreover, initial MTX monotherapy with a short step-down course of moderately-dosed glucocorticoids showed a more favourable safety profile, resulting in the best risk-benefit balance. (6-8) However, the long-term risk-benefit balance of these treatment regimens remains unknown. In this manuscript we assessed the 2-year effectiveness outcomes, sustainability of response, safety and need for treatment adaptations of each CareRA treatment arm.

METHODS

Study design

The CareRA study is a prospective 2-year randomised open-label pragmatic trial evaluating different treatment regimens, based on the original COBRA (Combination therapy for early Rheumatoid Arthritis) strategy for patients with early RA. (9) Investigators from 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium conducted this trial. The medical ethics committee of each centre approved the protocol (EudraCT number: 2008-007225-39) and all patients gave written informed consent. Included patients were diagnosed with RA less than 1 year ago, were naïve to and had no contraindications for csDMARDs or glucocorticoids (supplement 1).

Treatment protocol

Before randomisation, patients were allocated to a high-risk or low-risk group using a stratification scheme based on presence of classical predictors for radiographic damage (supplement 1). Randomisation was performed via a digitally generated sequence in the electronic case report form. Patients in the high-risk group were randomised into 1 of 3 treatment arms:

COBRA-Classic: 15 mg MTX weekly, 2g sulfasalazine daily and a weekly step-down scheme of oral prednisone (60-40-25-20-15-10-7.5 mg QD).
COBRA-Slim: 15 mg MTX weekly and a weekly step-down scheme of oral prednisone (30-20-12.5-10-7.5-5 mg QD).
COBRA-Avant-Garde: 15 mg MTX weekly, 10 mg leflunomide daily and a weekly step-down scheme of oral prednisone (30-20-12.5-10-7.5-5 mg QD).

Patients in the low-risk group were randomised into 1 of 2 treatment arms:

COBRA-Slim.
Tight Step Up (TSU): 15 mg MTX weekly, no oral glucocorticoids allowed.

Prednisone was tapered over the first weeks to 7.5 mg in COBRA-Classic and to 5 mg in the other arms, continued to week 28 and then tapered until discontinuation at week 34. In COBRA-Classic and COBRA-Avant-Garde combined csDMARD therapy was tapered to monotherapy at week 40, in patients achieving low disease activity (supplement 2). Prophylactic treatment with oral folic acid, calcium and vitamin D

was prescribed. Participants received face-to-face education, printed medication schemes and standardised info-material (leaflet, DVD and website).

Response to therapy was evaluated at each visit by measuring the 28 joint Disease Activity Score using C-reactive protein (DAS28-CRP). During the first year, from week 8 onwards, treatment had to be adapted following predefined steps in case low disease activity (DAS28-CRP≤3.2) was not achieved. As a first step, MTX dose was adjusted to 20mg weekly in all arms. As a second step, the dose of the other DMARD was adapted in the COBRA-Classic and COBRA-Avant-Garde arm. In COBRA-Slim and Tight Step Up the second step consisted of initiating leflunomide 10mg daily (supplement 2).

During the second year of the trial, treatment was at the discretion of the rheumatologist. Further application of the treat-to-target principle was recommended.

Study end points and assessments

Participants were assessed at screening, baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. Patients unable to continue the allocated treatment including predefined adaptations due to lack of efficacy, safety or practical reasons, were followed up every 6 months.

The main end point of CareRA reported in this paper is the proportion of patients achieving a DAS28-CRP <2.6 at year 2. Proportion of patients achieving this end point at week 16 and year 1 was already reported previously. (6-8)

Other clinical outcomes at year 2 were proportion of good European League Against Rheumatism (EULAR) responders and proportion of patients in remission or low disease activity according to Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and the American College of Rheumatology (ACR)-EULAR Boolean criteria. (10) Additionally, physical function was assessed by the Health Assessment Questionnaire (HAQ) (11) and radiographic evolution by the Sharp van der Heijde (SvdH) score. X-rays of hands and feet were obtained at baseline, week 28, year 1 and year 2. Radiographs were scored chronologically according to the SvdH method (12). Each X-ray was scored independently by 3 readers, retaining the mean score.

Sustainability of the initial response to therapy was analysed by the 2-year evolution of DAS28-CRP and HAQ over time. Additionally, Kaplan Meier survival analyses were performed to assess, in patients who achieved a DAS28CRP<2.6 at year 1, the probability of maintaining this state at every trimonthly visit during year 2.

Type of DMARD treatment taken by patients at every visit throughout the trial was assessed. Use of glucocorticoids outside of initial tapering schemes was quantified as numbers of patients who had a glucocorticoid injection and who were taking oral glucocorticoids chronically (continuously for more than 3 months out of protocol).

Patients were questioned about the occurrence of any adverse events (AEs) at each visit. AEs were registered and evaluated (relation to therapy, seriousness and severity) by the treating rheumatologist.

Statistical analysis

CareRA sample size calculation was based upon the expected proportion of patients with a DAS28-CRP<2.6 at week 16. (7) We needed 85 patients per treatment arm in the high-risk group to ascertain 80% power to detect a difference of at least 20% for this endpoint to demonstrate superiority. Analysis of the low-risk population was exploratory.

We performed an intention-to-treat analysis including all randomised patients. Screening variables were used to impute missing baseline variables and vice versa. To impute missing data at subsequent visits, the Expectation Maximization algorithm was applied. (13) Missing SvdH scores at year 2 were imputed via linear extrapolation of scores at w28 and w52. (14) A sensitivity analysis on the population completing the 2-year study was performed.

Clinical outcomes, safety and treatment adaptations were examined by Chi-square, Kruskal-Wallis or Mann-Whitney U test, when appropriate. We corrected clinical outcomes at year 2 for multiplicity by adjusting p-values by Holm test. (15) Significance level wat set at 0.05. DAS28-CRP and HAQ were longitudinally analysed over 2 years with linear mixed models (LMM), using treatment group, time and its interaction term as determinants. A Poisson regression was performed to predict the number of related AEs over 2 years based on the treatment arm. Analyses were carried out using SPSS V25.0.

RESULTS

Participants

After registration in EudraCT in November 2008, we screened 400 patients with early RA between January 2009 and May 2013 and included 379, of whom 289 were stratified in the high-risk and 90 in the low-risk group. High-risk patients were randomised to COBRA-Classic (n=98), COBRA-Slim (n=98) or COBRA-Avant-Garde (n=93). Patients in the low-risk group were randomised to COBRA-Slim (n=43) or TSU (n=47). All randomised participants received their allocated treatment at baseline. Over 2 years, 249 of 289 patients in the high-risk group (86%) and 73 of 90 patients in the low risk group (81%) completed the study. Frequencies and reasons for discontinuation were similar among treatment arms (figure 1). In both risk groups, baseline characteristics were well balanced between treatment arms (table 1).

Effectiveness analysis

Clinical outcomes at year 2

In the high-risk group, 204 (71%) patients reached a DAS28-CRP<2.6 at year 2. This state was achieved in 64 (65%) COBRA-Classic, 71 (72%) COBRA-Slim and 69 (74%) COBRA-Avant-Garde patients (p=1.00), with a difference of -7.1% (95% confidence interval -19.7 to 5.8) between Slim and Classic and of 1.7% (95% confidence interval -10.8 to 14.1) between Slim and Avant-Garde. We also found no significant differences in remission rates at year 2 (table 2) or at any study visit (data not shown) throughout the second study year according to SDAI, CDAI or ACR-EULAR Boolean criteria. All other clinical outcomes including physical function and good EULAR response rates were persistently high and comparable between the 3 treatment arms at year 2. Analyses using data from participants who completed the trial showed comparable outcomes (supplement 3).

In the low-risk population a DAS28-CRP<2.6 was reached by 63 (70%) patients at year 2, including 29 (67%) COBRA-Slim and 34 (72%) TSU patients (p=1.00). Numerically more patients were in remission according to other criteria like CDAI in the COBRA-Slim arm (21; 49%) versus the TSU arm (13; 28%) (table 2). Of patients who completed the trial, 27/32 (84%) achieved a DAS28-CRP<2.6 on COBRA-Slim compared to 31/41 (76%) on TSU at year 2 (supplement 3).

During the entire trial 14/314 patients (4%) had a radiographic progression above the smallest detectable difference of >3.3 and the overall mean (±SD) change in SvdH score was 0.6 (±1.4). Mean SvdH progression scores did not differ between treatment arms (p=1.00 in both risk groups) (table 2) (supplement 4).

Sustainability of treatment response

The evolution of mean disease activity and HAQ scores over the 2-year period showed a similar rapid and stable response in all high-risk treatment arms (figure 2) with minimal changes during the second year. In the LMM analysis, all treatment arms had comparable DAS28-CRP (p=0.72) and HAQ scores over time (p=0.99). Survival analysis demonstrated a probability of maintaining a DAS28-CRP<2.6 at every trimonthly evaluation during the second year of 45% for COBRA-Classic, versus 61% for COBRA-Slim and 61% for COBRA-Avant-Garde (log-rank; p=0.19) (figure 3).

In the low-risk group, there were minimal changes in mean disease activity or HAQ scores during the second year (figure 2). In the LMM analysis, participants on COBRA-Slim had lower DAS28-CRP scores over 2 years with a mean difference of 0.37 (95% Confidence Interval 0.0 to 0.7; p=0.04) compared to TSU. HAQ scores over time were numerically lower in COBRA-Slim patients (p=0.07). The probability of maintaining a DAS28-CRP<2.6 at every trimonthly visit during the second year was 75% in COBRA-Slim and 63% in TSU shown by survival analysis (log-rank; p=0.38) (figure 3).

Treatment adaptations

At the 2-year follow-up, 58/85 (68%) Classic, 56/87 (64%) Slim and 52/77 (68%) Avant-Garde patients were taking a single csDMARD, in most cases MTX, in the high-risk population (figure 4). A combination of csDMARDs was taken at this visit by 10/85 (12%) Classic, 18/87 (21%) Slim and 9/77 (12%) Avant-Garde patients (p=0.17), most frequently MTX and leflunomide. At year 2, 15/85 (18%) Classic, 11/87 (13%) Slim and 14/77 (18%) Avant-Garde patients were on biologic DMARD treatment (p=0.56), which was initiated after a median of 44, 60 or 51 weeks respectively.

In the low-risk population 22/32 (69%) Slim and 26/41 (63%) TSU patients were treated with csDMARD monotherapy, whereas 2 (6%) Slim and 8 (20%) TSU patients (p=0.10) were taking a combination of csDMARDs at the year 2 visit (figure 4). Biologic DMARD treatment was taken at this visit by 5/32 (16%) Slim and 4/41 (10%) TSU patients (p=0.45); it was started after a median of 83 or 40 weeks respectively.

The overall number of patients taking oral glucocorticoids chronically outside protocol was 64/379 (17%) at a median (IQR) prednisone equivalent dose of 5.6 mg (3.3) daily. Almost half of those patients (30/64) was treated simultaneously with a biological. Glucocorticoid injections were given in the high-risk population in 26 (27%) Classic, 35 (36%) Slim and 22 (24%) Avant-Garde patients (p=0.15). More low-risk patients in TSU arm (22; 47%) received glucocorticoid injections compared to patients in Slim arm (8; 19%) (p=0.005). Mean cumulative prednisone dose during the second year was 151 mg in COBRA-Slim patients and 235 mg in TSU patients (supplement 5).

Safety analysis

The total numbers of therapy-related AEs in the high-risk group, were 209 in 72 Classic patients, 164 in 69 Slim patients and 208 in 74 Avant-Garde patients (supplement 6). Being treated with COBRA-Slim regimen resulted in less therapy-related AEs compared to COBRA-Classic (p=0.02) or COBRA-Avant-Garde (p=0.005) regimens in the high-risk population. The total numbers of therapy-related AEs in the low-risk group, were 63 in 28 Slim patients and 69 in 34 TSU patients. The most common related AEs (>5% of all reported related AEs per treatment group) were abdominal pain, disturbances in liver function, nausea, diarrhoea and hair loss. There were 23 (24%) Classic, 16 (16%) Slim and 27 (29%) Avant-Garde patients who had to discontinue their csDMARD treatment temporarily or completely due to a related adverse event in the High-Risk group (p=0.11).

Figure 1: Flow chart of participants during the 2-year trial.

All randomised patients received the allocated treatment and were analysed in an intention to treat analysis.

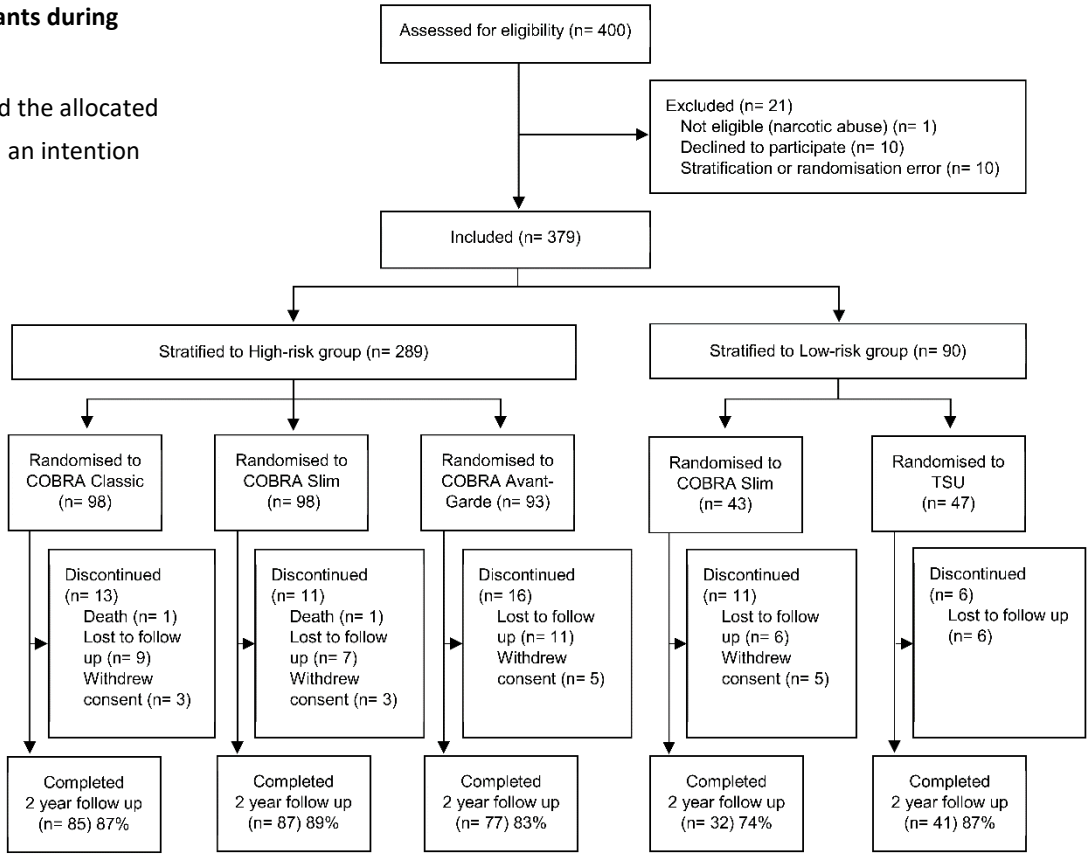


Table 1:
Baseline demographic and clinical characteristics of patients per treatment arm

	High-risk			Low-risk	
Variables	**COBRA Classic n=98**	**COBRA Slim n=98**	**COBRA Avant-Garde n=93**	**COBRA Slim n=43**	**TSU n=47**
Demographic variables					
Age, years	53 (12)	52 (13)	51 (13)	51 (14)	51 (14)
Body mass index, kg/m²	26 (4)	27 (4)	27 (4)	25 (4)	27 (4)
Women, n (%)	64 (65)	63 (64)	64 (69)	33 (77)	38 (81)
Smokers, n smoked ever (%)	56 (57)	58 (59)	56 (60)	21 (49)	18 (38)
Median (IQR) symptom duration	22 (14-44)	24 (15-39)	25 (15-51)	21 (14-35)	19 (13-33)
Median (IQR) disease duration	1 (1-3)	2 (1-3)	1 (1-4)	1 (1-3)	1 (0-4)
RF positive, n (%)	78 (80)	82 (84)	70 (75)	11 (26)	11 (23)
Anti-CCP positive, n (%)	76 (78)	78 (80)	72 (77)	12 (28)	11 (23)
Erosive disease, n (%)	32 (33)	32 (33)	32 (34)	1 (2)	0 (0)
Clinical variables					
DAS28-CRP	5.0 (1.2)	4.8 (1.1)	4.7 (1.2)	4.5 (1.6)	4.6 (1.6)
Tender Joint Count (0-68)	14 (9)	14 (8)	14 (9)	13 (11)	14 (9)
Swollen Joint Count (0-66)	12 (9)	11 (6)	11 (7)	11 (8)	10 (7)
PGA, mm (0-100)	60 (22)	56 (22)	55 (24)	49 (31)	50 (23)
Pain, mm (0-100)	59 (24)	57 (22)	57 (24)	48 (31)	52 (23)
Fatigue, mm (0-100)	51 (26)	49 (21)	49 (24)	39 (28)	46 (22)
PhGA, mm (0-100)	55 (19)	53 (18)	52 (18)	49 (21)	48 (23)
ESR, mm/h	33.5 (25.2)	32.1 (23.4)	25.0 (17.6)	30.0 (29.4)	23.0 (16.9)
CRP, mg/L	19.7 (28.9)	21.5 (33.2)	14.5 (19.2)	20.1 (39.3)	13.5 (18.6)
HAQ score (0-3)	1.2 (0.7)	1.0 (0.7)	1.0 (0.6)	0.9 (0.9)	1.0 (0.7)

Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; Disease duration= weeks elapsed between diagnosis of RA and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire.

Table 2:
Clinical and radiological outcomes per treatment arm in the high-risk group at the 2-year visit

	High-risk						
Outcomes	**COBRA Classic n=98**	**COBRA Slim n=98**	**COBRA Avant-Garde n=93**	**p value**	**Adjusted p value**	**Δ COBRA Slim versus Classic (95% CI)**	**Δ COBRA Slim versus Avant-Garde (95% CI)**
DAS28-CRP <2.6	64 (65)	71 (72)	69 (74)	0.36	1.00	-7.1 (-19.7 to 5.8)	1.7 (-10.8 to 14.1)
DAS28-CRP ≤3.2	86 (88)	86 (88)	85 (91)	0.65	1.00	0.0 (-9.4 to 9.4)	3.6 (-5.4 to 12.6)
DAS28-CRP change from BL	2.7±1.3	2.6±1.2	2.6±1.5	0.63	1.00	0.1 (-0.3 to 0.4)	0.0 (-0.4 to 0.4)
DAS28-CRP change from year 1	0.0±1.0	0.2±1.0	0.3±1.1	0.11	1.00	-0.2 (-0.5 to 0.1)	0.0 (-0.3 to 0.3)
Good EULAR response	81 (83)	81 (83)	73 (79)	0.70	1.00	0.0 (-10.7 to 10.7)	-4.2 (-15.4 to 7.1)
Moderate EULAR response	91 (93)	93 (95)	86 (93)	0.77	1.00	-2.0 (-9.5 to 5.2)	-2.4 (-10.2 to 4.9)
SDAI remission ≤3.3	31 (32)	28 (29)	41 (44)	0.06	0.96	3.1 (-9.7 to 15.7)	15.5 (1.9 to 28.4)
SDAI LDA ≤11	88 (90)	86 (88)	86 (93)	0.55	1.00	2.0 (-7.1 to 11,2)	4.7 (-4.1 to 13.5)
CDAI remission ≤2.8	30 (31)	29 (30)	44 (47)	0.02	0.34	1.0 (-11.7 to 13.7)	17.7 (3.9 to 30.6)
CDAI LDA ≤10	88 (90)	87 (89)	83 (89)	0.97	1.00	1.0 (-8.0 to 10.0)	0.5 (-8.8 to 9.6)
ACR-EULAR Boolean remission	21 (21)	20 (20)	21 (23)	0.94	1.00	1.0 (-10.4 to 12.4)	2.2 (-9.4 to 13.8)
HAQ change from BL	0.7±0.7	0.5±0.7	0.6±0.7	0.18	1.00	0.2 (0.0 to 0.4)	0.1 (-0.1 to 0.2)
HAQ change from year 1	0.0 ±0.3	0.0±0.4	0.0±0.3	0.97	1.00	0.0 (-0.1 to 0.1)	0.0 (-0.1 to 0.1)
Clinically meaningful HAQ change	71 (72)	62 (63)	64 (69)	0.38	1.00	9.2 (-3.9 to 21.8)	5.6 (-7.8 to 18.6)
HAQ = 0	34 (35)	34 (35)	29 (31)	0.84	1.00	0.0 (-13.1 to 13.1)	-3.5 (-16.5 to 9.7)

No of X-ray pairs BL and year 2	80 (82)	80 (82)	80 (86)				
SvdH change from BL	0.5±1.3	0.9±1.7	0.6±1.2	0.23	1.00	-0.3 (-0.8 to 0.2)	-0.3 (-0.8 to 0.2)
SvdH progression >SDD	3 (4)	6 (8)	3 (4)	0.45	1.00	-3.8 (-12.0 to 4.1)	-3.8 (-12.0 to 4.1)

Data are presented as absolute numbers (percentages) or as means±SD. P values are adjusted by the Holm test to correct for multiplicity.
DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; BL= baseline; LDA= low disease activity. Good EULAR response= low disease activity with a DAS28-CRP change from BL >1.2; moderate EULAR response= DAS28-CRP change from BL >1.2 or a DAS28-CRP≤5.1 and a DAS28-CRP change from BL between 0.6 and 1.2; SDAI= Simplified disease activity index; CDAI= Clinical disease activity index; ACR-EULAR Boolean Remission= tender joint count 28 ≤1 and swollen joint count 28 ≤1 and CRP≤1 mg/dL and patient global assessment ≤1 (0-10); HAQ= Health assessment questionnaire; clinically meaningful HAQ change= HAQ change >0.22; No of X-ray pairs BL and year 2= number of available X-rays pairs at baseline and year 2 after imputation; SvdH= Sharp van der Heijde score; SDD= Smallest detectable difference

Table 2 (continued): Clinical and radiological outcomes per treatment arm in the low-risk group at the 2-year visit

	Low-risk				
Outcomes	**COBRA Slim n=43**	**TSU n=47**	**p value**	**Adjusted p value**	**Δ COBRA Slim versus TSU (95%CI)**
DAS28-CRP remission <2.6	29 (67)	34 (72)	0.61	1.00	4.9 (-13.7 to 23.3)
DAS28-CRP LDA ≤3.2	36 (84)	41 (87)	0.64	1.00	3.5 (-11.3 to 18.8)
DAS28-CRP change from BL	2.4±1.7	2.2±1.9	0.58	1.00	-0.2 (-0.9 to 0.6)
DAS28-CRP change from year 1	0.1±0.8	0.1±0.9	0.61	1.00	-0.1 (-0.4 to 0.3)
Good EULAR response	27 (63)	28 (60)	0.76	1.00	-3.2 (-22.4 to 16.4)
Moderate EULAR response	38 (88)	37 (79)	0.22	1.00	-9.6 (-24.8 to 6.2)
SDAI remission ≤3.3	20 (47)	13 (28)	0.06	0.96	-18.9 (-36.9 to 1.0)
SDAI LDA ≤11	37 (86)	42 (89)	0.63	1.00	3.3 (-10.7 to 17.9)
CDAI Remission ≤2.8	21 (49)	13 (28)	0.04	0.68	-21.2 (-39.1 to -1.2)
CDAI LDA ≤10	37 (86)	40 (85)	0.90	1.00	-0.9 (-15.7 to 14.3)
ACR-EULAR Boolean Remission	16 (37)	9 (19)	0.06	0.96	-18.1 (-35.4 to 0.5)
HAQ change from BL	0.6±0.8	0.5±0.7	0.81	1.00	-0.1 (-0.4 to 0.2)
HAQ change from year 1	0.0±0.3	0.0±0.3	0.86	1.00	0.0 (-0.2 to 0.1)
Clinically meaningful HAQ change	25 (58)	26 (55)	0.79	1.00	-2.8 (-22.3 to 17.1)
HAQ = 0	17 (40)	15 (32)	0.45	1.00	-7.6 (-26.4 to 11.8)
No of X-ray pairs BL and year 2	33 (77)	41 (87)			
SvdH change from BL	0.3±0.7	0.5±1.3	0.6	1.00	0.2 (-0.3 to 0.7)
SvdH progression >SDD	0 (0)	2 (5)	0.2	1.00	4.9 (-6.1 to 16.1)

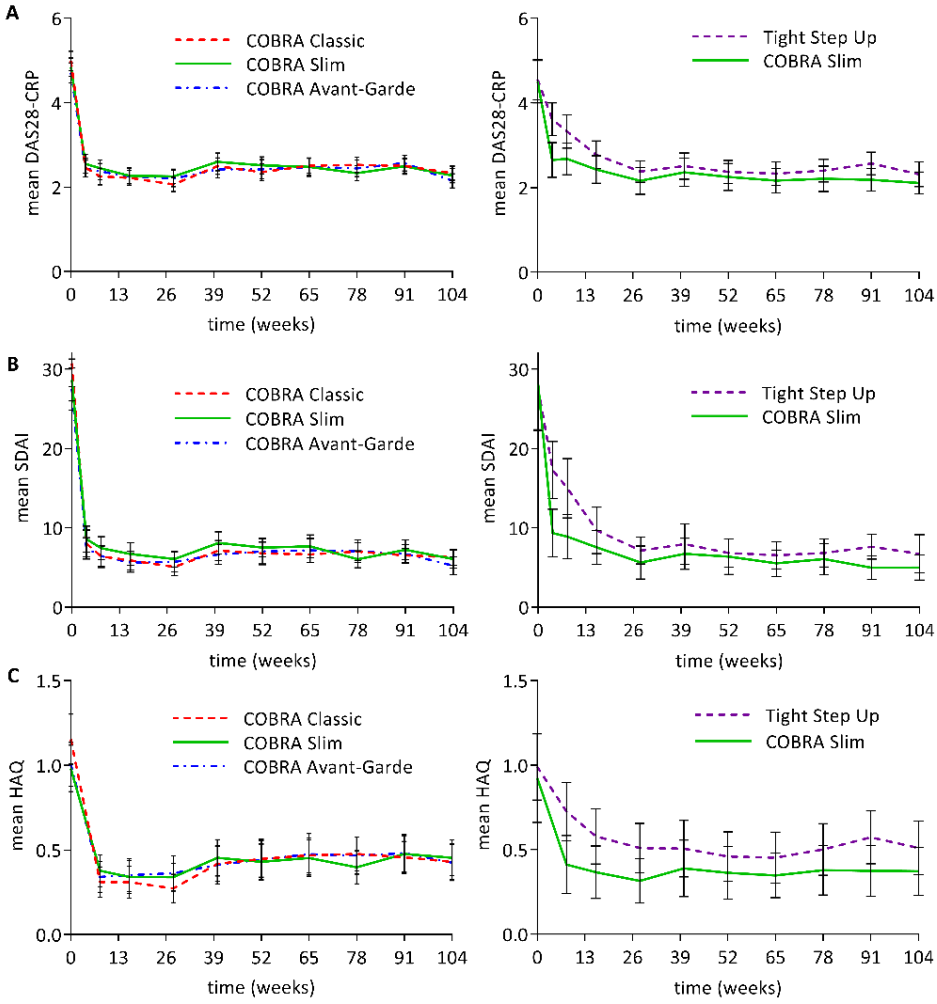


Figure 2: Clinical efficacy outcomes during 2 years of follow up

Error bars indicate the 95% CIs; DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; SDAI= Simplified disease activity index; HAQ= Health assessment questionnaire.

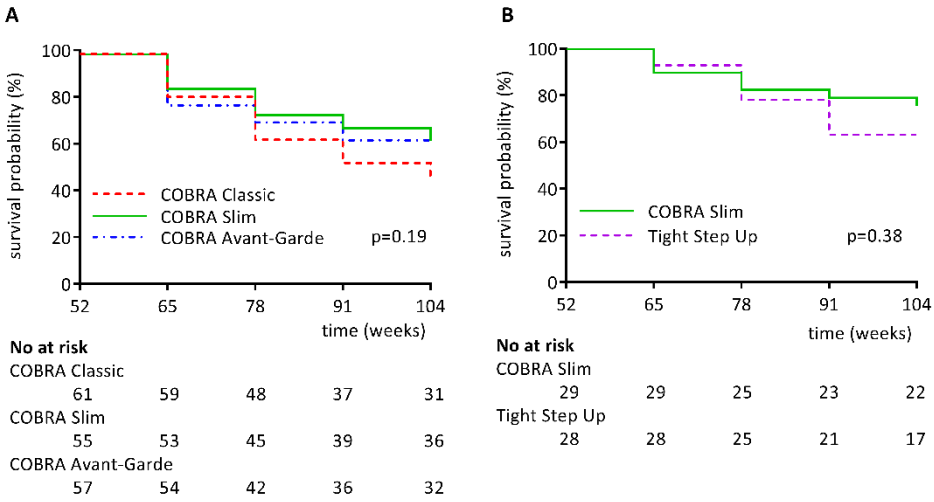


Figure 3: Survival curves for length of time after achievement of DAS28-CRP<2.6 at year 1 until loss of this state

Kaplan-Meier survival curves for the different treatment arms in the high-risk group (A) and low-risk group (B); No at risk = Numbers at risk; Survival curves compared with log-rank test.

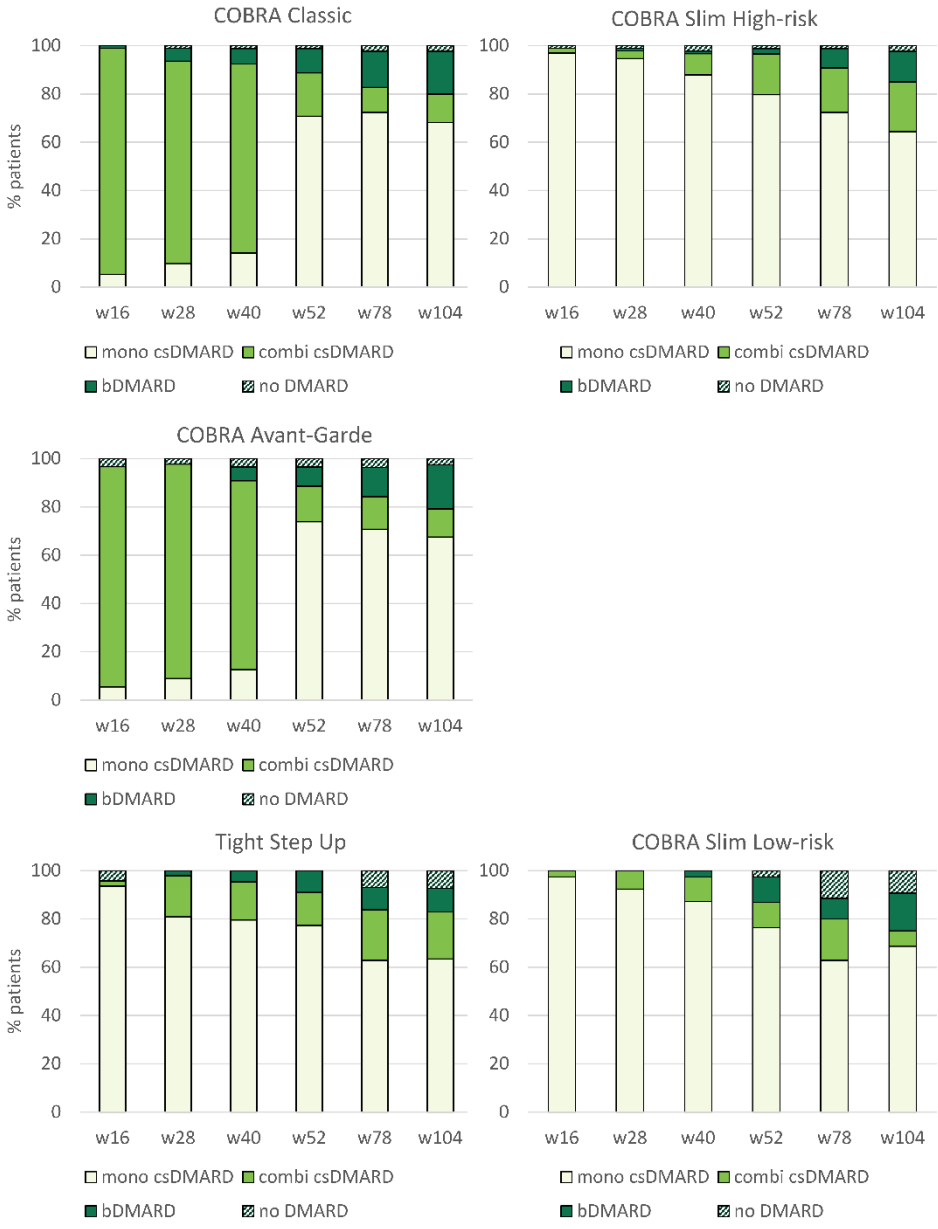


Figure 4: DMARD treatment taken by participants during 2 years of follow up in each treatment arm

w = week; csDMARD = conventional synthetic disease-modifying antirheumatic drug; bDMARD = biological DMARD taken with or without a csDMARD. Percentages of patients calculated on patients still in follow-up at each visit.

DISCUSSION

Our study has shown that patients with recent-onset RA, irrespective of their prognostic profile can achieve a significant, rapid and stable clinical response over 2 years by reinforcing csDMARD therapy with an initial step-down scheme of prednisone. In treatment arms combining csDMARDs with glucocorticoids, disease activity was well controlled (DAS28-CRP<2.6) in 65% to 74% of patients at year 2. Additionally, physical function improved rapidly, radiographic progression was well suppressed, and the initial clinical response was well maintained in all COBRA arms. Only few patients were taking glucocorticoids chronically, indicating that patients can very likely stop taking glucocorticoids within 7 months (16, 17). These results demonstrate the effectiveness of initiating a short-term glucocorticoid scheme early in the disease course, a principle recently adopted in the European recommendations to treat RA (2).

The COBRA-Slim regimen, with only MTX and prednisone bridging, resulted in similar efficacy at year 2 compared to csDMARD combinations with prednisone bridging in patients with markers of poor prognosis. While achieving similar sustained response, comparable numbers of COBRA-Slim patients were on csDMARD monotherapy after 2 years, versus the other treatment arms. At the 2-year visit, slightly more COBRA-Slim patients were taking a combination of csDMARDs, instead of a biologic DMARD at year 2, compared to the other arms. This trend towards a lower or delayed initiation rate of more expensive biologicals, especially during year 1, can potentially lead to a better cost effectiveness (18). Moreover, this treatment scheme demonstrated a more favourable safety profile and seemed better tolerated over 2 years. In the COBRA-Slim arm only patients insufficiently responding to MTX monotherapy were exposed to csDMARD combination therapy, resulting in less adverse reactions. Additionally, slightly fewer COBRA-Slim patients discontinued study treatment due to side effects. Hence, this simplified strategy with fewer drugs could avoid unnecessary overtreatment in patients sufficiently responding (19).

In patients assumed to have a better prognosis, both treatment strategies resulted in good disease control after 2 years, with only a numerically better efficacy in the COBRA-Slim group. However, for rapid remission induction, the COBRA-Slim treatment seemed more beneficial than the traditional TSU, as previously reported.

This strategy resulted in a trend towards higher probability of sustained control of disease activity during the second year. Furthermore, patients in TSU arm needed more glucocorticoid injections and seemingly more often initiation of a second csDMARD. Based on these results, in addition to a comparable safety profile, the COBRA-Slim regimen should be considered instead of MTX monotherapy, also in patients with an assumed better prognosis.(8)

We included a heterogeneous study population with varied disease severity and from different types of routine practice settings throughout Flanders. Moreover, we had high retention rates of participants, probably related to the speed and stability of response, highly preferred by patients in our trial. (20, 21) These features support the external validity of our results and are indicative for a good applicability in daily clinical practice.

This was an open label trial without blinding, leaving room for bias in treatment decisions, which could have influenced differences in outcomes between arms. Additionally, patients' adherence to treatment was not formally assessed and in the second year, treatment was at the discretion of the rheumatologist. However, this pragmatic design is closer to daily practice, and enabled us to study the effectiveness of COBRA regimens more realistically than in a blinded trial.

The primary endpoint was based on the DAS28-CRP which might not be stringent enough since this outcome measure is known to potentially overestimate remission rates. (10) However, remission results based on more stringent criteria like CDAI, SDAI and ACR-EULAR Boolean criteria yielded similar results while comparing the treatment groups.

We aimed for remission but used the cut-off of low disease activity (DAS28-CRP≤3.2) to decide whether to adapt treatment; this threshold was deliberately set not lower to avoid changing therapy too rapidly or too often which might increase risk of side effects and of rheumatologists' non-adherence to the protocol in the initial treatment phase. An analysis of the BeST and IMPROVED trial showed that rheumatologists' adherence to a DAS steered treatment protocol in early arthritis patients was worse if the target was remission. (22)

Similarly to CareRA, the COBRA-light trial demonstrated that a combination of 25 mg MTX weekly and a step-down scheme of prednisolone, starting at 30 mg/day, had

major effects on disease control after 1 year in early RA. (23, 24) However, addition of etanercept (a biological DMARD) was prescribed in case DAS44>1.6, which was often not implemented by treating rheumatologists or resulted in limited additional benefit.

In contrast, the Treatment in the Rotterdam Early Arthritis CoHort (tREACH) trial concluded that triple DMARD therapy was more effective than MTX monotherapy (25). One reason for this might be that in CareRA we used a more solid and lengthier prednisone bridging scheme in anticipation of the effect of csDMARDs, resulting in similar effectiveness of initial monotherapy with adjustment depending on response, compared to DMARD combination therapy. However, there are no properly designed studies comparing COBRA-Slim directly with triple DMARD therapy until today.

In conclusion, patients with recent onset RA, regardless of their risk profile, were effectively treated with COBRA-Slim up to 2 years. MTX monotherapy with glucocorticoid bridging, provided the best balance between efficacy and safety in a treat-to-target setting.

Key Messages

1. Compared to DMARD combi-therapy, methotrexate monotherapy with glucocorticoid bridging (COBRA-Slim) resulted in similar 2-year effectiveness.

2. COBRA-Slim is an effective induction regimen, avoiding overtreatment and adverse reactions within a treat-to-target-strategy.

3. All patients with early RA might benefit from an initial moderately-dosed glucocorticoid bridging scheme.

SUPPLEMENTAL MATERIAL

Supplement 1a: Exclusion criteria of the CareRA study

Exclusion criteria included:

- Previous treatment with methotrexate, leflunomide, cyclophosphamide, azathioprine, cyclosporine, sulfasalazine for more than three weeks, hydroxychloroquine for more than six weeks

- Oral glucocorticoids at a dosage of more than 10 mg prednisone or dosage equivalent within four weeks before baseline

- Oral glucocorticoids at a dosage equal to or less than 10 mg prednisone or dosage equivalent within two weeks before baseline, oral glucocorticoids for more than four weeks, intra-articular glucocorticoids within four weeks before baseline or an investigational drug for the treatment or prevention of RA

- Contra indications for glucocorticoids

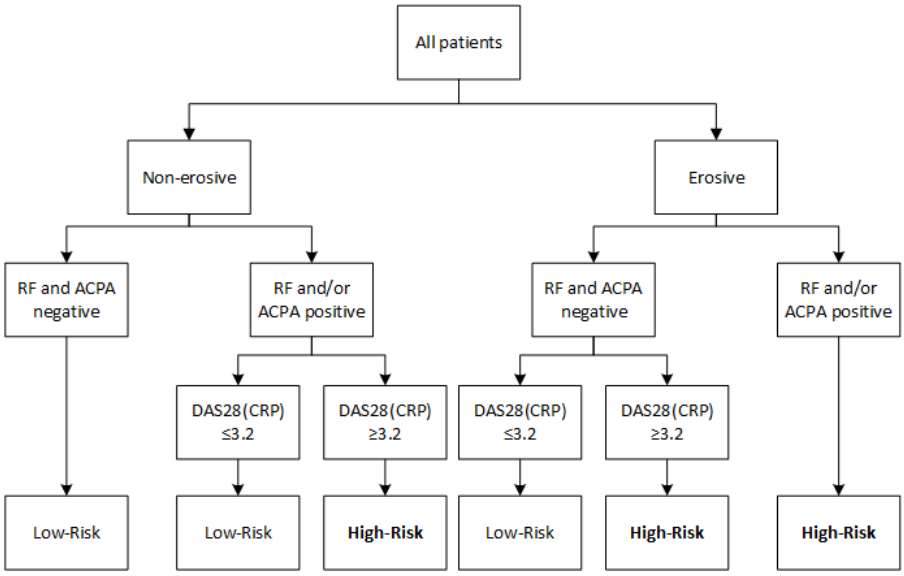
- Contra indication for methotrexate, sulfasalazine or leflunomide at the discretion of the investigator: chronic hepatic diseases, pulmonary interstitial disease or fibrosis, chronic renal failure, history of malignant neoplasm within five years, hematologic problems

- Patients with psoriatic arthritis

- Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study

- Pregnancy; Breastfeeding; No use of a reliable method of contraception

Supplement 1b: stratification scheme of the CareRA study



Stratification scheme: Classification of patients in high or low-risk according to classical prognostic factors. RF= Rheumatoid Factor; ACPA= Anti-Citrullinated Protein Antibody; DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

Supplement 2: Treatment regimens and adaptation steps

Treatment regimens in the induction phase (Year 1)

COBRA Classic:
MTX 15 mg with SSZ 2g and a step down scheme of steroids (60-40-25-20-15-10-7,5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks). At week 40, patients will continue MTX (min. 15 mg/week) in mono therapy if disease activity is acceptable low (DAS 28 CRP ≤ 3,2)

COBRA Slim:
MTX 15 mg with a step down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks).

COBRA Avant-Garde:
MTX 15 mg with Leflunomide 10 mg and a step down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks). At week 40, patients will be randomly assigned to maintenance therapy with either MTX (≥15 mg/week) or leflunomide (20 mg daily) if disease activity is acceptable low (DAS 28 CRP ≤ 3,2).

Tight Step Up:
MTX 15 mg and no additional oral steroids allowed

Predefined adaptation steps in the induction phase (Year 1)

If patients fail to respond (DAS28-CRP > 3.2), treatment adjustments will be made from 8 weeks of treatment onwards, if desirable and feasible.

First step: methotrexate dose increase to 20 mg per week in all groups

Second step: COBRA-Classic: sulfasalazine dose increase to 3 g

COBRA-Slim and Tight Step Up: add leflunomide 10 mg

COBRA-Avant-Garde: leflunomide dose increase to 20 mg

An intramuscular depot-corticoid injection is allowed together with these treatment adjustments, but not within 4 weeks preceding week 16, 28, 40 and week 52 visits. As an alternative an oral bridging scheme could be considered, after discussion with the principal investigator

Intra-articular corticosteroids are allowed maximally once every 8 weeks but not within 4 weeks preceding week 16, 28, 40 and week 52 visits

Further DMARD treatment adjustments are only allowed from 8 weeks after prior treatment adjustments onwards.

Treatment regimen in the maintenance phase (Year 2)

Treatment adjustments during the maintenance phase from week 52 onwards will be at the discretion of the local physician according to good clinical practice.

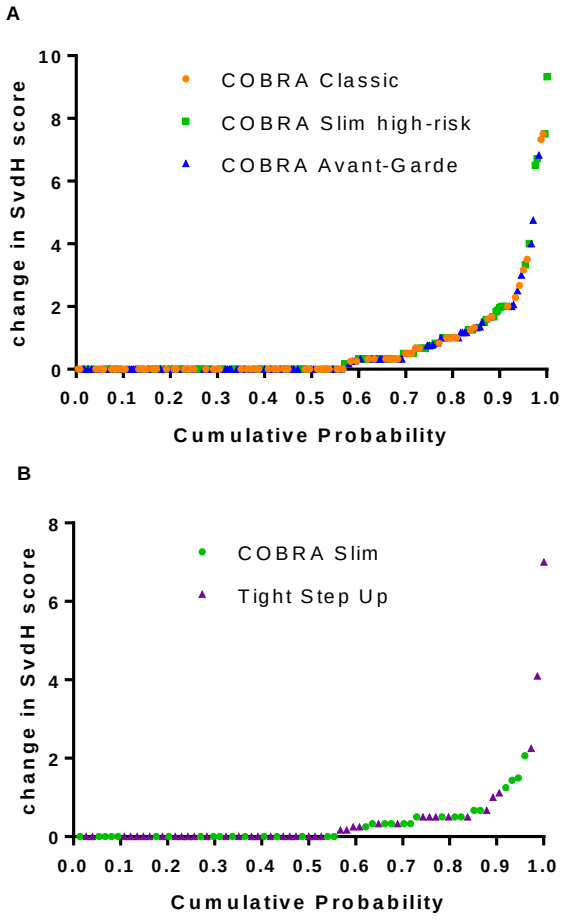
Supplement 3:

Outcomes per treatment arm at the 2-year visit in participants who completed the 2-year trial

	High-risk					Low-risk			
Outcomes	**COBRA Classic n=85**	**COBRA Slim n=87**	**COBRA Avant-Garde n=77**	**p value**	**Adj. p value**	**COBRA Slim n=32**	**TSU n=41**	**p value**	**Adj. p value**
DAS28-CRP <2.6	59 (69)	66 (76)	63 (82)	0.19	1.00	27 (84)	31 (76)	0.36	1.00
DAS28-CRP ≤3.2	75 (88)	78 (90)	72 (94)	0.51	1.00	28 (88)	37 (90)	0.71	1.00
Good EULAR response	73 (86)	73 (84)	66 (86)	0.92	1.00	23 (72)	27 (66)	0.58	1.00
Moderate EULAR response	80 (94)	82 (94)	71 (92)	0.84	1.00	30 (94)	32 (78)	0.06	0.60
SDAI remission ≤3.3	30 (35)	28 (32)	39 (51)	0.04	0.48	19 (59)	13 (32)	0.02	0.22
SDAI LDA ≤11	75 (88)	77 (89)	71 (92)	0.66	1.00	28 (88)	38 (93)	0.46	1.00
CDAI remission ≤2.8	30 (35)	29 (33)	41 (53)	0.02	0.26	20 (63)	13 (32)	0.01	0.13
CDAI LDA ≤10	75 (88)	78 (90)	69 (90)	0.95	1.00	28 (88)	36 (88)	0.97	1.00
ACR-EULAR Boolean remission	21 (25)	20 (23)	20 (26)	0.91	1.00	16 (50)	9 (22)	0.01	0.13
Clinically meaningful HAQ change	64 (75)	54 (62)	55 (71)	0.15	1.00	21 (66)	23 (56)	0.41	1.00
HAQ = 0	34 (40)	34 (39)	29 (38)	0.95	1.00	17 (53)	15 (37)	0.16	1.00
No of X-ray pairs BL and year 2	75 (88)	78 (90)	74 (96)			29 (91)	38 (93)		
SvdH change from BL	0.6±1.4	0.9±1.8	0.6±1.2	0.18	1.00	0.4±0.6	0.4±1.2	0.24	1.00
SvdH progression >SDD	3 (4)	6 (8)	3 (4)	0.50	1.00	0 (0)	1 (3)	0.38	1.00

Supplement 4:

Cumulative probability plots of the radiographic progression



Cumulative probability plots shown of the radiographic progression for the different treatment arms in the high-risk group (A) and low-risk group (B). SvdH= Sharp van der Heijde score; Change in SvdH scores= change from baseline till year 2.

Supplement 5:

Use of glucocorticoids by participants over the 2-year follow-up period

	High-risk			Low-risk	
Outcomes	**COBRA Classic**	**COBRA Slim**	**COBRA Avant-Garde**	**COBRA Slim**	**TSU**
Cumulative prednisone dose during year 1 (mg)	2597±667	1527±379	1586±423	1554±308	36±50
Cumulative prednisone dose during year 2 (mg)	415±891	367±970	423±1428	151±346	235±696
Patients taking oral GC chronically, n(%)	22 (22)	16 (16)	16 (17)	5 (12)	5 (11)
Median (IQR) daily dose in patients taking GC chronically	5.8 (3.0)	5.3 (6.0)	5.0 (2.5)	5.4 (2.9)	6.7 (3.3)
Patients who had GC injections, n (%)	26 (27)	35 (36)	22 (24)	8 (19)	22 (47)
GC injections, n	43	55	34	11	37

Data are presented as means±SD unless specified otherwise. GC= glucocorticoids; Cumulative prednisone dose calculated of all systemic GC (oral, intramuscular, intra articular). Patients taking oral GC chronically were defined as patients taking oral GC consecutively for > 3 months outside of initial prednisone schemes prescribed by protocol. Median daily dose= median daily dose of prednisone equivalent in mg.

Supplement 6:

Safety analysis over 2-year follow-up

	High-risk			Low-risk	
Outcomes	**COBRA Classic n=98**	**COBRA Slim n=98**	**COBRA Avant-Garde n=93**	**COBRA Slim n=43**	**TSU n=47**
Total related AE	209	164	208	63	69
Patients with related AE	72 (73)	69 (70)	74 (80)	28 (65)	34 (72)
Total SAE	29	29	25	10	11
Patients with SAE	21 (21)	22 (22)	16 (17)	9 (21)	7 (15)
Patients with serious infection	2 (2)	4 (4)	3 (3)	4 (9)	1 (2)
Patients deceased	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
AE causing treatment interruption	22	14	27	7	8
Patients interrupting treatment due to related AE	17 (17)	12 (12)	19 (20)	6 (14)	7 (15)
AE causing treatment stop	12	6	13	0	0
Patients stopping treatment due to related AE	9 (9)	5 (5)	12 (13)	0 (0)	0 (0)

Data are presented as absolute numbers (percentages); (S)AE = (Serious) Adverse Event; serious infection= infection resulting in hospitalization.

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Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S14-36.

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COMMENT ON: WHAT IS THE BEST TREATMENT FOR EARLY RHEUMATOID ARTHRITIS?

Dear Editor,

In a recent issue of Rheumatology, Professor Pope discusses our paper on the 2-year results of the CareRA trial (1) and reflects on early RA treatment strategies (2). We would like to respond to and clarify several points raised in the editorial: whether potential differences between treatments have been minimized, how MTX should be used (dose, route of administration and as single csDMARD or within a triple therapy), and whether bridging glucocorticoids should be used in all patients.

The first issue raised was if differences in treatment efficacy could have been minimized due to our use of DAS28 as opposed to CDAI remission as primary outcome, or because of treating-to-target. While indeed at week 104 CDAI results were statistically better with COBRA Avant-Garde versus COBRA Slim, CDAI and SDAI remission status at all other time points showed no difference between treatment groups in high-risk patients (table 1). Additionally, when analyzing disease activity longitudinally over 2 years, no differences were shown via a linear mixed model with CDAI (p=0.723) or SDAI (p= 0.605). We do of course agree that we succeeded in achieving remission in a high number of patients across treatment arms by treating to target, adding to the relevance of our data for daily practice. However, we want to emphasize that proportions of patients who had to adapt DMARD treatment (switch or add-on) outside of the predefined schedules, were comparable after 2 years between the 3 treatment arms in the high-risk group (34% in Classic, 39% in Slim and 31% in Avant-Garde). Therefore, we think applying treat-to-target could not have eliminated important differences between treatment arms.

Secondly, the dose and route of administration of MTX was questioned and whether it should be combined with other csDMARDs. We started oral MTX at a dose of 15mg weekly but the dose had to be increased per protocol from week 8 onwards when a target of DAS28-CRP ≤3.2 was not met. In the high-risk group 37%, 42% and 33% of patients did so within the 2 years follow up in the COBRA Classic, Slim and Avant-Garde arm respectively. By consequence, overall 63% of high-risk patients were not exposed to unneeded higher dosages, potentially leading to less side effects population wise. Within a strict treat-to-target approach, 15mg/weekly seems

sufficient as initial therapy for the majority of patients. We also want to clarify that within CareRA switching to IM or SC MTX was allowed and even advocated in case of oral intolerance. In the 1-year results paper of CareRA (3) we extensively discussed the difference in efficacy and effectiveness between treatments, the latter pointing to less patients being able to tolerate the initial csDMARD combinations and partly therefore switching earlier to biologicals. Although we agree that some patients might benefit from initial combination of csDMARDs, it remains difficult to effectively identify such patients in practice without better predictive markers. We would like to highlight that COBRA Slim therapy matches with the most recent EULAR recommendations (4). Actually, recommendation n°4 (MTX monotherapy and not csDMARD combination as preferred initial strategy) ultimately had a very high level of agreement among participating experts (LoA 9.8), as extensively detailed in the manuscript. Nevertheless, current recommendations do not preclude choosing for csDMARD combination.

The last and ever returning discussion raised was on glucocorticoids. First of all, we feel that framing the use of glucocorticoids as an “addiction” should be avoided and the attention should be focused on proper guidance of patients in care programs practicing shared decision making to avoid overuse. Moreover, we would like to highlight our findings on early strategic glucocorticoid use in an observational study, published in this journal early 2008 (5). Patients with a better prognosis who did not receive initial glucocorticoids ended up in the long term with less disease control, poorer functionality and more ongoing glucocorticoid use compared to high-risk patients having received initial bridging therapy with glucocorticoids. The authors agree that unnecessary glucocorticoid use should be avoided, but in CareRA the use after 2 years is low (and much lower than we see in the baseline characteristics of participants of RCT’s in MTX refractory RA in recent years). Moreover, we need to balance our perceptions on glucocorticoids based on all available additional evidence (6, 7). Taking into account our results and the high preference of patients for rapid disease control and a return to normality (8), the advantages of glucocorticoids within a step-down-bridge strategy should not be overlooked, as long as prices of other fast acting drugs like biologics and JAK inhibitors stay high and stopping data with these drugs show no clear advantages compared to glucocorticoids.

In summary, our study convincingly shows that rheumatologists can change the fate of patients with RA significantly by choosing their initial treatment strategy wisely and without prejudices.

Table 1: CDAI or SDAI remission at every visit during second year of CareRA in high-risk group

	High-risk				
Outcomes	**COBRA Classic n=98**	**COBRA Slim n=98**	**COBRA Avant-Garde n=93**	**p value**	**Adjusted p value**
CDAI rem w52	35 (36)	25 (26)	34 (37)	0.19	0.94
CDAI rem w65	31 (32)	26 (27)	37 (40)	0.14	0.92
CDAI rem w78	34 (35)	34 (35)	34 (37)	0.95	1.00
CDAI rem w91	26 (27)	30 (31)	32 (34)	0.50	1.00
CDAI rem w104	30 (31)	29 (30)	44 (47)	0.02	0.17
SDAI rem w52	36 (37)	27 (28)	39 (42)	0.11	0.86
SDAI rem w65	27 (28)	20 (20)	31 (33)	0.13	0.92
SDAI rem w78	26 (27)	32 (33)	31 (33)	0.53	1.00
SDAI rem w91	24 (24)	29 (30)	28 (30)	0.63	1.00
SDAI rem w104	31 (32)	28 (29)	41 (44)	0.06	0.53

Data are presented as absolute numbers (percentages). P values are adjusted by the Holm test to correct for multiplicity. rem= remission; CDAI= Clinical disease activity index; CDAI remission ≤2.8. SDAI= Simplified disease activity index; SDAI remission ≤3.3.

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CHAPTER 1.2

Five-year outcomes of early intensive treatment for rheumatoid arthritis with csDMARDs and temporary glucocorticoids: data from the CareRA trial

This chapter will be submitted as an original article:

Stouten V, Westhoven R, Pazmino S, De Cock D, Van der Elst K, Joly J, Bertrand D, Verschueren P for the CareRA study group. Five year outcomes of early intensive treatment for rheumatoid arthritis with csDMARDs and temporary glucocorticoids: data from the CareRA trial

ABSTRACT

Objectives

To compare long-term outcomes of early intensive and tightly controlled treatment combinations in the Care in early RA (CareRA) trial over a 5-year follow-up.

Methods

In the 2-year CareRA trial, patients with DMARD naïve RA were stratified in a high- or low-risk group based on classical prognostic markers. High-risk patients were randomised to COBRA Classic (MTX+sulphasalazine with highly dosed glucocorticoids (GC)), COBRA Avant-Garde (MTX+leflunomide with moderately dosed GC) or COBRA Slim (MTX with moderately dosed GC). Low-risk patients were randomised to COBRA Slim or MTX tight step up (TSU). Patients completing CareRA were eligible for 3 years follow-up in the current CareRA-plus trial. Evolution in disease activity (DAS28-CRP), functionality (HAQ) and X-ray damage over 5 years was compared between treatments using longitudinal models. Adverse events (AEs) and DMARD adaptations were registered.

Results

Of 322 eligible patients, 252 (78%) entered CareRA-plus, of which 203 (81%) completed the study. High-risk treatment arms showed comparable DAS28-CRP ($p=0.539$) and HAQ scores over 5 years ($p=0.374$). Low-risk patients starting COBRA Slim had lower DAS28-CRP ($p<0.001$) and HAQ scores ($p=0.041$) over time than those receiving TSU. Of patients completing the study, 114/203 (56%) did not need to intensify their original DMARD therapy during 5 years without differences between treatment arms. The numbers of AEs throughout the observational follow-up were comparable between arms in high-risk patients ($p=0.182$); in the low-risk group there were 18 AEs in 10 Slim and 36 in 17 TSU patients ($p=0.048$).

Conclusion

All intensive treatments with bridging GC resulted in excellent long-term outcomes. Initial COBRA Slim showed comparable 5-year effectiveness as COBRA Classic and COBRA Avant-Garde in high-risk early RA patients and better efficacy than MTX step-up in low-risk patients.

INTRODUCTION

It is recommended to treat patients with early rheumatoid arthritis (RA) immediately, intensively and to a predefined target in order to rapidly control disease activity and avoid joint damage and functional decline [1,2].

The 'Care in early RA' (CareRA) trial evaluated the effectiveness of different csDMARD combinations and glucocorticoid bridging schemes in patients with early RA in a treat-to-target setting close to daily clinical practice. It was demonstrated that remission induction with csDMARD combinations and step-down glucocorticoids (GCs) was not superior over MTX monotherapy with moderately dosed step-down GCs (COBRA Slim) in RA patients with a high-risk profile. The results after 16 weeks, 1 and 2 years were previously reported [3–5]. Moreover, COBRA Slim showed benefit over a tight step-up with MTX in monotherapy (TSU) in RA patients with a low-risk profile [5,6]. The COBRA Slim regimen, MTX monotherapy with glucocorticoid bridging, provided the best balance between efficacy and safety after 1 and 2 years, was cost-effective, and was further endorsed in the updated EULAR recommendations of 2019 to treat RA [7,8].

As EULAR recommendations emphasize also the importance of sustained remission or at least low disease activity, long term follow of treatment schemes is necessary. The 11 year follow up of the original COBRA trial already showed reassuring long term efficacy and safety of early intensive combination therapy, even without a strict treat-to-target approach [9]. More recently the 10 year follow up of the BeSt trial, incorporating tight treatment control, confirmed the importance of early intensive combination therapy and demonstrated that even drug-free remission and normalized mortality have become realistic outcomes [10]. Despite all evidence above, current guidelines are still debated, specifically the early use of GC's [11]. Therefore we aimed to study the long-term effectiveness of the initial treatments used in CareRA within the 3 year observational CareRA-plus follow-up study. We compared maintenance of disease control, use of the different DMARD classes and safety over 5 years between groups according to the initial treatment allocation at baseline in the original CareRA study.

METHODS

Study design

The CareRA plus trial was a 3-year observational follow-up study of the CareRA trial, a 2-year investigator-initiated, multicentre, randomized controlled trial, set up to evaluate the effectiveness of different treatment regimens for patients with early RA. In CareRA, we included patients with early RA (diagnosis <1 year), who were naïve to and had no contraindications for csDMARDs or glucocorticoids. Detailed enrolment criteria were published previously [4]. Participants completing the 2-year visit of CareRA were eligible for inclusion in CareRA plus. This study was conducted in 10 Belgian rheumatology centres (1 academic centre, 6 general hospitals and 3 private practices). The medical ethics committee of each centre approved the study protocol and all patients gave written informed consent before participation.

Initial and subsequent treatments

Before randomization in CareRA, patients were stratified into a high-risk or low-risk group based on presence of classical prognostic factors, including RF / ACPA positivity, high baseline disease activity and having erosions. Patients in the high-risk group were randomized to one of three remission induction schemes following a treat-to-target principle: COBRA Classic: initial combination of methotrexate (MTX) and sulfasalazine; COBRA Slim: MTX monotherapy; COBRA Avant-Garde: initial combination of MTX and leflunomide. All COBRA schemes included an initial step-down scheme of oral prednisone, started at a high or moderate dose, and tapered weekly over 6 or 7 weeks to a low maintenance dose which was discontinued at week 28. The schemes combining two csDMARDs were tapered to csDMARD monotherapy at week 40 in case patients achieved low disease activity. Patients in the low-risk group were randomized to one of two schemes: the same COBRA Slim schedule or Tight Step-up: MTX monotherapy without glucocorticoids. When a target of low disease activity (DAS28-CRP ≤3.2) was not reached, treatment was adjusted by two predefined adaptation steps, from week 8 onwards and during the first study year. As a first step, MTX dose was adjusted to 20mg weekly in all arms. As a second step, the dose of the other csDMARD was adapted in the COBRA Classic and COBRA Avant-Garde arm. In COBRA Slim and Tight Step Up the second step consisted of initiating leflunomide 10mg daily. During the second year, treatment was at the discretion of

the rheumatologist. The protocol has been described into detail in previous publications [4,5]. In CareRA plus, further application of the treat-to-target principle was recommended, but adaptation of treatment was left to the decision of rheumatologist and patients.

Assessments and outcomes

During CareRA plus, participants were assessed every 6 months for 3 years. Disease activity (DAS28-CRP and SDAI), clinical parameters and functionality measured by the Health Assessment Questionnaire (HAQ) were registered. All (serious) adverse events ((S)AEs) considered to be relevant according to the investigators, were recorded. Comorbidities were registered at baseline.

DMARD and glucocorticoid intake were registered at every visit throughout the study. We assessed DMARD changes from baseline CareRA over 5 years, resulting in 3 possible trajectories: Patients adding or switching a csDMARD, patients initiating a biologic DMARD (bDMARD) and patients who never had an intensification. In the latter, patients stayed on csDMARD monotherapy from week 40 in COBRA Classic and COBRA Avant-Garde, or from baseline in COBRA Slim till year 5 or discontinued all DMARD therapy.

Radiographs of hands and feet were performed at baseline, week 28, year 1 and thereafter yearly to assess progression of joint damage. All radiographs were read chronologically using the Sharp van der Heijde (SvdH) score by one blinded reader (TK) [12]. This reader was trained by an experienced reader DC who scored previously all radiographs of the 2-year CareRA trial in the same manner. Based on scores of radiographs of the 2 years of CareRA, an intra-class correlation coefficient for agreement between the two readers was calculated as 0.83 (95% CI: 0.81 to 0.85). Radiographic progression was assessed by the change in the total SvdH score from baseline CareRA till year 5 and was visualized using a cumulative probability plot in patients who completed the study.

Statistical analysis

Each analysis compared the outcomes between the different treatments allocated at baseline. Potential differences in clinical outcomes, were examined by Chi-square, ANOVA or Kruskal-Wallis, independent t-test or Mann-Whitney U test, when appropriate.

Percentages of patients in low disease activity or in remission according to DAS28-CRP or to Simplified Disease Activity Index (SDAI) were calculated based on an 'intention-to-treat' analysis including all randomised patients. Missing data of components of the disease activity indices were imputed with multiple imputation by chained equations (100 imputed datasets) [13]. The imputation model included terms for observed disease activity, HAQ score, treatment randomization, demographics, classical prognostic factors, comorbidity status, treatment intensifications, and SvdH scores.

The changes in DAS28-CRP, SDAI and HAQ were analysed over 5 years using linear mixed models (LMM). Remission and low disease activity rates over 5 years were analysed by generalized linear mixed models (GLMM). These mixed models incorporated a random intercept and a random slope for time with an unstructured correlation structure. This accounts for the repeated observations within a patient and allows the estimation of a different regression line for each patient with a different baseline value and rate of change over time. SvdH scores over time were compared using a generalized estimating equations analysis with a negative binomial working distribution to address skewness of these data. For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time. The number of occurring AEs during CareRA plus were compared using poisson regression. Significance level was set at 0.05. Analyses were carried out using SPSS version 26 and R version 4.0.1.

RESULTS

Participants

Of 322 patients who completed the 2-year CareRA study, 252 (78%) were enrolled in the CareRA plus study. We analysed patients according to their originally allocated treatment in the high-risk group: COBRA Classic (n=69) versus COBRA Slim (n=75) or COBRA Avant-Garde (n=59) and in the low-risk group: COBRA Slim (n=23) versus TSU (n=26). In both risk groups, demographic and clinical characteristics at baseline CareRA were well balanced between treatment arms (table 1). Patients entering CareRA-plus had similar demographics and clinical characteristics at the final 2-year visit of the preceding CareRA trial as patients not entering the follow-up study. CareRA plus patients were enriched for ACPA, compared to non-participants, but ACPA positivity did not differ between treatment groups (supplement 1). In total, 203 (81%) participants completed the 5-year follow up, with similar frequencies or reasons for discontinuation between treatment arms (figure 1).

Disease activity over time

Disease activity improved rapidly during the first 16 weeks and remained stable over the following 5 years among patients of the high-risk group (figure 2). There were no differences in DAS28-CRP or SDAI scores over time between treatment arms (LMM: respectively p=0.539 and p=0.431 for overall comparison; supplement 2A). In the low-risk group, results indicated that disease activity measured by DAS28-CRP over 5 years was lower in patients who started COBRA Slim compared with TSU (LMM: β=-0.46; CI [-0.63 to -0.29]; p<0.001). Accordingly, SDAI scores over the 5-year follow-up were lower in the COBRA Slim strategy (LMM: β=-2.46; CI [-3.87 to -1.04]; p=0.001; supplement 2B).

Remission and low disease activity states

Based on available data of participants who competed the 5-year study, overall 89% of patients had low disease activity reflected by a DAS28-CRP<3.2, and 74% were in remission according to a DAS28CRP<2.6. Low disease activity measured by SDAI was achieved by 89% of all patients and SDAI remission by 40% of patients. DAS28-CRP<2.6 at year 5 in high-risk patients was 72%, 77% and 64% for the Classic, Slim and Avant-Garde group respectively (p=0.403). In the low-risk population, 83% of

patients in the Slim and 82% in the TSU arm had a DAS28-CRP<2.6 at year 5 (p=0.945). Remission rates at year 5 based on an intention-to-treat analysis with missing data imputed by multiple imputation were comparable (supplement 3). Remission and low disease activity rates are shown per time point in figure 3 and supplement 4. Occurrence of remission over time assessed by DAS28-CRP or SDAI was similar between treatments in the high-risk group (GLMM: respectively p=0.798 and p=0.224 for overall comparison; supplement 2A). In the low-risk group, patients on COBRA Slim had over time higher odds of achieving remission, compared to patients started on TSU (OR=2.62 CI [1.43 to 4.81]; p=0.002 for DAS28-CRP remission, OR=3.27 CI [1.35 to 7.91]; p=0.009 for SDAI remission) (supplement 2B).

Functionality

In the high-risk group the mean HAQ scores over 5 years were comparable between treatment arms (LMM: p= 0.374 for overall comparison; supplement 2A). Among patients of the low-risk group, those treated with initial COBRA Slim strategy had lower HAQ scores and thus better functionality over 5 years (LMM: β= 0.21 CI [-0.41 to -0.01]; p=0.041; supplement 2B).

Radiographic progression

After 5 years, radiographic progression, measured as increase in SvdH score, in patients completing the study was limited and comparable between treatment arms in the high-risk population. More specifically, 3 patients in Classic, 3 in Slim high-risk and 1 in Avant-garde had an increase in SvdH score >5. There were 11 patients in Classic, 9 in Slim and 5 in Avant-Garde who had an increase in SvdH score >0.5 (p= 0.399). In the low-risk group there were no patients with a change in SvdH > 5, and there was 1 Slim patient with a change >0.5 (p=0.283). A cumulative probability plot of radiographic progression is shown in supplement 5. Longitudinal analyses demonstrated that the mean change in SvdH score over 5 years was similar in the high-risk group and in the low-risk group (GEE: p= 0.524 and p=0.928 for overall comparison respectively; supplement 2).

Treatment intensifications

At the year 5 visit, 71%, 61% and 50% of high-risk patients were on csDMARD monotherapy (mostly MTX) in Classic, Slim and Avant-Garde respectively. Of the low-risk group, 65% in COBRA Slim and 62% in TSU were taking a single csDMARD. At the year 5 visit, 9% of all participants received chronic oral GC therapy (>3 months). Overall, of patients completing the study, 56% never had their DMARD therapy intensified. More specifically, 64% of Classic, 58% of Slim high-risk, 48% of Avant-Garde, 50% of Slim low-risk and 52% of TSU patients never had an intensification in their DMARD therapy during 5 years of the study. Treatment profiles at every visit are shown in figure 4. During the 5-year study, biologics were initiated in 22% of all patients: 23% of Classic, 23% of Slim high-risk, 25% of Avant-Garde, 17% of Slim low-risk, and 15% of TSU patients.

Safety

In high-risk patients, the total numbers of AEs throughout CareRA-plus, were 70 in 36 Classic, 95 in 48 Slim and 80 in 36 Avant-Garde patients (p=0.182). In the low-risk group, there were 18 AEs in 10 Slim and 36 in 17 TSU patients (p=0.048) (Table 2).

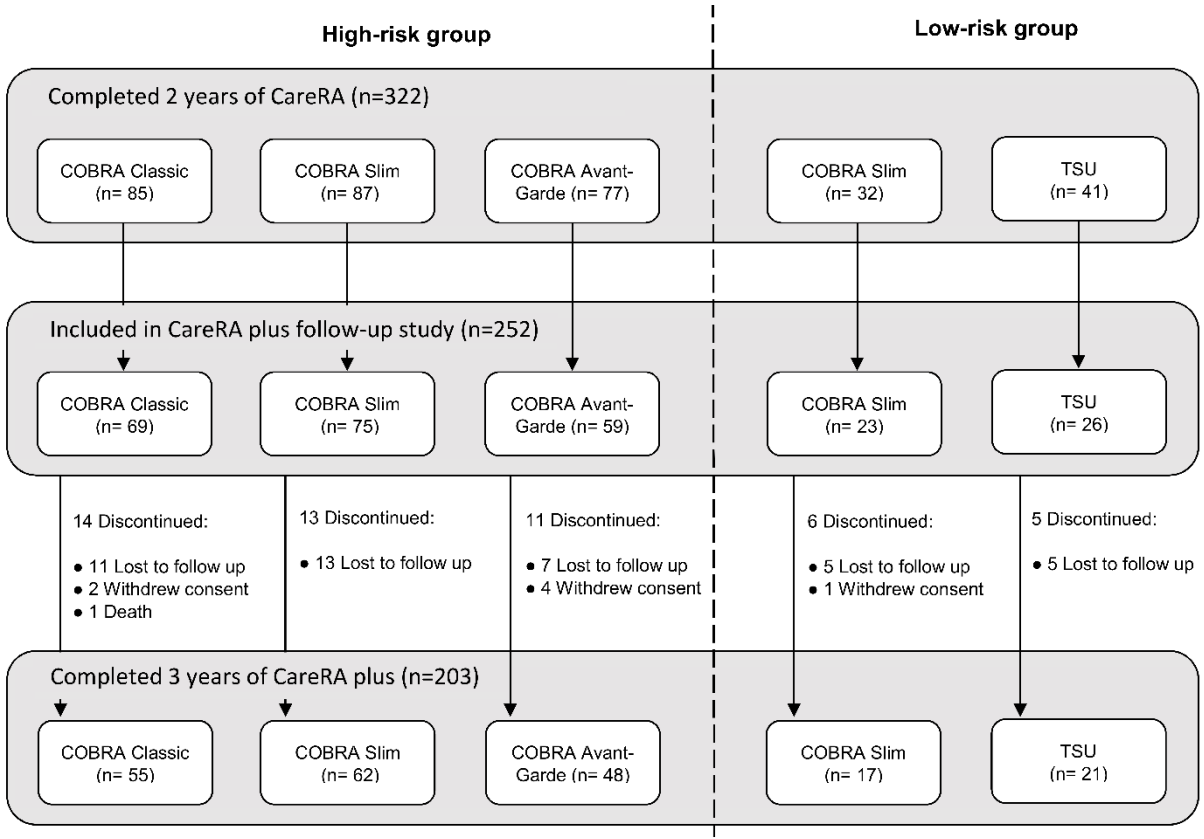


Figure 1: Flow chart of participants during the 3-year observational CareRA plus study.

Table 1: Demographic and clinical characteristics of patients enrolled in CareRA plus per original treatment arm, as recorded at baseline CareRA

	High-risk			Low-risk	
Variables	**COBRA Classic n=69**	**COBRA Slim n=75**	**COBRA Avant-Garde n=59**	**COBRA Slim n=23**	**TSU n=26**
Demographic variables					
Age, years	54 (12)	52 (13)	53 (13)	53 (14)	51 (13)
Body mass index, kg/m²	26 (4)	27 (4)	27 (4)	25 (4)	28 (4)
Women, n (%)	43 (62)	53 (71)	39 (66)	16 (70)	20 (77)
Smokers, n smoked ever (%)	41 (59)	43 (57)	38 (64)	13 (57)	11 (42)
Median (IQR) symptom duration	22 (13-44)	23 (14-38)	27 (14-52)	23 (16-36)	19 (10-30)
RF positive, n (%)	52 (75)	62 (83)	46 (78)	8 (35)	6 (23)
ACPA positive, n (%)	53 (77)	60 (80)	52 (88)	10 (43)	6 (23)
Erosive disease, n (%)	25 (36)	24 (32)	18 (31)	0 (0)	0 (0)
Comorbidity present, n(%)	31 (45)	41 (55)	30 (51)	10 (43)	8 (31)
RDCI	0.8 (1.0)	1.0 (1.1)	0.9 (1.1)	1.0 (1.3)	0.6 (1.3)
Clinical variables					
DAS28-CRP	5.0 (1.1)	4.8 (1.1)	4.7 (1.2)	4.4 (1.9)	4.5 (1.6)
Tender Joint Count (0-68)	14 (9)	14 (9)	14 (8)	13 (13)	13 (8)
Swollen Joint Count (0-66)	11 (7)	11 (7)	10 (6)	11 (8)	8 (7)
PGA, mm (0-100)	62 (20)	55 (22)	55 (24)	48 (32)	44 (23)
Pain, mm (0-100)	60 (22)	57 (20)	58 (24)	45 (31)	48 (23)

Fatigue, mm (0-100)	50 (24)	48 (22)	50 (24)	39 (28)	41 (21)
PhGA, mm (0-100)	52 (17)	52 (18)	49 (17)	46 (19)	43 (24)
ESR, mm/h	34.6 (24.8)	33.2 (24.0)	26.0 (18.8)	32.4 (31.1)	25.3 (18.1)
CRP, mg/L	18.8 (25.5)	24.0 (35.9)	13.8 (18.3)	27.3 (50.9)	13.6 (18.5)
HAQ score (0-3)	1.2 (0.7)	0.9 (0.7)	1.0 (0.6)	1.0 (1.0)	0.9 (0.7)

Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; IQR= Inter Quartile Range; RF= Rheumatoid factor; ACPA= Anti-Cyclic Citrullinated Protein; RDCI= Rheumatic Diseases Comorbidity Index; Comorbidity present= presence of at least 1 comorbidity as selected by the RDCI; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire. Comparisons of variables between treatment groups performed via ANOVA or Kruskal-Wallis test, unpaired t-test or Mann-Whithey U test, or Chi^2 test when appropriate. There were no significant differences in characteristics between treatment arms in high or in low-risk groups.

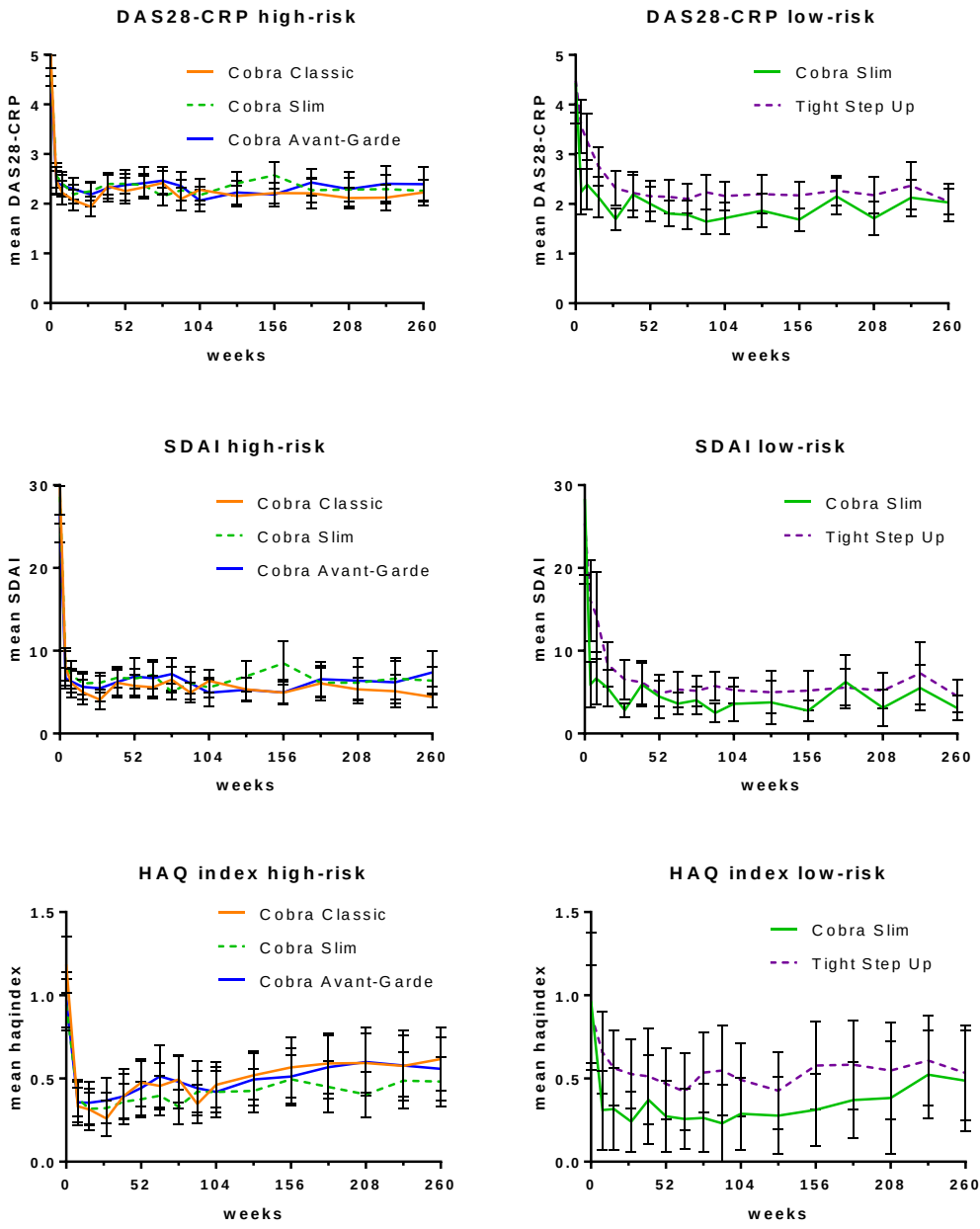
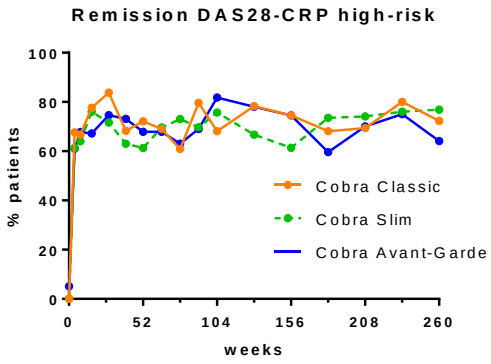
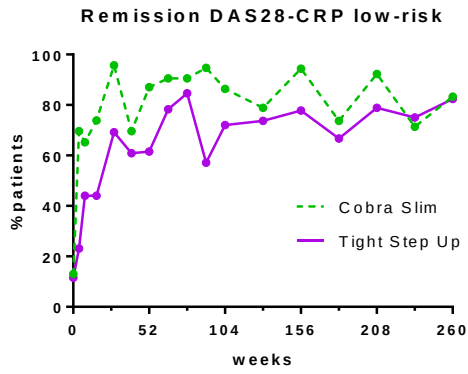
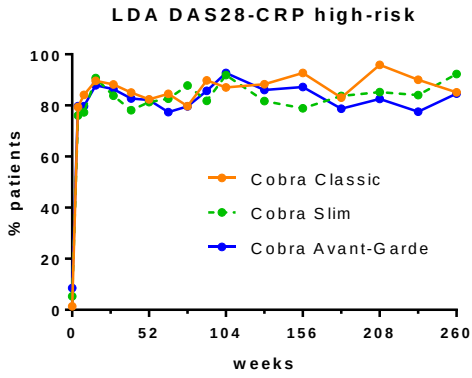
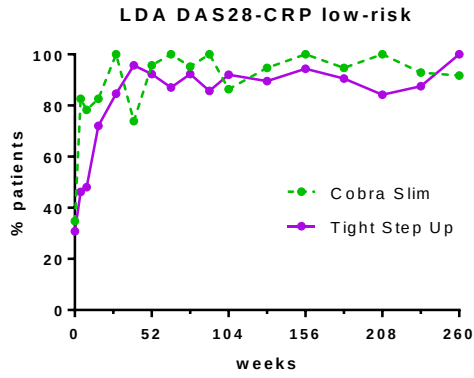


Figure 2: Disease activity and physical functioning during 5 years of follow up
Data are shown as observed. Error bars indicate the 95% confidence intervals. DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; SDAI= Simplified Disease Activity Index; HAQ= Health assessment questionnaire.









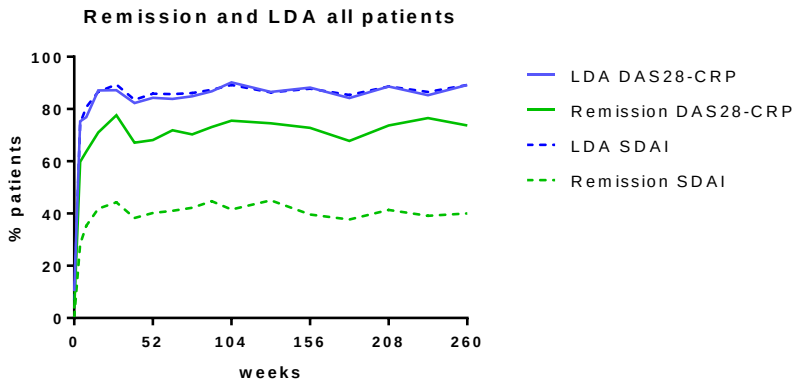


Figure 3: Remission rates during 5 years of follow up
Data are shown as observed; DAS28-CRP= Disease activity score based on 28 joints calculated with C-reactive protein; SDAI= Simplified Disease Activity Index.

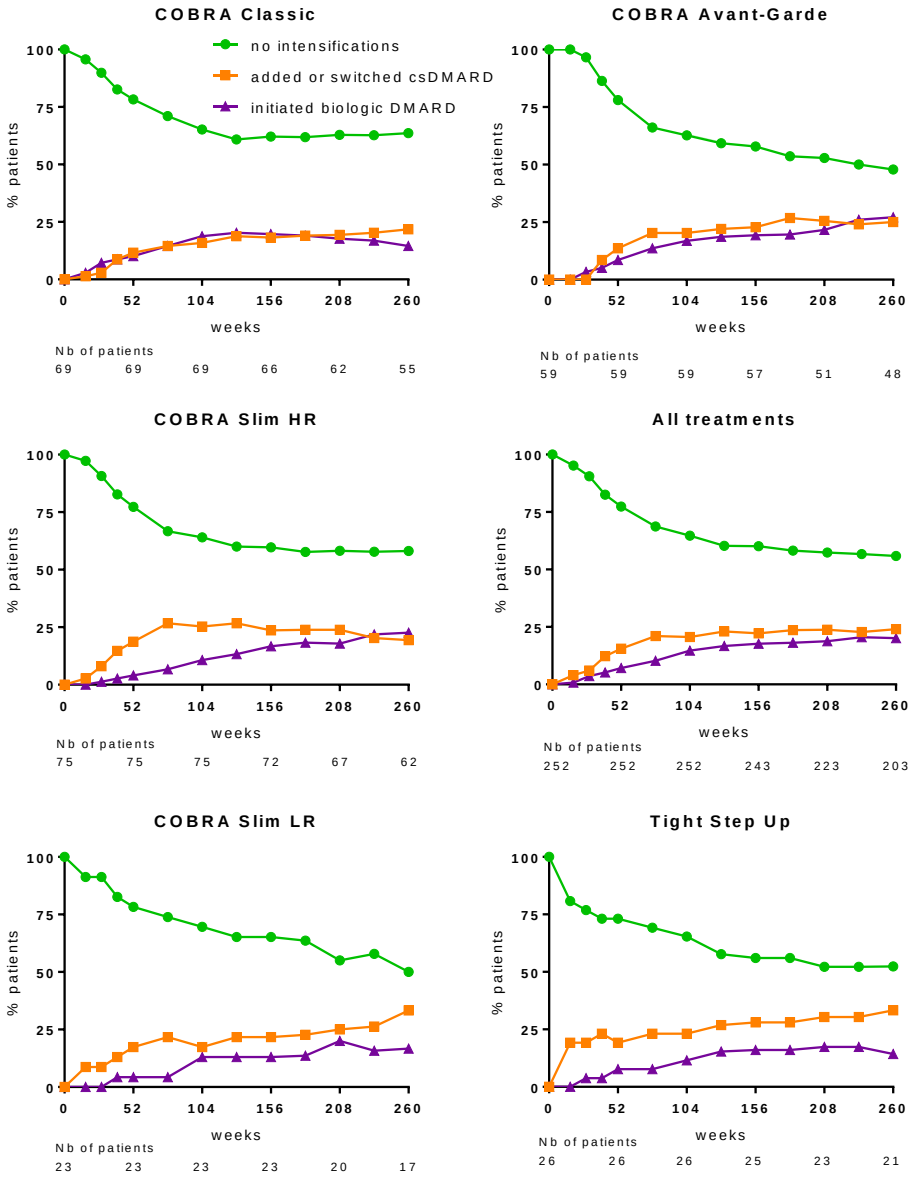


Figure 4: Medication profiles taken by participants during 5 years of follow up in each treatment arm. No intensifications = participants who did not have to intensify their DMARD treatment; Added or switched csDMARD = participants who added or switched a csDMARD; Initiated biologic = participants who initiated biologic DMARD(s); Percentages are calculated on patients still in follow up at each time point.

Table 2: Safety analysis during observational follow-up within CareRA plus

	High-risk			Low-risk	
Outcomes	**COBRA Classic n=69**	**COBRA Slim n=75**	**COBRA Avant-Garde n=59**	**COBRA Slim n=23**	**Tight Step Up n=26**
Total Nb of AE	70	95	80	18	36
Patients with AE	36 (52%)	48 (64%)	36 (61%)	10 (43%)	17 (65%)
Total Nb of SAE	9	20	11	3	6
Patients with SAE	7 (10%)	15 (20%)	11 (19%)	2 (9%)	6 (23%)
Severe infection	16	18	17	1	6
Orthopedic intervention	6	10	10	1	4
Fracture	6	3	8	1	6
Severe cardiovascular problem	0	5	5	2	1
Malignancy	1	5	1	0	1
Diabetes Mellitus	2	1	0	0	0
RA related extra-articular disease	1	0	1	0	0
vasculitis	1	1	0	0	0

Data are presented as absolute numbers (percentages); (S)AE = (Serious) All adverse Events were reported considered to be clinically relevant by investigators

DISCUSSION

Initial intensive treatment in combination with glucocorticoids, followed by adapting treatment to a target of low disease activity, resulted in stable disease control, with sustained good functional ability and limited progression in joint damage over 5 years. Moreover, half of all patients did not need an intensification in DMARD treatment during this period.

The CareRA study was set up to investigate whether MTX should be combined with an additional csDMARD and with highly dosed glucocorticoids to induce a rapid and stable clinical response in patients with early RA. Previous results showed that MTX monotherapy combined with glucocorticoid bridging (COBRA Slim) had a better effectiveness in patients with poor prognostic factors in the first 2 years with similar efficacy outcomes and a better safety profile than combinations of two csDMARDs with glucocorticoids [5]. The observational follow up in CareRA plus allowed us to demonstrate that all intensive treatments schemes in patients with poor prognostic factors led to a sustained clinical response, with good disease control, improved functionality and suppressed radiographic progression in the majority of patients over 5 years in total. During the 3 year follow up with further targeted treatment, safety measures were comparable and most patients remained on a csDMARD monotherapy.

Patients without markers of poor prognosis who started MTX monotherapy in combination with glucocorticoids bridging had better disease control and functionality over time than patients starting MTX without glucocorticoids. This COBRA Slim treatment did not lead to more safety issues on the long term. Suppression of joint damage progression over 5 years was comparable in both good-prognosis treatment groups. Overall our results confirm the benefit of combining initial treatment with bridging glucocorticoids over 5 years, also in patients with an assumed good prognosis [14,15].

Interestingly, 56% of all patients who initiated the intensive treatment schemes did not need an intensification in DMARD therapy during the first 5 years of treatment. There were no differences in these rates between treatment arms. This indicated on one hand that 58% of patients who started only 1 csDMARD with glucocorticoids in the COBRA Slim high-risk strategy, were able to maintain their MTX monotherapy

from baseline till year 5. On the other hand, also about half of patients who started a combination of csDMARD with glucocorticoids (64% in Classic and 48% in Avant-Garde) could taper their treatment to csDMARD monotherapy once they achieved low disease activity after the first 40 weeks, without further intensifications needed till year 5. Moreover, the chronic use of glucocorticoids was limited, indicating that the vast majority of patients could stop taking glucocorticoids within 7 months. All treatment schemes showed similar trajectories of changes in csDMARD or bDMARD use over 4 years after the protocolized phase of the trial. Further, overall bDMARD use was low with 20% of patients initiating a bDMARD during 5 years. These results indicate not only a sustained long-term effectiveness of the studied treatment strategies with glucocorticoids, but could also indicate a good feasibility of these strategies in daily clinical practice.

Our results support findings regarding the long-term sustained effectiveness of initial remission induction schemes within the original COBRA, the BeSt and the COBRA-Light trial [9,10,16,17]. Results of the BeSt trial showed that initial combination therapy of MTX, SSZ and prednisone resulted in sustained clinical improvement over 10 years, including well controlled disease activity, as well as improved functional ability, supressed joint damage progression and tapering and discontinuing medication in most patients [10]. The COBRA-light trial demonstrated that early RA patients, initially treated with a combination of MTX and prednisolone bridging had similar efficacy and safety outcomes over a 4-year period compared with patients initiated on a combination of MTX, SSZ and prednisolone bridging [17]. However, this protocol prescribed the addition of etanercept (a bDMARD) in case DAS44<1.6 was not achieved, which was often not implemented by treating rheumatologists or resulted in limited additional benefit [18].

Our results were obtained in a study population resembling closely a general population of patients with early RA. We included patients with varied disease severity, erosive and non-erosive, autoantibody positive and negative, from different types of routine practices, without excluding patients with comorbidities such as controlled diabetes and followed them up for a long period with frequent visits. These features support the external validity of our results and are indicative for a good applicability of intensive treatment schedules in daily clinical practice.

A limitation of our follow-up study was that we were not able to include all patients completing the preceding CareRA study, mainly due to practical reasons. However, patients that were not included did not differ in demographics, nor in clinical characteristics from patients enrolled into CareRA plus, except for being less ACPA positive. This enrichment for ACPA positive patients might have resulted in an underestimation of treatment effect since ACPA is assumed to be a prognostic factor of poor outcome [19].

Our treatment effect might also have differed if we used a more stringent treatment target, like remission, which is considered the optimal treatment target according to current guidelines. However, continued treatment adjustments in patients who achieve low disease activity but not remission may lead to relative overtreatment and lower adherence to the treat-to-target principle. An analysis of the BeSt and IMPROVED trial showed that rheumatologists' adherence to a DAS steered treatment protocol in early arthritis patients was worse if the target was remission [20]. Therefore, a DAS28-CRP≤3.2 seems a more realistic target for treatment steering, especially in the early disease phase, while remission should be aimed for as ultimate treatment goal.

Long term results of the CareRA plus study are in line with the results on the short term from CareRA. This strengthens the insight that a rapid remission induction with a combination of MTX and glucocorticoid bridging including subsequent treatment adaptations based on a realistic disease activity target, the so-called COBRA Slim strategy, can lead to comparable sustained treatment responses as more complex strategies, also on the long term. Moreover, this simplified strategy with fewer drugs did not lead to a higher need for DMARD intensifications on the long term compared to the initial combinational regimens.

In conclusion, we demonstrated that all intensive treatment strategies using bridging steroids resulted in excellent long-term clinical outcomes without chronic GC use in the majority of patients. Initial COBRA Slim therapy showed comparable 5-year effectiveness as COBRA Classic and Avant-Garde in high-risk early RA patients and better efficacy than conservative step up treatment in low-risk patients.

SUPPLEMENTAL MATERIAL

Supplement 1:

Demographic characteristics at baseline and clinical characteristics at the final year 2 visit of CareRA, comparing patients participating or not in CareRA plus

	Participated in CareRA plus n=252	**Not participated in CareRA plus n=70**	**p-value**
Demographic variables			
Age, years	53 (13)	52 (13)	0.826
Body mass index, kg/m²	27 (4)	26 (5)	0.662
Women, n (%)	171 (68)	46 (66)	0.735
Smokers, n smoked ever (%)	146 (58)	32 (46)	0.069
Median (IQR) symptom duration	23 (14-43)	22 (13-32)	0.357
RF positive, n (%)	174 (69)	43 (61)	0.229
ACPA positive, n (%)	181 (72)	34 (49)	<0.001
Erosive disease, n (%)	67 (27)	19 (27)	0.926
Clinical variables			
DAS28-CRP	2.1 (0.8)	2.2 (1.1)	0.558
Tender Joint Count (0-28)	1 (2)	1 (3)	0.593
Swollen Joint Count (0-28)	1 (1)	1 (3)	0.357
PGA, mm (0-100)	26 (22)	24 (22)	0.418
Pain, mm (0-100)	26 (22)	24 (25)	0.261
Fatigue, mm (0-100)	30 (23)	26 (25)	0.139
PhGA, mm (0-100)	10 (13)	15 (18)	0.122
ESR, mm/h	15.4 (12.2)	18.3 (19.7)	0.958
CRP, mg/L	4.8 (7.1)	6.8 (15.7)	0.113
HAQ score (0-3)	0.4 (0.6)	0.4 (0.5)	0.514

Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire. Comparisons performed via independent t-test, Mann-Whitney U test, or Chi² test when appropriate.

Supplement 2a:

Test statistics of the longitudinal analyses of evolution in outcomes between treatment arms in the high-risk population

Linear Mixed Model Analyses		**β**	**95% CI**	**p-value**
HAQ	COBRA Classic vs COBRA Slim	0.06	-0.03 to 0.15	0.218
	COBRA Avant-Garde vs COBRA Slim	0.06	-0.04 to 0.15	0.246
	Time in weeks	0.00	-0.03 to 0.03	0.997
	(constant)	0.44	0.38 to 0.51	<0.001
DAS28-CRP	COBRA Classic vs COBRA Slim	-0.06	-0.18 to 0.05	0.270
	COBRA Avant-Garde vs COBRA Slim	-0.02	-0.14 to 0.09	0.695
	Time in weeks	0.00	0.00 to 0.00	<0.001
	(constant)	2.73	2.65 to 2.81	<0.001
SDAI	COBRA Classic vs COBRA Slim	-0.45	-1.31 to 0.42	0.312
	COBRA Avant-Garde vs COBRA Slim	-0.54	-1.44 to 0.36	0.237
	Time in weeks	-0.03	-0.03 to -0.02	<0.001
	(constant)	10.06	9.40 to 10.72	<0.001
Generalized Linear Mixed models		**OR**	**95% CI**	**p-value**
DAS28-CRP<2.6	COBRA Classic vs COBRA Slim	1.14	0.77 to 1.69	0.502
	COBRA Avant-Garde vs COBRA Slim	1.06	0.71 to 1.58	0.778
	Time in weeks	1.01	1.00 to 1.01	<0.001
	(constant)	1.25	0.95 to 1.64	0.108
SDAI <3.3	COBRA Classic vs COBRA Slim	1.61	0.93 to 2.77	0.087
	COBRA Avant-Garde vs COBRA Slim	1.36	0.77 to 2.40	0.290
	Time in weeks	1.00	1.00 to 1.00	0.024
	(constant)	0.29	0.19 to 0.43	<0.001
Generalized Estimating Equations		**β**	**95% CI**	**p-value**
Total SvdH scores	COBRA Classic vs COBRA Slim	0.32	-0.56 to 1.19	0.481
	COBRA Avant-Garde vs COBRA Slim	0.57	-0.42 to 1.56	0.256
	Time in weeks	0.00	0.00 to 0.00	0.002
	(constant)	-0.45	-1.21 to 0.32	0.250

Coefficients or odds ratios stem from longitudinal models with either HAQ, DAS28-CRP, SDAI, remission rate according to DAS28-CRP or SDAI, or total SvdH score as dependent variable; For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time, which was not observed for any of the outcomes. HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease Activity Score using 28 joints and C-reactive Protein; SDAI= Simplified Disease Activity Index; SvdH= Sharp van der Heijde score; CI= confidence intervals. OR= odds ratio.

Supplement 2b:

Test statistics of the longitudinal analyses of evolution in outcomes between treatment arms in the low-risk population

Linear Mixed Model Analyses		**β**	**95% CI**	**p-value**
HAQ	COBRA Slim vs Tight Step-Up	-0.21	-0.41 to -0.01	0.041
	Time in weeks	0.00	-0.09 to 0.09	0.991
	(constant)	0.61	0.47 to 0.75	<0.001
DAS28-CRP	COBRA Slim vs Tight Step-Up	-0.46	-0.63 to -0.29	<0.001
	Time in weeks	0.00	-0.01 to 0.00	<0.001
	(constant)	2.92	2.78 to 3.06	<0.001
SDAI	COBRA Slim vs Tight Step-Up	-2.46	-3.87 to -1.04	0.001
	Time in weeks	-0.04	-0.05 to -0.03	<0.001
	(constant)	11.50	10.26 to 12.74	<0.001
Generalized Linear Mixed models		**OR**	**95% CI**	**p-value**
DAS28-CRP<2.6	COBRA Slim vs Tight Step-Up	2.62	1.43 to 4.81	0.002
	Time in weeks	1.01	1.01 to 1.02	<0.001
	(constant)	0.70	0.43 to 1.15	0.155
SDAI <3.3	COBRA Slim vs Tight Step-Up	3.27	1.35 to 7.91	0.009
	Time in weeks	1.01	1.00 to 1.01	0.023
	(constant)	0.23	0.12 to 0.44	<0.001
Generalized Estimating Equations		**β**	**95% CI**	**p-value**
Total SvdH scores	COBRA Slim vs Tight Step-Up	-0.07	-1.68 to 1.53	0.928
	Time in weeks	0.00	0.00 to 0.01	0.856
	(constant)	-0.50	-1.94 to 0.93	0.491

Coefficients or odds ratios stem from longitudinal models with either HAQ, DAS28-CRP, SDAI, remission rate according to DAS28-CRP or SDAI, or total SvdH score as dependent variable; For each model, treatment and time were used as determinants and it was tested whether there was an interaction between treatment and time, which was not observed for any of the outcomes. HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease Activity Score using 28 joints and C-reactive Protein; SDAI= Simplified Disease Activity Index; SvdH= Sharp van der Heijde score; CI= confidence intervals. OR= odds ratio.

Supplement 3:

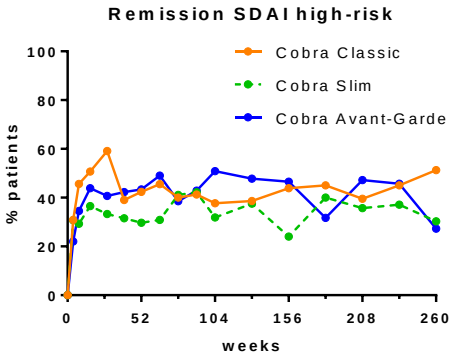
Percentages of patients in low disease activity or in remission according to different criteria, per time point and per treatment arm

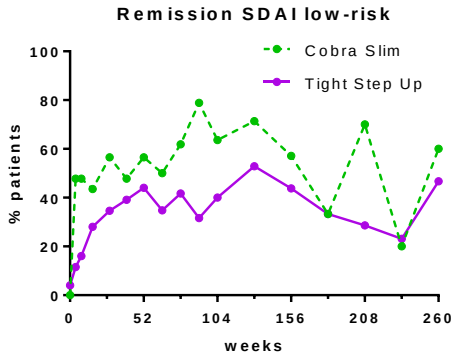
Treatment	Week 16	Year 1	Year 2	Year 3	Year 4	Year 5
COBRA Classic						
LDA DAS28-CRP	88%	82%	87%	90%	89%	83%
LDA SDAI	90%	81%	86%	86%	87%	86%
Rem DAS28-CRP	77%	73%	68%	73%	66%	68%
Rem SDAI	49%	42%	38%	37%	36%	35%
COBRA Slim HR						
LDA DAS28-CRP	91%	81%	91%	82%	87%	88%
LDA SDAI	87%	84%	89%	84%	85%	88%
Rem DAS28-CRP	76%	61%	75%	65%	75%	72%
Rem SDAI	38%	29%	33%	29%	37%	33%
COBRA Avant-Garde						
LDA DAS28-CRP	88%	80%	93%	88%	83%	84%
LDA SDAI	88%	82%	93%	90%	88%	85%
Rem DAS28-CRP	68%	66%	83%	74%	71%	64%
Rem SDAI	45%	41%	52%	45%	43%	34%
COBRA Slim LR						
LDA DAS28-CRP	83%	96%	87%	98%	97%	91%
LDA SDAI	87%	96%	87%	99%	96%	91%
Rem DAS28-CRP	74%	87%	87%	89%	86%	80%
Rem SDAI	43%	57%	65%	50%	62%	50%
Tight Step Up						
LDA DAS28-CRP	73%	92%	92%	89%	81%	99%
LDA SDAI	73%	92%	96%	87%	88%	93%
Rem DAS28-CRP	46%	62%	73%	67%	72%	80%
Rem SDAI	28%	42%	38%	34%	28%	37%

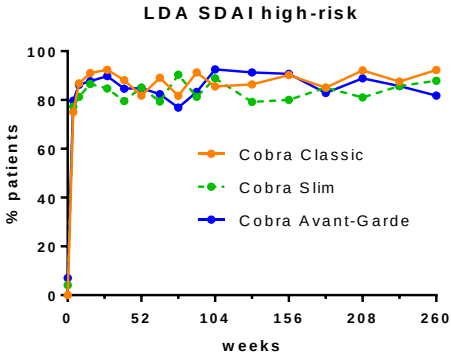
Values are percentages based on an intention-to-treat analysis. Missing data were imputed via multiple imputation resulting in 100 datasets which were analysed separately. Results were pooled using Rubin's rules. Percentages were compared between treatment arms in high and low-risk separately using Chi^2 test. There were no significant differences observed in the high or low risk-groups after correction for multiplicity by Holm's test.

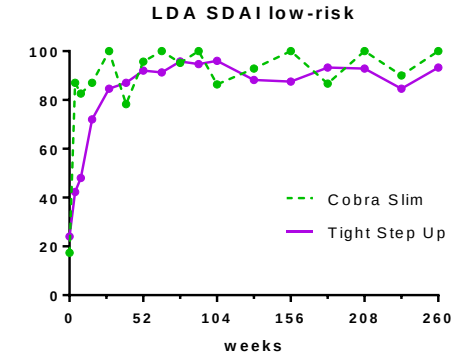
Supplement 4:

Remission rates during 5 years of follow up measured by SDAI





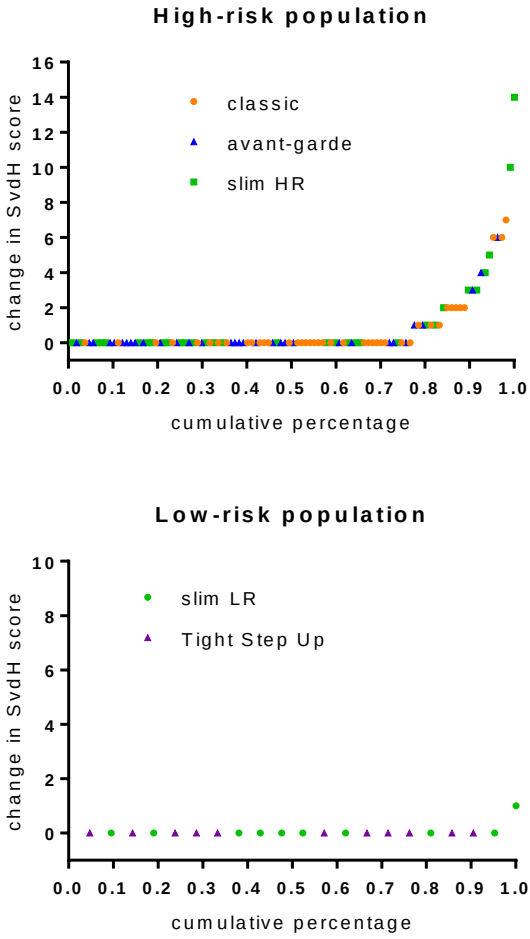




Data are shown as observed. SDAI= Simplified Disease Activity Index. LDA= Low Disease Activity.

Supplement 5:

Probability plots of radiographic progression defined by change in SvdH scores in patients completing the 5-year follow up.



SvdH score = Sharp van der Heijde score.

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CHAPTER 2

Refinement of an optimal treatment strategy for early RA in daily clinical practice

CHAPTER 2.1

Effectiveness of maintenance therapy with methotrexate compared with leflunomide for patients with RA having achieved disease control with both these drugs:

This chapter was published as:

Stouten V*, Michiels S*, Westhovens R, De Cock D, Belba A, Pazmino S, Van der Elst K, Joly J, & Verschueren P. Effectiveness of maintenance therapy with methotrexate compared with leflunomide for patients with RA having achieved disease control with both these drugs: results of a predefined sub-analysis of CareRA, a pragmatic RCT. *Clin Rheumatol*. 2020;39(9):2593-2601. * shared first author

ABSTRACT

Objectives

Evidence regarding the effectiveness of step-down strategies for patients with well-controlled early rheumatoid arthritis (RA) on a combination of methotrexate (MTX) and leflunomide (LEF) is currently lacking.

Methods

The Care in early RA (CareRA) trial is a 2-year randomized pragmatic trial comparing different remission induction strategies in treatment-naïve patients with early RA. For this study, we included participants who achieved low disease activity (LDA) (DAS28-CRP≤3.2) between 40 to 52 weeks after starting a combination of MTX, LEF and a prednisone bridging scheme followed by a treat to target approach. Patients were re-randomized to a maintenance monotherapy of either MTX 15mg weekly or LEF 20mg daily. Remission rates (DAS28-CRP<2.6) at week 65 counted from re-randomization, as well as drug retention rates and safety during the 65 weeks of follow up were compared.

Results

Remission rates at week 65 after re-randomization were numerically higher in patients assigned to MTX (29/32; 90.6%) compared to patients on LEF (20/27; 74.1%) (p=0.091). Of patients assigned to MTX, 60% (19/32) maintained LDA while continuing their assigned monotherapy until week 65 after re-randomization versus 44% (12/27) in the LEF group (p=0.25). Patients re-randomized to MTX were more frequently in LDA measured by CDAI (32/32; 100%) compared to patients on LEF (23/27; 85.2%) (p=0.024) 65 weeks after re-randomization. According to survival analyses the probability of maintaining MTX monotherapy was higher (81%) than maintaining LEF monotherapy (55%) for 65 weeks (p=0.025) after re-randomization. Safety analysis after re-randomization showed a good safety profile in both groups.

Conclusion

MTX monotherapy seems not significantly more efficacious as maintenance treatment compared to LEF monotherapy, but has a better retention rate and is well tolerated in early RA patients in LDA after combination therapy with both.

INTRODUCTION

Although methotrexate (MTX) is the cornerstone of RA treatment, leflunomide (LEF) has been adopted as another potent conventional synthetic disease modifying anti-rheumatic drug (csDMARD) to treat early RA since 1999. Initial trials showed a significant response to LEF compared with placebo and a similar efficacy compared with MTX [1-10]. Most frequent side effects of LEF were diarrhea, nausea, transient elevations of transaminases, reversible alopecia and skin rash [10-12]. For patients refractory to MTX, LEF proved to be an option, both as an alternative or in combination with this anchor drug [13-20].

In the 2016 update of the European league against rheumatism (EULAR) recommendations for the management of RA, LEF is mentioned in first line as alternative option for MTX in case of contra-indication. In second line, add-on of LEF or switch to LEF is recommended for patients with MTX-refractory disease or toxicity, and in absence of unfavorable prognostic factors [21]. It is suggested that adding LEF may be a reasonable and cost-effective strategy prior to initiation of a biologic DMARD (bDMARD). In our pragmatic Care in early RA (CareRA) study, we compared the effectiveness of the combination of LEF and MTX versus MTX monotherapy as initial treatment scheme, both with bridging glucocorticoids and following a treat to target approach. The combination therapy was equally effective to induce remission, but showed more frequent side effects [22]. Therefore, only patients insufficiently responding to initial MTX monotherapy with bridging glucocorticoids should be treated with add-on LEF to avoid unnecessary overtreatment [23].

After having achieved a sufficient treatment response with a combination of csDMARDs, stepping down to a csDMARD monotherapy is recommended. To our knowledge no conclusive data exist as to which drug to stop preferentially after reaching disease control with the combination of MTX and LEF. In this study, restricted to the CareRA subpopulation originally assigned to a combination of MTX and LEF, patients were re-randomized to a MTX or LEF monotherapy in case they achieved an adequate initial treatment response with a combination of both drugs after 40 weeks. The objective was to evaluate efficacy, drug retention rate and potential adverse effects, in view of determining the optimal maintenance therapy.

MATERIAL AND METHODS

Study design originating study

The CareRA trial is a 2-year prospective, randomized, open-label study comparing the effectiveness of three different combination therapies, based on the original COBRA (Combination therapy for early Rheumatoid Arthritis) strategy, in patients with early RA [24]. At entry into CareRA, patients had been diagnosed with RA less than 1 year ago, were DMARD unexperienced, and had no contra-indications for initiating csDMARDs, including MTX or glucocorticoids. Detailed enrolment criteria were published previously (4).

Before randomization in CareRA, patients were allocated to a high-risk or low-risk group using a stratification scheme based on the presence of classical predictors for radiographic damage (supplement 1). Participants in the high-risk group were randomized via a digitally generated sequence in the electronic case report form into 1 of 3 treatment arms. Patients allocated to the COBRA-Avant-Garde arm received a combination of 15 mg MTX weekly, 10 mg LEF daily and a weekly step-down scheme of oral prednisone starting at 30mg daily. Prednisone was tapered over the first 5 weeks to a maintenance dose of 5mg daily, which was given until week 28, and then further tapered and discontinued at week 34. Prophylactic treatment with oral folic acid, calcium and vitamin D was prescribed. Participants received face-to-face education, printed medication schemes and standardised info-material (leaflet, DVD and website).

Response to therapy was evaluated at each visit by measuring the 28 joint Disease Activity Score using C-reactive protein (DAS28-CRP). In case patients did not reach low disease activity (LDA) defined by a DAS28-CRP ≤3.2, from week 8 onwards, treatment had to be adapted according to protocol. The first step was a dose optimization of MTX from 15mg to 20mg weekly and the second step was predefined as a dose increase of LEF from 10mg to 20mg daily.

Study design predefined sub-analysis of CareRA

A subpopulation of CareRA participants assigned to the COBRA-Avant-Garde schedule achieving a state of LDA after a maximum of 2 predefined treatment adaptation steps by week 40 or at least by week 52 counted from baseline, was

eligible for stepping down to csDMARD monotherapy (figure 1). Patients were not eligible for step-down if LDA was not achieved after this remission induction phase, or if they had not completed this phase due to safety issues, protocol violations, withdrawal of consent or loss of follow-up.

Eligible participants were re-randomized 1:1 to receive monotherapy with either MTX 15mg weekly or LEF 20mg daily as maintenance therapy. Re-randomization occurred via a digitally generated sequence in the web-based electronic case report. If at that moment patients were receiving MTX 20mg weekly or LEF 20mg daily as part of their combination therapy due to previous adaptations, they remained on the same dose in their assigned monotherapy.

Participants were allowed to receive background non-steroidal anti-inflammatory drugs. Upon entering the step-down study, patients were not taking oral glucocorticoids anymore since prednisone had to be discontinued at week 34 per protocol. Rescue therapy was permitted at any time after re-randomization at the discretion of the investigator, following the treat-to-target principle.

This trial was conducted in 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium. The medical ethics committee of each participating centre approved the study protocol (EudraCT number: 2008-007225-39) and all patients gave written informed consent before study inclusion.

Assessments and study outcomes

After re-randomization, we followed patients for an additional 65 weeks, with the purpose of assessing the efficacy, tolerability and retention of these monotherapies. Participants were assessed clinically every 3 months. Disease activity was measured by DAS28CRP, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI). Functionality was measured by the Health Assessment Questionnaire score (HAQ). Radiographic evolution was assessed by the Sharp van der Heijde (SvdH) score. X-rays of hands and feet were obtained at baseline, week 28, year 1 and year 2 of the CareRA study. Radiographs were scored chronologically according to the SvdH method by one experienced reader (DDC) and 5 trained medical students [25]. Each X-ray was scored independently by 3 readers, including DDC and 2 students, retaining the mean score.

Efficacy and effectiveness

The main outcome of this sub-analysis was the remission rate (DAS28-CRP<2.6) at 65 weeks after re-randomization, coinciding with the week 104 co-primary endpoint of CareRA. Secondary outcomes included proportions of patients in LDA or remission according to DAS28-CRP, CDAI or SDAI criteria and radiographic progression at 65 weeks after re-randomization.

In addition, treatment effectiveness was evaluated as the proportion of patients who maintained a state of LDA (defined by a DAS28-CRP≤3.2) and continued their assigned monotherapy during 65 weeks after re-randomization. These patients were considered responders. Patients who did not maintain LDA or did not maintain monotherapy or discontinued the trial before week 65 counted from re-randomization were considered non-responders.

Retention rate and need to adapt therapy

Retention of the assigned monotherapy was assessed by calculating the proportion of patients still on MTX or LEF monotherapy 65 weeks after re-randomization and recording the reasons to discontinue monotherapy. Time until discontinuation of the assigned monotherapy was evaluated by Kaplan Meier survival analysis. Additionally, a multivariate Cox regression was performed for predicting discontinuation of monotherapy based on re-randomization status and adjusting for imbalanced variables between randomization arms. Furthermore, the number and type of subsequent changes in DMARD treatment were assessed, including the proportion of patients requiring bDMARD therapy. Use of glucocorticoids was quantified as the total cumulative dose of oral, intra-articular and intramuscular glucocorticoids and numbers of patients in need of a glucocorticoid injection.

Safety

The occurrence of all adverse events (AE) after re-randomization was recorded and evaluated by the treating rheumatologist in terms of relation to study therapy, seriousness, severity and whether they led to discontinuation of study treatment.

Statistical analysis

Analysis of this re-randomized subpopulation of the COBRA Avant-garde arm was exploratory and therefore no assessment of sample size or statistical power for efficacy analysis was performed in view of this study.

We performed an intention-to-treat analysis including all re-randomized patients. Sensitivity analyses were based on patients in DAS28-CRP remission at the moment of stepping down treatment and on patients in LDA at 2 consecutive visits before re-randomization (at the visit preceding and the visit of re-randomization, with 3 months in between). To impute missing data, the Expectation Maximization algorithm was applied. [26] Missing SvdH scores at year 2 were imputed via linear extrapolation of scores at week 28 and week 52 counted from baseline in the CareRA study. [27]

Comparison of continuous or dichotomous outcomes was performed by a t-test, Chi-square, Kruskal-Wallis or Mann-Whitney U test, when appropriate. All statistical analyses were performed at a two-sided significance level of 0.05, using SPSS version 25.0. As this was a sub-study included in a RCT protocol, no corrections for multiplicity were applied.

RESULTS

Participants

In the CareRA trial, 93 participants were allocated to the Avant-Garde arm. Of this population 59 (63%) were re-randomized and evaluated in this sub-study. Re-randomization resulted in 32 patients stepping down to MTX monotherapy and 27 to LEF monotherapy (figure 2). Dropout rates at 65 weeks after re-randomization were 9% for the MTX monotherapy group and 7% for the LEF monotherapy group. Both at baseline of the originating study and of the sub-study, demographics and clinical characteristics were well balanced between groups, except for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (Anti-CCP) positivity (table 1). At step-down randomization a comparable number of patients was in remission (DAS28-CRP<2.6) in the MTX monotherapy arm (26/32; 81%) compared to the LEF monotherapy arm (24/27; 89%) (p=0.42). Few patients had undergone a treatment adaptation according to protocol before entry in the step-down study. More specifically 5 patients of the MTX monotherapy group and 8 patients of the LEF monotherapy group had received a first MTX dose increase, while 1 patient in both groups had undergone a MTX and LEF dose increase.

Efficacy and effectiveness

At the week 65 follow-up visit counted from re-randomization, patients in the MTX monotherapy arm had numerically better clinical outcomes in terms of remission and low disease activity rates according to different criteria (table 2). Radiographic progression was very limited and did not differ between groups.

The effectiveness analysis showed that 60% (19/32) of patients in the MTX monotherapy group were responders since they were in sustained LDA and receiving MTX as only DMARD at week 65 after re-randomization. In the LEF monotherapy group 44% (12/27) were responders at week 65 after re-randomization (p=0.25) (figure 3).

A sensitivity analysis of patients in remission according to DAS28CRP at step-down randomization demonstrated similar efficacy results 65 weeks after re-randomization with 65% (17/26) responders in the MTX monotherapy group versus 50% (12/24) in the LEF monotherapy group (p=0.27) (Supplement 1). Most re-

randomized patients were in LDA at 2 consecutive visits before stepping down treatment (56/59; 95%). These patients had better efficacy outcomes in terms of remission rates at week 65 counted from re-randomization according to all different criteria, compared to patients in LDA only at time of re-randomization (Supplement 2).

Need to adapt treatment

Out of the patients allocated to the MTX arm, 72% (23/32) were still taking MTX as monotherapy 65 weeks after re-randomization, versus 52% (14/27), on LEF monotherapy in the LEF arm. At the end of the study, in patients remaining on MTX monotherapy the mean dose was 15.3 mg weekly versus a mean dose of 17.1 mg daily in patients remaining on LEF monotherapy. Reasons for not maintaining the assigned monotherapy were comparable except for efficacy issues, these were numerically more frequently reported in the LEF versus the MTX monotherapy arm (9 vs 4 cases) (figure 2).

Survival analysis using Kaplan Meier showed that participants in the LEF monotherapy group discontinued their assigned monotherapy significantly more rapidly than participants on MTX monotherapy (log-rank; p=0.025). The probability of maintaining MTX monotherapy was higher (81%) than the probability of maintaining LEF monotherapy (55%) during a 65 weeks follow-up (figure 4). In a Cox regression model, the risk of discontinuing the assigned monotherapy was significantly lower in participants stepping down to MTX than in those stepping down to LEF, adjusting for seropositivity of RF and anti-CCP (hazard ratio 0.30, 95% confidence interval 0.11-0.84; p=0.022).

The cumulative prednisone dose from re-randomization until 65 weeks later was 85.2 (±333.6) in the MTX monotherapy group, versus 135.9 mg (±284.2) in the LEF monotherapy group (p=0.17). After re-randomization 8 patients on MTX received 9 glucocorticoid injections and 6 patients on LEF received 13 injections.

During the 65-week follow up after re-randomization, 9 patients did not maintain their assigned MTX monotherapy: 3 patients restarted combination MTX+LEF, 1 patient started on MTX+bDMARD, 2 patients stopped MTX due to a desire for pregnancy and 3 dropped out of the study. Of the 13 patients not maintaining the allocated LEF monotherapy, 6 patients restarted the combination MTX+LEF, 2

patients started on MTX+bDMARD, 2 patients switched to MTX monotherapy, 1 continued on MTX+LEF, and 2 dropped out. DMARD treatment taken at every visit is shown in detail in figure 5.

Safety analysis

There were no relevant differences between groups with regards to number or type of adverse events (AEs). Number of patients with AEs or with therapy-related AEs were comparable between monotherapy groups. The incidence of the AEs most likely to be related to MTX or LEF intake like infections, gastrointestinal discomfort and liver function disturbances was evenly distributed between randomization arms. There were no patients who had to discontinue the assigned monotherapy due to an AE, and only a few patients in both groups for whom a dose reduction of the assigned monotherapy due to an AE was performed (table 3).

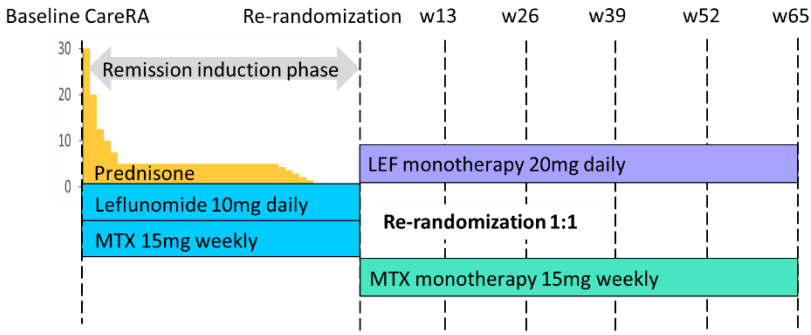


Figure 1: Study design with COBRA Avant-Garde schedule

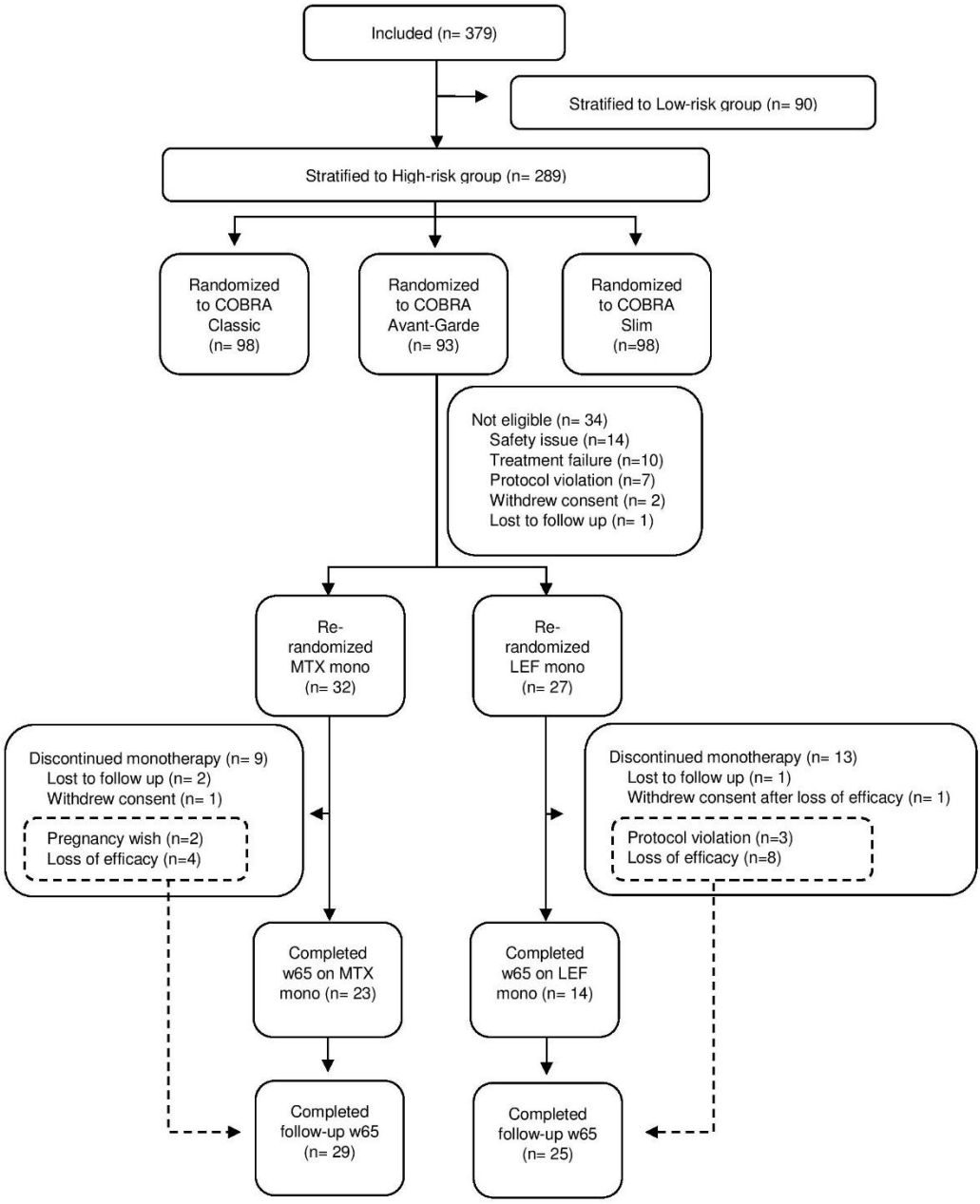


Figure 2: Flow chart of the participants during the trial. All randomized patients received the allocated treatment and were analyzed in an intention-to-treat analysis

Table 1: Baseline demographic and clinical characteristics of patients per re-randomized group

Variables	MTX mono n=32	LEF mono n=27
Demographic variables at original randomization		
Age, years	50 (14)	50 (12)
Body mass index, kg/m²	26 (4)	27 (5)
Women, n (%)	22 (69)	18 (67)
Smokers, n smoked ever (%)	20 (63)	15 (56)
Median (IQR) symptom duration	21 (40)	29 (30)
Median (IQR) disease duration	1 (3)	2 (4)
RF positive, n (%)	21 (66)	24 (89)
Anti-CCP positive, n (%)	23 (72)	25 (93)
Erosive disease, n (%)	12 (38)	8 (30)
Clinical variables at re-randomization		
DAS28-CRP	1.9 (0.6)	2.0 (0.6)
Tender Joint Count (0-28)	0.4 (1.0)	0.6 (0.8)
Swollen Joint Count (0-28)	0.3 (0.8)	0.3 (0.7)
PGA, mm (0-100)	19 (20)	20 (18)
PhGA, mm (0-100)	4 (5)	6 (7)
ESR, mm/h	12.5 (11.2)	15.6 (12.4)
CRP, mg/L	7.1 (14.7)	3.4 (3.7)
HAQ score (0-3)	0.3 (0.4)	0.2 (0.3)

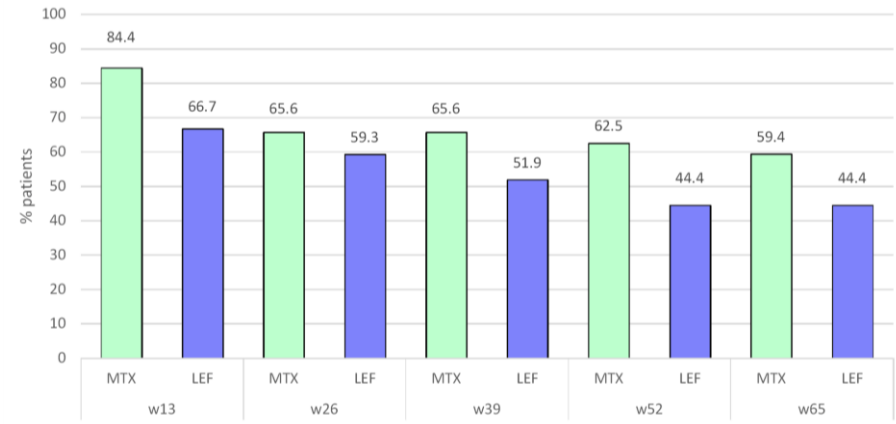
Values reported as means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; Disease duration= weeks elapsed between diagnosis of RA and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire.

Table 2: Efficacy endpoints at week 65 counted from re-randomization

Efficacy at week 65 counted from re-randomization	**Methotrexate n=32**	**Leflunomide n=27**	**p-value**
Remission DAS28-CRP <2.6	29 (90.6%)	20 (74.1%)	0.091
LDA DAS28-CRP ≤3.2	32 (100%)	24 (88.9%)	0.053
Δ DAS28-CRP from re-randomization	0.1±0.7	-0.1±1.0	0.573
Remission CDAI ≤2.8	20 (62.5%)	16 (59.3%)	0.799
LDA CDAI ≤10	32 (100%)	23 (85.2%)	0.024
Δ CDAI change from re-randomization	0.4±2.7	-1.9±7.7	0.933
Remission SDAI ≤3.3	19 (59.4%)	15 (55.6%)	0.767
LDA SDAI ≤11	32 (100%)	24 (88.9%)	0.053
Δ SDAI change from re-randomization	0.5±3.3	-2.1±7.7	0.558
HAQ (0-3)	0.3±0.4	0.3±0.4	0.734
Change in SvdH from baseline CareRA	0.4±0.7 (n=32)	0.8±1.5 (n=25)	0.409
Radiographic progression > SDD	0 (0.0%)	1 (4.0%)	0.254

Data are presented as mean±SD or number of patients (percentages); DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; LDA= low disease activity; CDAI= Clinical disease activity index; SDAI= Simplified disease activity index; HAQ= Health assessment questionnaire; SvdH= Sharp van der Heijde score; SDD= Smallest detectable difference.

Figure 3: Effectiveness of step down strategy via responder analysis over 65 weeks.



Patients were considered responder if they maintained a state of low disease activity (DAS28-CRP ≤ 3.2), were still treated with the assigned monotherapy and were still in follow-up

Figure 4: The probability of maintaining MTX monotherapy versus the probability of maintaining LEF monotherapy during a 65-week followup. Survival curves differ significantly (p = 0.025; Log-rank test)

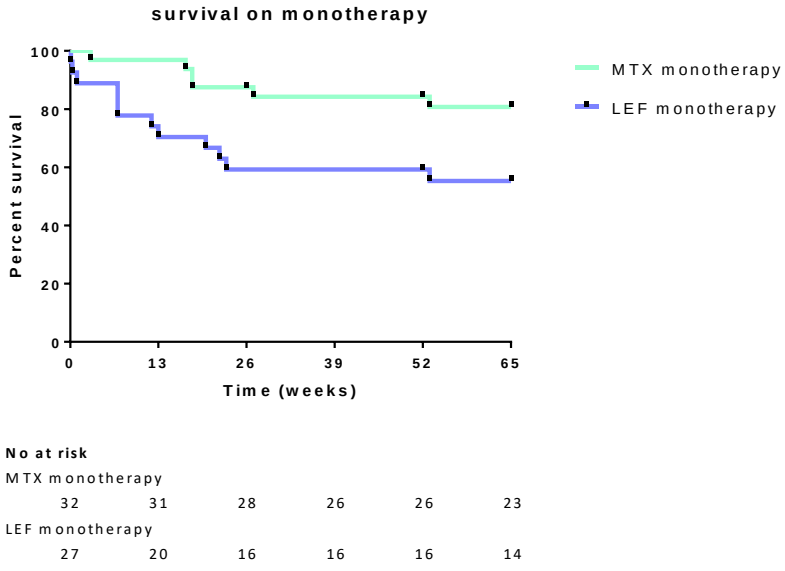


Figure 5: DMARD treatment taken at every visit following re-randomization

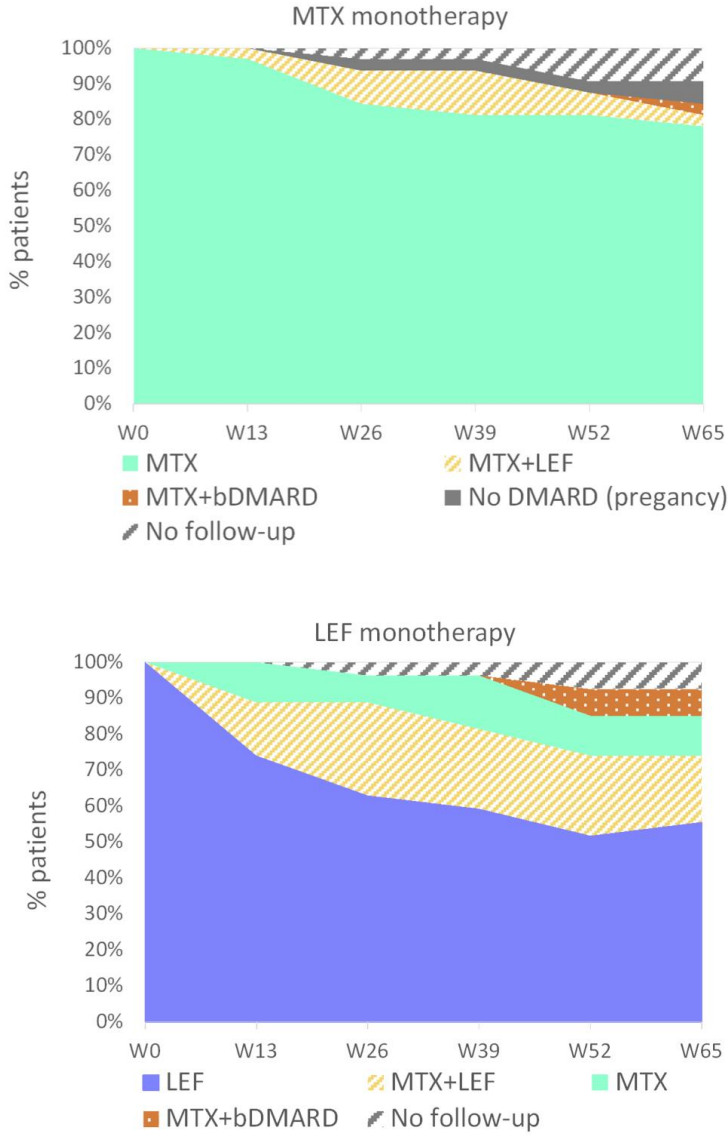


Table 3: Safety analysis from re-randomization onwards of re-randomized patients during the 65-week study.

Outcomes	**Methotrexate n=32**	**Leflunomide n=27**
Patients with AE	23 (71.9%)	20 (74.1%)
Patients with AE related to study therapy	10 (31.3%)	9 (33.3%)
Number of AE	78	85
Infection	14	17
Gastrointestinal discomfort	7	13
Liver function disturbances	3	1
Other AE	54	54
Number of AE related to study therapy	16	20
Number of SAE	7	4
Number of SAE related to study therapy	2	0
Patients who discontinued assigned monotherapy due to AE	0	0
Patients with dose reduction of assigned monotherapy due to AE	2	3

AE, adverse event; SAE, serious adverse event; other AEs include all other AEs less likely to be related to methotrexate or leflunomide intake.

DISCUSSION

Based on the results of this study, it seems more beneficial to step down to MTX rather than to LEF, in patients reaching LDA after being treated initially with a combination of these csDMARDs. Stepping down to MTX seemed to lead to a more stable disease control, with a trend towards better efficacy on the long term. Additionally, more patients remained on monotherapy with MTX than with LEF, showing a better drug retention rate. Finally, both monotherapies were well tolerated and had a comparable safety profile.

This is to our knowledge the first RCT trial comparing different step-down regimens after having achieved a sufficient clinical response with a combination of MTX and LEF. The results are a first indication of which monotherapy should be preferred on the long term to maintain disease control and avoid treatment changes, which is in the interest of the patients. Although this trial was not specifically designed to demonstrate that stepping down to MTX is better than stepping down to LEF after having followed a step-up approach adding LEF to MTX because of insufficient response, we provide also a first clue as to which DMARD could be stopped preferably in such circumstances.

More stringent selection criteria for stepping down from combination therapy in terms of required degree and duration of disease control could have led to better efficacy outcomes or a better monotherapy retention rate by the end of the trial. However, a sensitivity analysis in patients in remission according to DAS28CRP at re-randomization showed similar efficacy outcomes after 65 weeks compared to the analysis in patients who were in LDA when stepping down treatment. In a second sensitivity analysis we included the condition that patients had been in LDA for a longer period of time, e.g. at 2 consecutive visits with an interval of at least 3 months before stepping down treatment, as a more solid selection criterion. The vast majority of our re-randomized patients was in ongoing LDA at the 2 visits preceding the stepping down and showed indeed better efficacy outcomes at the end of the trial compared to a small minority in LDA only at the time of re-randomization. Because of the limited sample size, these results should be confirmed in a larger cohort. However, it seems that patients who are longer in LDA are more suitable for tapering combination DMARD therapy.

This study also had some limitations, as we did not blind rheumatologist nor patients for the assigned monotherapy and we did not stipulate potential rescue procedures in our protocol, which might have an impact on the observed results. However, this pragmatic trial design allowed us to make observations reflecting daily practice more closely, giving a valuable insight in the effect of maintenance therapy choice. Additionally, background concomitant medication was allowed (NSAIDs or GC), which might have influenced outcomes. The dose or frequency of glucocorticoids used, however, did not differ statistically significantly between randomization groups.

In conclusion, step-down to MTX monotherapy instead of LEF monotherapy seems similarly efficacious, is well tolerated and leads to a better drug retention rate in early RA patients achieving LDA with a combination therapy of both these drugs.

Key Points:

1. Methotrexate should be preferred over leflunomide as maintenance therapy after an initial intensive combination of these two drugs.
2. Methotrexate shows a better retention rate to leflunomide as maintenance therapy in this context.

SUPPLEMENTAL MATERIAL

Supplement 1:

Sensitivity analysis comparing efficacy at week 65 counted from re-randomization between treatment arms in patients in remission (DAS28CRP<2.6) at step-down randomization.

Efficacy at week 65 counted from re-randomization	**Methotrexate n=26**	**Leflunomide n=24**	**p-value**
Remission DAS28-CRP <2.6	24 (92.3%)	18 (75.0%)	0.095
LDA DAS28-CRP ≤3.2	26 (100%)	22 (91.7%)	0.133
Δ DAS28-CRP from re-randomization	-0.1±0.6	-0.2±0.9	0.892
Remission CDAI ≤2.8	17 (65.4%)	14 (58.3%)	0.608
LDA CDAI ≤10	26 (100%)	21 (87.5%)	0.063
Δ CDAI change from re-randomization	-0.1±2.2	-1.7±7.0	0.669
Remission SDAI ≤3.3	16 (61.5%)	13 (54.2%)	0.598
LDA SDAI ≤11	26 (100%)	22 (91.7%)	0.133
Δ SDAI change from re-randomization	-0.2±2.2	-2.0±7.0	0.977
HAQ (0-3)	0.2±0.3	0.3±0.4	0.686
Change in SvdH from baseline CareRA	0.3±0.7 (n=26)	0.9±1.5 (n=22)	0.139
Radiographic progression > SDD	0 (0.0%)	1 (4.5%)	0.272
Responders during 65 weeks (effectiveness analysis)	17 (65.4%)	12 (50%)	0.271

Data are presented as mean±SD or number of patients (percentages); DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; LDA= low disease activity; CDAI= Clinical disease activity index; SDAI= Simplified disease activity index; HAQ= Health assessment questionnaire; SvdH= Sharp van der Heijde score; SDD= Smallest detectable difference. Patients were considered responder if they had sustained low disease activity (DAS28-CRP≤3.2), were still treated with the assigned monotherapy and were still in follow-up. Patients who did not maintain low disease activity or did not maintain monotherapy or discontinued the trial were considered non-responders.

Supplement 2:

Sensitivity analysis comparing efficacy at week 65 in patients with or without sustained low disease activity (LDA) at 2 consecutive visits before step-down randomization.

Efficacy at week 65 counted from re-randomization	**Sustained LDA at entry n=56**	**Non-sustained LDA at entry n=3**	**p-value**
Remission DAS28-CRP <2.6	48 (85.7%)	1 (33.3%)	**0.018**
LDA DAS28-CRP ≤3.2	54 (96.4%)	2 (66.7%)	**0.022**
Δ DAS28-CRP from re-randomization	0.0±0.8	-1.0±1.7	0.202
Remission CDAI ≤2.8	36 (64.3%)	0 (0.0%)	**0.026**
LDA CDAI ≤10	54 (96.4%)	1 (33.3%)	**<0.001**
Δ CDAI change from re-randomization	0.0±3.9	-13.2±15.8	0.214
Remission SDAI ≤3.3	34 (60.7%)	0 (0.0%)	**0.038**
LDA SDAI ≤11	55 (98.2%)	1 (33.3%)	**<0.001**
Δ SDAI change from re-randomization	0.0±4.3	-12.7±16.6	0.255
HAQ (0-3)	0.3±0.4	0.8±0.8	0.217
Change in SvdH from baseline CareRA	0.5±0.8 (n=54)	2.3±3.9 (n=3)	0.844
Radiographic progression > SDD	0 (0.0%)	1 (33.3%)	**<0.001**
Responders during 65 weeks (effectiveness analysis)	30 (53.6%)	1 (33.3%)	0.494

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CHAPTER 2.2

Rheumatologists' adherence to the treat-to-target principle in early RA patients within the pragmatic CareRA trial: room for improvement?

This chapter will be submitted as original article:

Stouten V, De Cock D, Pazmino S, Van der Elst K, Joly J, Bertrand D, Westhovens R, Verschueren P. Rheumatologists' adherence to the treat-to-target principle in early RA patients within the pragmatic CareRA trial: room for improvement?

ABSTRACT

Objectives

To evaluate rheumatologists' adherence to a treat-to-target (T2T) approach at a threshold of low disease activity for patients during the 2-year Care in early RA (CareRA) study.

Methods

CareRA was a pragmatic multicentre RCT in patients naïve to csDMARDs (n=379). Participants were randomized to different remission induction schemes. Following the T2T principle, specific treatment adaptations had to be performed in case of DAS28CRP>3.2 during the first study year. In case rheumatologists chose not to intensify treatment, they had to provide a reason. From week 52 onwards, treatment adaptation was left at the rheumatologists' discretion. Adherence to this T2T approach, defined as a dose escalation or changing/adding DMARDs was assessed for every study visit over 2 years. Multivariate regression analyses were used to investigate associations between adherence patterns and remission (DAS28CRP<2.6) rates at week 104.

Results

The frequency of T2T adherence varied from 59% (55/93) at week 8 to 17% (5/30) at week 104. The most frequent reason not to intensify treatment during the first study year was that rheumatologists considered the disease already well controlled. The second most frequent reason was that giving glucocorticoids or NSAIDs temporarily was preferred over changing DMARDs. T2T was applied at all visits in 41/110 (37%) patients requiring at least 1 adaptation during the 2-year trial. Imperfect application of the treat to target principle led to lower chances of achieving remission at week 104 compared to always treating to target (OR: 0.05 (95% CI 0.01 to 0.22); p<0.001).

Conclusion

This study shows difficulties of applying T2T strictly, both with and without a fixed protocol to follow. In the majority of cases rheumatologists gave as reason for overruling the T2T rule that they estimated disease activity to be sufficiently controlled. However, patients in which the T2T principle was applied strictly, showed higher chances of achieving remission after 2 years of treatment.

INTRODUCTION

Treating to a predefined target is a principle adopted in guidelines to treat rheumatoid arthritis (RA)[1]. It is currently the most efficient strategy to control disease activity, but its implementation in daily clinical practice remains challenging although some progress seems to have been made [2,3]. We aimed to evaluate rheumatologists' adherence to a treat-to-target (T2T) approach at a threshold of low disease activity (DAS28CRP≤3.2) in patients with early RA treated according to current recommendations during the 2-year Care in early RA (CareRA) study [4]. Moreover, eventual consequences for control of disease activity were explored.

METHODS

Participants and treatment schemes

We used data from the CareRA trial which is a 2-year investigator-initiated, pragmatic, multicentre randomized trial, including 379 patients with early RA who were naïve to conventional synthetic disease modifying anti-rheumatic drugs (csDMARD). Detailed enrolment criteria were published previously [5].

Participants were treated with different remission induction schemes, based on the original COBRA (Combination therapy for early Rheumatoid Arthritis) strategy (Figure 1). We applied four different remission induction schemes following a treat-to-target principle: 1) COBRA classic: initial combination of methotrexate (MTX) and sulfasalazine 2) COBRA slim: MTX monotherapy 3) COBRA avant-garde: initial combination of MTX and leflunomide. 4) Tight Step-up: MTX monotherapy without glucocorticoids. All COBRA schemes included an initial step-down scheme of oral prednisone. Initial combination csDMARD therapy was tapered to monotherapy from week 40 in case patients achieved low disease activity.

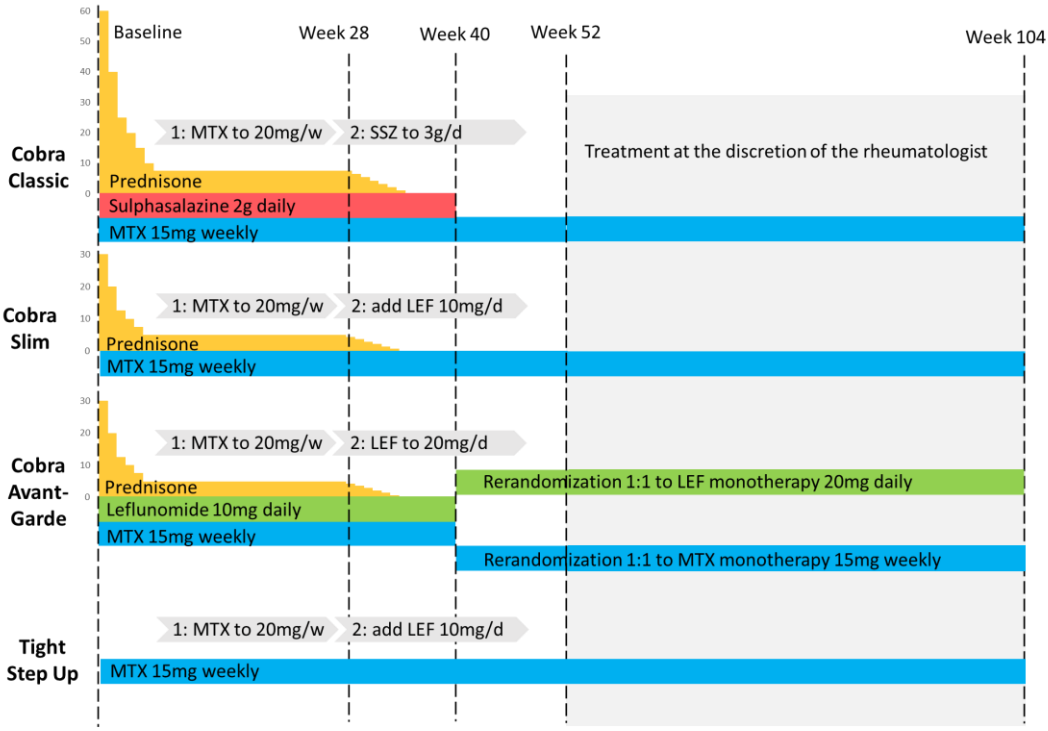

Figure 1: treatment regimens of the CareRA trial.
MTX = Methotrexate; LEF= Leflunomide; SSZ= Sulphasalazine; w=weekly; d=daily. Arrows show the first and second adaptation step per protocol in case the low disease activity threshold was not met, during the first year of follow up.

Adherence to T2T

Following the T2T approach, specific treatment adaptations had to be performed in case of DAS28CRP>3.2 during the first study year from week 8 onwards (Figure 1). In case rheumatologists chose not to intensify treatment per protocol, they had to provide a reason. As first step, the dose of MTX had to be increased from 15mg to 20mg weekly. As second step, the dose of the other csDMARD was escalated in the combination arms and leflunomide was added in the MTX monotherapy arms. An intra-articular or intramuscular injection with glucocorticoids was allowed by protocol, but not within 4 weeks preceding the week 16, 28, 40 and 52 visit. Alternatively, an oral glucocorticoid bridging scheme could be considered, after consulting the principal investigator. From week 52 onwards, further T2T was advised but type of treatment adaptation was left at the rheumatologists' discretion.

Disease activity was measured by DAS28-CRP at every 3-monthly visit for 2 years and DMARD therapy was registered. We assessed at every time point whether low disease activity (DAS28-CRP≤3.2) was achieved and whether the T2T principle was applied. Adherence was defined as performing a dose escalation or changing/adding DMARDs in case of DAS28CRP>3.2. The adherence rates were calculated as the number of visits where the T2T principle was applied divided by the number of visits where this was required per protocol.

Outcome and statistical analyses

Only data from patients for which DAS28-CRP scores were available were taken into account to evaluate the low disease activity state. Adherence rates were compared between treatment arms by Chi^2 test. Within the population of patients who had at least once a DAS28-CRP>3.2, and a DAS28-CRP score available at every visit (from week 8 till week 104), three different adherence patterns were defined: 1) adherence at all visits (patients were always treated to target), 2) adherence at all but one visit (patients only once not treated to target), 3) non-adherence at multiple visits (patients not treated to target more than once). Remission (DAS28CRP<2.6) rates at week 104 were compared depending on these adherence patterns by Chi^2 test. Additionally, the association between the adherence pattern and remission at week 104 was explored by multivariate logistic regression, while adjusting for possible confounders including age, sex, baseline DAS28-CRP, RF and ACPA status at baseline, symptom duration and randomized treatment. As a sensitivity analysis, this potential association was also investigated only in patients with more difficult-to-control disease. For this purpose, the multivariate regression analysis was repeated in patients requiring ≥2 adaptations according to the predefined T2T rule. Statistical analyses were carried out using SPSS version 25.0. All tests were performed as two-sided ones with significance level 0.05.

RESULTS

In CareRA 379 patients were included of which 322 (85%) completed the 2-year study. There was a total of 2851 visits over the entire follow-up and at 2375 visits (83%) the disease activity state was assessed as low (DAS28-CRP<3.2). The proportion of patients above the low disease activity threshold (DAS28CRP>3.2) was 26% (93/365) at week 8 but decreased to a stable average of 16% on the following visits and diminished further to 10% (30/303) at week 104 (Figure 2).

In 231/476 (49%) visits at which no low disease activity was achieved, a DMARD adaptation was performed, as required according to the T2T rule. The frequency of T2T adherence in patients above the low disease activity threshold varied from 59% (55/93) at week 8 to 17% (5/30) at week 104 (Figure 3). An adherence rate of 60% was observed during the first study year in which treatment had to be adjusted according to protocol, while a rate of 30% was seen during the second year in which treatment was adjusted at the discretion of rheumatologists. The most frequent reason not to intensify treatment during the first study year was that rheumatologists considered the disease already well-controlled. This reason was reported in 50% of non-adherent cases at week 8, in 15% at week 16, 14% at week 28, and 24% at week 40. The second most frequent explanation for non-adherence was that giving alternative treatment such as glucocorticoids or NSAIDs temporarily was preferred over changing DMARDs, as reported in 3% of cases at week 8, 15% at week 16, 27% at week 28, and 35% at week 40. More specifically, out of 17 cases in which giving alternative treatment was preferred instead of intensifying DMARDs, the following treatment was given: in 6 cases oral glucocorticoids, in 3 cases an intra-articular glucocorticoid injection, in 1 case both oral and intra-articular glucocorticoids, in 5 cases a NSAID, and in 2 cases other analgesic treatment. Other reasons were less frequently reported and included: recent toxicity (related to study therapy), recent infection, discomfort of medication, comorbidity, intermittent flares, patient refusal, or practical issues. Adherence rates never differed between treatment arms at any visit.

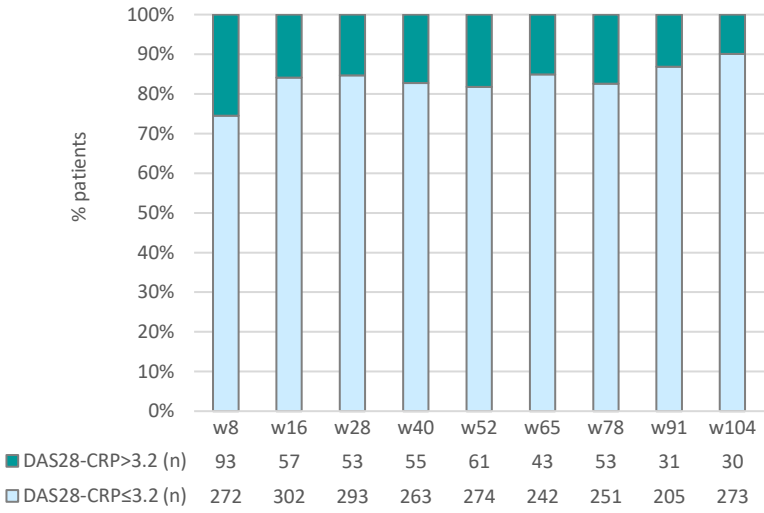

Figure 2: Proportions of patients with a DAS28-CRP >3.2, theoretically requiring a treatment adaptation, at every visit during 2-year study.

DAS28-CRP= Disease Activity Score using 28 joints with C-reactive Protein; w=week.

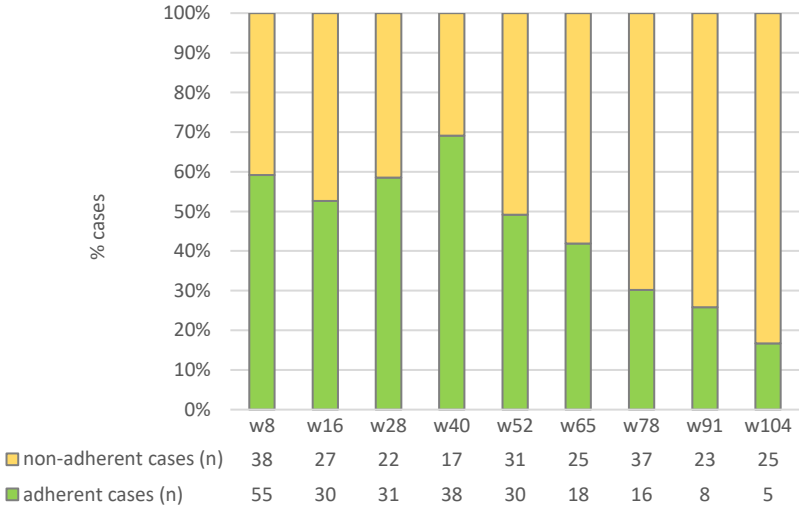

Figure 3: Adherence to T2T calculated as the number of visits where the T2T principle was applied divided by the number of visits where it was required per protocol, shown at every visit during 2 years.

DAS28-CRP= Disease Activity Score using 28 joints with C-reactive Protein; w=week.

Out of 210 patients with a DAS score available at every visit, 110 had a DAS28-CRP>3.2 at least once. Most patients needed only once an adaption, as shown in figure 4 which depicts the number of times disease activity was above the threshold versus the number of times an adaptation in DMARD therapy was prescribed by the rheumatologist.

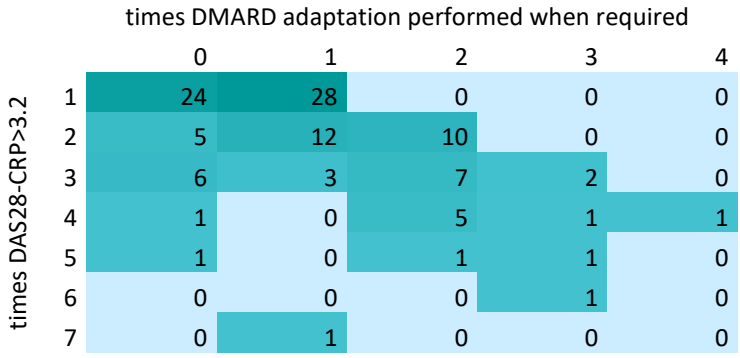

Figure 4: Heat map of 110 patients who had a DAS28-28>3.2 at least once, organised per number of times their disease activity was above the threshold versus number of times their DMARD therapy was adapted for that reason. More intense colour depicts a higher number of patients in that scenario.

Among these 110 patients, 41 (37%) were always treated to target, 44 (40%) were only once not treated to target, and 25 (23%) were not treated to target more than once. Remission rates in patients treated according to these different T2T adherences patterns were respectively 88% (36/41), 70% (31/44) and 36% (9/25), which differed significantly ($p<0.001$). In multivariate logistic regression analysis, the adherence pattern was significantly associated with being in remission at week 104 (overall $p<0.001$). This analysis was adjusted for potential confounders including age, sex, baseline DAS28-CRP, RF and ACPA status at baseline, symptom duration and randomized treatment, and none of these was significantly associated with remission at week 104. More specifically, the adherence pattern in which patients were on several occasions not treated to target, led to lower chances of achieving remission at week 104 in contrast to perfect treat to target adherence (OR: 0.05 (95% CI 0.01 to 0.22); $p<0.001$; table 1). However, the pattern in which patients were only once not treated to target was not significantly associated with lower odds of achieving remission compared to always treating to target.

To investigate the possibility that increased remission rates were merely due to more responsive disease (with less opportunity to be non-adherent), rather than to better adherence to T2T, we repeated the analyses in a population with less responsive disease. We obtained similar results in 58 patients who had at least twice a DAS28-CRP >3.2 during follow-up. Of these patients, 85% (11/13) was in remission at week 104 in the group always treated-to-target, 75% (15/20) in the group which was treated to target except once, and 36% (9/25) in the group not treated to target more than once (p=0.004). Within this population, the multivariate regression analysis also showed comparable results (Table 1).

	Remission at week 104			
	Patients in need for ≥1 adaptation (n=110)		Patients in need for ≥2 adaptations (n=58)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Only once not T2T	0.30 (0.08 to 1.07)	0.064	0.57 (0.06 to 5.50)	0.629
More than once not T2T	0.05 (0.01 to 0.22)	<0.001	0.07 (0.01 to 0.70)	0.023

Table 1: Multivariate regression analyses with remission status at w104 as dependent variable and adherence pattern as independent variable. The adherence pattern including patients always treated to target was used a reference category.

Analyses were adjusted for age, sex, baseline DAS28-CRP, RF and ACPA status at baseline, symptom duration and randomized treatment. A separate model was fitted in the population with a DAS28-CRP>3.2 at least once, and in the population having a DAS28-CRP>3.2 more than once. T2T= treated-to-target

DISCUSSION

This study shows the difficulty of applying T2T strictly during the first 2 years of treatment since in only half of visits theoretically requiring a treatment adaptation, treatment was intensified. During the first year, in the majority of non-adherent cases rheumatologists gave as reason for overruling the T2T guidance that they estimated disease activity to be sufficiently controlled. During the second year without a fixed adaptation protocol to follow, applying T2T strictly was more challenging. Patients in which the T2T principle was applied strictly at all visits, had higher chances of achieving remission after 2 years than patients in which the T2T approach was not followed on several occasions, while chances of achieving remission were comparable in patients in which T2T was not applied only once.

Other studies have reported on physician's adherence to a T2T approach or protocol with the rate of adherence ranging between 42% and 79% [6–11]. However, due to the difference in design and in definition of adherence we are not able to compare these rates between studies. Few studies have investigated the impact of physicians' adherence on clinical outcomes. In the NEO-RACo trial good physician adherence was associated with improved remission rates and decreased disease activity, which is in accordance with our findings [11]. The independent association between adherence to a T2T approach and remission was also observed in a study by Wabe et al using real-life clinical data[8]. However, these studies were performed in RA populations treated differently, with schemes based on triple DMARD therapy (MTX + sulphasalazine + hydroxychloroquine) and varying adaptation strategies, which may have influenced adherence or remission rates, which make it difficult to compare results.

A strength of our study is that we studied adherence in a pragmatic, prospective trial, in a well characterized study population, treated according to current recommendations. Moreover, reasons not to intensify treatment during first study year were provided by rheumatologists themselves based on a predefined checklist, rather than being retrieved from medical charts which may be prone to bias. This enabled us to get a valuable insight into why T2T is (not) applied in a setting close to daily clinical practice. We have set the treatment goal at low disease activity, which can be considered not stringent enough, although setting the threshold not too low

could also have avoided adherence problems, seen in other trials with remission as target [12].

A limitation of our study is that we defined adherence very strictly as performing an adaptation in case low disease activity was not achieved, which does not take into account valid reasons for not adapting treatment [13]. In case of safety issues, an intensification of DMARD therapy could be precluded. Additionally, we noticed that rheumatologists during the first weeks after treatment initiation, often estimated disease to be sufficiently controlled, thereby not agreeing with the evaluation of disease control by the DAS28-CRP score. Indeed, the DAS28-CRP score is suggested to be less reliable in patients with low disease activity, since this composite measure is sensitive to small changes in CRP and in patients' assessments of global health, when joint counts are low [14,15]. Moreover, other treatment options including giving temporarily oral or intra-articular glucocorticoids or NSAIDs were also often mentioned as reasons not to intensify DMARDs. These reasons may be valid in the context of a flexible tight control approach, advocating that decisions to adapt treatment should not be made blindly when a specific treatment goal is not met, but should be based on the individual clinical picture [16,17]. This implies taking into consideration whether the treatment target is nearly fulfilled, safety issues, other valuable treatment alternatives for DMARD changes. Moreover, treatment adaptations should be based on shared decision making with patients, taking into account their preferences. Considering valid reasons for not adapting treatment may lead to a more realistic estimation of adherence rates to a T2T principle.

Better adherence to the T2T principle was associated with better remission outcomes. Given the fact that easier-to-control RA is likely to be associated with better outcomes and higher adherence, we performed a sensitivity analysis in patients with more difficult-to-control disease. This analysis confirmed the independent association between non-adherence at several visits and lower chances of achieving remission. Nevertheless, slightly less-strict adherence, with only 1 non-adherent visit over 2 years, was not associated with lower chances of achieving remission compared to perfect adherence. This provides an indication that a flexible tight control does not necessarily lead to worse outcomes.

This study shows the difficulty of applying T2T strictly during the first 2 years after treatment initiation, especially without a fixed protocol to follow. During the first protocolized year, the most frequent reason given by rheumatologists for overruling the T2T guidance was that they estimated disease activity to be sufficiently controlled. Patients in which the T2T principle was applied strictly at all visits, showed higher remission rates after 2 years of treatment.

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CHAPTER 3

Prevalence of comorbidities and their influence on outcomes of RA treatment in CareRA

This chapter was submitted to *Rheumatology* and is currently under revision:

Stouten V, Westhovens R, De Cock D, Van der Elst K, Pazmino S, Bertrand D, Joly J, Verschueren P. Having a comorbidity predicts worse outcome in early rheumatoid arthritis despite intensive treatment: a post-hoc evaluation of the pragmatic randomised controlled CareRA trial.

ABSTRACT

Objectives

To quantify the prevalence of comorbidities in patients with early Rheumatoid Arthritis (RA) and determine their prognostic value for effectiveness outcomes in a randomized trial.

Methods

We included patients from the 2-year pragmatic randomized CareRA trial, who had early RA (diagnosis<1 year), were DMARD naïve and then treated-to- target with different remission induction schemes. Prevalence of comorbidities was registered at baseline and the Rheumatic Diseases Comorbidity Index (RDCI; range 0-9) was calculated. We tested the relation between baseline RDCI and outcomes including disease activity (DAS28-CRP), physical function (HAQ index), quality of life (SF36 domains) and hospitalizations over 2 years, using linear mixed models or generalized estimating equations models.

Results

Of 379 included patients, 167 (44%) had a RDCI of minimum 1. RDCI scores of 1, 2 or ≥3 were obtained in 65 (17%), 70 (19%) and 32 (8%) participants respectively. The most frequent comorbidity was hypertension (22%). Patients with comorbidities had significantly higher HAQ (β=0.215 CI[0.071;0.358]), DAS28-CRP (β=0.225 CI[0.132;0.319]) and lower PCS of SF36 (β=-3.195 CI[-4.844;-1.546]) over 2 years than patients without comorbidities, after adjusting for possible confounders including disease activity and randomized treatment. Patients with comorbidities had over time lower chances of achieving remission (OR=0.724 CI[0.604;0.867]) and a higher risk of hospitalization (OR=3.725 CI[2.136;6.494]).

Conclusion

At disease onset, almost half of RA patients had at least one clinically important comorbidity. Having comorbidities was associated with worse functionality and disease activity outcomes over 2 years, despite intensive remission induction treatment.

INTRODUCTION

When treated early, intensively and to target, patients with Rheumatoid Arthritis (RA) may expect an improved long-term outcome in terms of disease activity, physical function, and quality of life. However, patients with RA have a higher prevalence of comorbidities, compared to the general population, even in the early phase of the disease (1). These comorbidities in RA are associated with worse disease outcomes, affecting disease activity, physical function, health related quality of life and healthcare utilization as studied in several cohort studies (2–9). Responses to treatment can also be negatively affected by the presence of comorbidities. In established RA, having multiple comorbidities was shown to lower chances of achieving remission after DMARD initiation and affected retention rate and efficacy of biologic DMARDs (10–14). Since most research in this field has focused on patients with established disease, the prevalence and impact of comorbidities in early rheumatoid arthritis is not yet fully understood. Moreover, it is not yet known whether having comorbidities at diagnosis of RA impacts response to early, intensive treatment with csDMARDs and glucocorticoid bridging, the current treatment standard for early RA.

The total burden of comorbidity can be quantified using comorbidity indices, since not all types of comorbidities have the same impact on the outcomes of interest. The Rheumatic Diseases Comorbidity Index (RDCI) was validated to measure more accurately the burden and prognostic impact of overall comorbidity, based on a weighted preselection of relevant comorbidities. This index also has clinical applications in identifying patients with worse prognosis in terms of functional status, health-related quality of life, hospitalization frequency and mortality (15).

We aimed to assess the impact of comorbidity status at treatment initiation on the response. Therefore, we investigated whether having relevant comorbidities, measured by RDCI, at diagnosis of RA affected physical function, disease activity, quality of life, and occurrence of hospitalizations over 2 years, based on data from the Care in early RA (CareRA) trial.

METHODS

Study design and participants

For this post-hoc analysis, data from the pragmatic 2-year CareRA randomized controlled trial were used, evaluating different intensive treatment regimens in patients with early RA. CareRA was designed and conducted by investigators from 13 Flemish rheumatology centres (2 academic centres, 7 general hospitals and 4 private practices) in Belgium. Patients were diagnosed with RA (<1 year) and were naïve to and had no contraindications for csDMARDs or glucocorticoids. Detailed enrolment criteria were published previously (16). The medical ethics committee of each participating centre approved the study protocol (EudraCT number: 2008-007225-39) and all patients gave written informed consent before participation.

Treatment schemes

Participants were treated with different remission induction schemes, based on the original COBRA (Combination therapy for early Rheumatoid Arthritis) strategy. We stratified patients into a high or a low risk group, based on presence of classical prognostic factors. In the high-risk group, we applied three different remission induction schemes following a treat-to-target principle: COBRA classic: initial combination of methotrexate (MTX) and sulfasalazine; COBRA slim: MTX monotherapy; COBRA avant-garde: initial combination of MTX and leflunomide. All COBRA schemes included an initial step-down scheme of oral prednisone, started at a high or moderate dose, and tapered weekly over 6 or 7 weeks to a low maintenance dose which was discontinued at week 28. In the low-risk group, we applied two schemes: the same COBRA slim or Tight Step-up: MTX monotherapy without glucocorticoids. Treatment was adjusted to a target of low disease activity (DAS28-CRP ≤3.2), ultimately aiming for remission (DAS28-CRP <2.6). The protocol has been described into detail in previous publications (16,17). All regimens combining DMARDs with glucocorticoids were effective for patients with early RA up to 2 years. The COBRA-Slim regimen, MTX monotherapy with glucocorticoid bridging, provided the best balance between efficacy and safety after 1 and 2 years and was endorsed in the updated European League Against Rheumatism 2016 recommendations of 2019 to treat RA (16–18).

Comorbidity measures

Presence of all past and current comorbidities was recorded by rheumatologists at inclusion in the CareRA trial. The rheumatologist did an extensive anamnesis in all participants, existing medical history records were systematically reviewed, and the indication of all current medication was revised in view of registering all comorbidities.

We evaluated the following comorbidities, based on their inclusion in the RDCI: lung disease, cardiovascular disease (myocardial infarction, stroke, or other), hypertension, fracture of spine/hip/leg, depression, diabetes mellitus, cancer, peptic ulcer or stomach problem. The RDCI formula sums the prevalence of these comorbidities and weights lung and cardiovascular diseases with a factor 2, whereas a co-existing prevalence of cardiovascular diseases and hypertension can only have a maximum of 2 points. The resulting score ranges from 0 to 9. Based on this information the RDCI was calculated to obtain a weighted comorbidity score per patient.

Assessments and outcomes

Participants were assessed at the following visits: baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. Patients unable to continue the allocated treatment including predefined adaptations due to lack of efficacy, safety or practical reasons, were followed up every 6 months. Demographics and clinical characteristics were registered on screening. Disease activity was measured at every visit by the 28 joint Disease Activity Score using C-reactive protein (DAS28-CRP). Physical function was assessed by the Health Assessment Questionnaire (HAQ, range 0-3, higher scores are worse) at all patient visits, except for week 4. The Short Form 36 (SF36) questionnaire (version 1) as a measure of health-related quality of life was completed by participants at baseline, week 16, year 1 and year 2. Outcomes of this questionnaire were grouped into physical component summary (PCS) and mental component summary (MCS) (19). These scores range from 0-100 and higher scores indicate better perceived quality of life. Finally, all hospitalizations, defined as an admission to the hospital for longer than 24 hours were registered during the 2-year trial. For analyses, these hospitalizations were converted into a dichotomous variable of been hospitalized (yes/no) since the previous visit, assessed at all visits.

Statistical analysis

We evaluated differences in baseline characteristics between patients with and without comorbidities, as selected by the RDCI, using the Chi-square test for categorical variables and the t-test for independent samples or Mann-Whitney U test for continuous variables. The predictive value of comorbidity status at baseline for functionality, disease activity and quality of life over time was assessed by linear mixed models (LMM) and for hospitalizations and remission status according to DAS28-CRP<2.6 by generalized estimating equations (GEE) models with a binominal logit link function. Comorbidity status was assessed as either RDCI dichotomized to 0 or ≥1, or as the RDCI score. A separate model was fitted for each outcome including DAS28-CRP, HAQ, SF36, occurrence of hospitalizations or remission status, measured from baseline till year 2. Comorbidity status, time and treatment scheme were included as predictors with all interaction terms initially, following backward selection of the interaction terms. All LMM models incorporated a random intercept and a random slope for time with an unstructured correlation structure, which accounts for the repeated observations within individuals. In the GEE model, an unstructured working correlation matrix was used for time. All models were adjusted for age, gender, RF, ACPA, having erosions, smoking status (ever), symptom duration and BMI at baseline and for DAS28-CRP at every visit. To account for the higher baseline value affecting the linear trajectory of continuous outcomes over time, analyses were controlled for having a different intercept. Missing data were inferred by full information maximum likelihood. As a secondary analysis, we investigated the predictive value of the different types of comorbidities on the same outcomes. A sensitivity analysis was based on the population being treated with intensive regimens including glucocorticoid schemes (without the TSU treatment). All tests were performed as two-sided ones with significance level 0.01. Statistical analyses were carried out using SPSS version 25.0.

RESULTS

Prevalence of comorbidities at disease onset

We included all 379 randomized patients of the CareRA trial. The majority of patients was female (69%) and the mean ± SD age was 52 ±13 years. All baseline patients and disease characteristics can be found in table 1. At baseline, there were 167 (44%) patients with at least one comorbidity considered to be clinically important based on inclusion in the RDCI. Patients with comorbidities were older, were more likely to have erosions and had more severe disease characteristics in terms of DAS28-CRP and HAQ score at baseline. A RDCI score of 1 was recorded for 65/379 (17%) patients, a score of 2 for 70/379 (18%) and a score of ≥3 for 32/379 (8%) participants. The mean ± SD of the RDCI score (range 0-9) was 0.8 ± 1.2 with a maximum score of 6. The most common comorbidities were hypertension (22%), cardiovascular events (myocardial infarction/stroke or other cardiac diseases) (17%) and pulmonary diseases (8%) (table 2).

Impact comorbidity on function

The longitudinal evolution of functionality and disease activity over 2 years of follow-up are shown for patients with and without comorbidities in figure 1. We tested for potential differences between patients with and without comorbidities by fitting linear mixed models for each outcome including HAQ, DAS28CRP, mental and physical component score of SF36 (table 3). Having an RDCI of ≥1 at baseline was associated with significantly worse HAQ scores over 2 years (β= 0.21 CI [0.07 to 0.36]; p<0.001). This means that patients who had at least one important comorbidity at baseline, had higher HAQ scores and thus lower functionality, even after intensive treatment, when adjusted for baseline age, gender, RF, ACPA, erosive disease, BMI, smoking, symptom duration and for DAS28-CRP at each visit. This comorbidity status (RDCI≥1) at baseline was related with an increase in HAQ scores over time of 0.215. There was also a significant association of the RDCI score at baseline with worse HAQ scores over 2 years (β=0.04 CI [0.02 to 0.06]; p <0.001).

Impact comorbidity on disease activity

In models predicting DAS28-CRP, having at least one clinically important comorbidity at disease onset was related to higher disease activity scores over time (β=0.23

CI[0.13 to 0.32]; p<0.001). Accordingly, a higher RDCI score was associated with higher DAS28-CRP scores over 2 years (β=0.09 CI [0.05 to 0.13]; p<0.001). The odds ratio of achieving remission according to DAS28-CRP in patients having at least one comorbidity was 0.72 (CI 0.60 to 0.87; p<0.001), compared to patients without comorbidities, indicating a decrease of 28% in the odds of achieving remission. Also, a higher RDCI score decreased the odds of achieving remission over 2 years (OR: 0.90 CI [0.82 to 0.97]; p=0.008), indicating that per unit increase in the RDCI the odds of achieving remission decreased with 10%. All regression coefficients for fixed factors are shown in Supplementary Table S1.

Impact of comorbidity on quality of life

The impact of comorbidity status on the PCS and MCS of the SF36 questionnaire was investigated using LMM analyses. Having comorbidities at baseline was associated with lower scores of the PCS, indicating lower physical health related quality of life. More specifically, having an RDCI of minimum 1, was related to a decrease of approximately 3.19 (CI -4.84 to -1.55; p<0.001) on the PCS, compared to having no comorbidities. Accordingly, a higher RDCI was related to worse PCS scores (β=-1.12 CI [-1.85 to -0.40]; p=0.002). There was no clear association between having comorbidities and MCS (β=-1.64 CI [-3.02 to -0.26]; p=0.020), so there seemed to be no indication that baseline RDCI status was associated with improvement of mental health related quality of life.

Impact of comorbidity on occurrence of hospitalizations

Of the 379 patients included in CareRA, 56 (34%) of 167 patients with a baseline RDCI≥1 needed to be hospitalized at some time during 2 years of follow-up compared with 19 (9%) of 212 with a baseline RDCI of zero (p<0.001). An adjusted GEE model showed that patients having comorbidities were more likely to become hospitalized (OR=3.73 CI [2.14 to 6.49]; p<0.001). Higher RDCI scores were also significantly associated with a higher risk of hospitalization (OR=1.46 CI [1.27 to 1.67]; p<0.001).

Impact comorbidity independent of intensive treatment

Treatment was found to be also predicting functionality and disease activity over 2 years, although this was attributable to the TSU treatment alone, which was related with worse functionality and disease activity scores compared to the other

treatments (Supplementary Table S1). Therefore, we performed a sensitivity analysis, within patients treated with intensive treatment including a tapering down scheme of glucocorticoids, and not with TSU, applying the same models. All results regarding the impact of comorbidity status on outcomes resembled the results obtained within the entire population (Supplementary Table S2). Within this subpopulation, there was no longer a relation between any of the COBRA schemes and any of the outcomes tested.

Impact of different types of comorbidity

The predictive value of the different types of comorbidities was tested by repeating the LMM and GEE analyses for the same outcomes (table 4 and Supplementary Table S3). Hypertension was significantly associated with functionality, disease activity and physical health related quality of life. Additionally, depression was significantly related with functionality, disease activity and the mental health related quality of life. Occurrence of hospitalization was not significantly related to any specific type of comorbidity present at baseline. Achievement of remission was only related to fractures.

Key messages:

1. Almost half of patients with early RA had at least one clinically important comorbidity
2. Having a comorbidity was associated with worse functionality and disease activity over 2 years
3. This negative effect of having comorbidities could not be mitigated with intensive treatment strategies

Table 1: Baseline demographic and clinical characteristics of patients with and without comorbidities.

Variables	Overall n=379	Without comorbidities n=212	With comorbidities n=167	p-value
Demographic variables				
Age, years	52 (13)	47 (12)	58 (12)	<0.001
Body mass index, kg/m²	26 (4)	26 (4)	27 (4)	0.020
Women, n (%)	262 (69)	145 (68)	117 (70)	0.728
Smoking status				0.752
Current smoker	97 (26)	57 (27)	40 (24)	
Ex-smoker	112 (29)	60 (28)	52 (31)	
Never smoked	170 (45)	95 (45)	75 (45)	
Median (IQR) symptom duration	23 (26)	21 (27)	25 (26)	0.210
Median (IQR) disease duration	1 (3)	1 (3)	1 (2)	0.470
RF positive, n (%)	252 (66)	142 (67)	110 (66)	0.820
Anti-CCP positive, n (%)	249 (66)	137 (65)	112 (67)	0.619
Erosive disease, n (%)	97 (26)	41 (19)	56 (34)	0.002
Clinical variables				
DAS28-CRP	4.8 (1.3)	4.5 (1.2)	5.1 (1.2)	<0.001
Tender Joint Count (0-68)	14 (9)	13 (8)	15 (9)	0.007
Swollen Joint Count (0-66)	11 (7)	10 (7)	12 (7)	0.001
PGA, mm (0-100)	55 (24)	53 (23)	58 (24)	0.031
Pain, mm (0-100)	56 (24)	54 (23)	59 (25)	0.024
Fatigue, mm (0-100)	48 (24)	48 (23)	48 (25)	0.682
PhGA, mm (0-100)	52 (19)	51 (19)	54 (20)	0.108
ESR, mm/h	29.3 (22.9)	26.0 (22.1)	33.6 (23.3)	<0.001
CRP, mg/L	18.2 (28.5)	15.6 (27.3)	21.4 (29.7)	0.001
HAQ score (0-3)	1.0 (0.7)	0.9 (0.7)	1.1 (0.7)	0.007
PCS of SF36	27 (13)	27 (13)	25 (12)	0.138
MCS of SF36	49 (12)	50 (12)	48 (13)	0.114

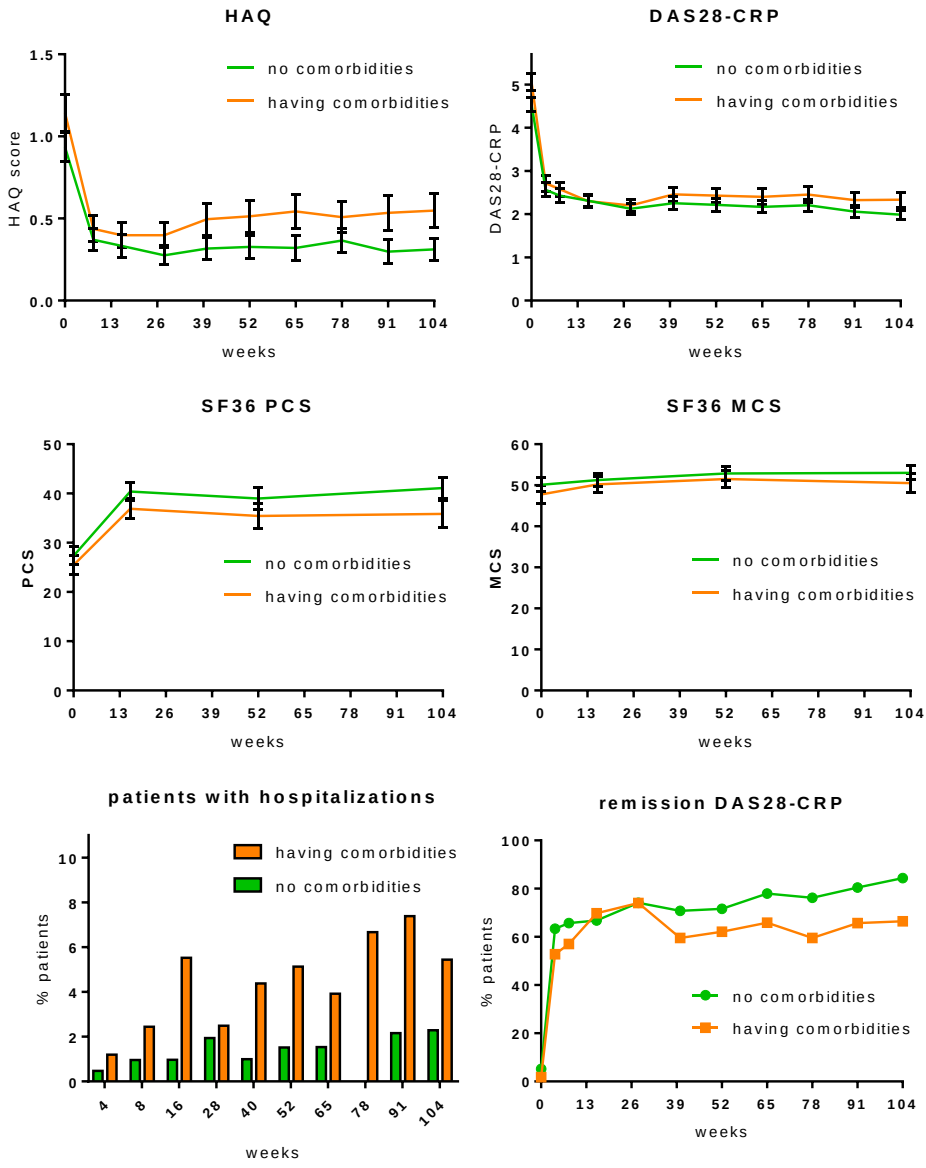
Values reported are means (standard deviation) unless specified otherwise. Symptom duration= weeks elapsed between onset of symptoms and start of treatment; Disease duration= weeks elapsed between diagnosis of RA and start of treatment; RF= Rheumatoid factor; Anti-CCP= Anti cyclic citrullinated protein; DAS28= Disease activity score based on 28 joints; CRP= C-reactive protein; PGA= Patient's global assessment; PhGA= Physician's global assessment; ESR= Erythrocyte sedimentation rate; HAQ= Health assessment questionnaire.

Table 2: Prevalence of comorbidities in participants of CareRA trial at screening

Variable	Results n=379
RDCI, mean (S.D.)	0.84 (1.15)
RDCI, median (IQR)	0 (2)
RDCI = 0	212 (56)
RDCI = 1	65 (17)
RDCI = 2	70 (19)
RDCI ≥ 3	32 (8)
Hypertension	85 (22)
Cardiovascular disease	63 (17)
Pulmonary disease	32 (8)
Peptic ulcer or stomach disease	27 (7)
Depression	22 (6)
Diabetes mellitus	12 (3)
Malignancies	9 (2)
Fractures (spine/hip/leg)	3 (1)

Data are presented as absolute numbers (percentages) unless specified otherwise. Cardiovascular disease = myocardial infarction/stroke/other cardiac disease

Figure 1: Progression of disease outcomes over 2 years of follow-up.



Mean values or percentages are depicted, and error bars indicate the 95% confidence interval. Comorbidity status was assessed as having an RDCI of ≥1 or 0; HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; SF36= Short form 36 questionnaire; PCS= Physical Component Score; MCS= Mental Component Score; CI= Confidence Interval; OR= Odds Ratio.

Table 3: Results of the longitudinal analyses to investigate the impact of comorbidity status on different outcomes over 2 years.

RDCI dichotomized 2 groups

Linear mixed model analyses			
outcome	Beta	95% CI	p-value
HAQ	0.215	0.071 to 0.358	0.003
DAS28-CRP	0.225	0.132 to 0.319	<0.001
PCS of SF-36	-3.195	-4.844 to -1.546	<0.001
MCS of SF-36	-1.643	-3.024 to -0.262	0.020
Generalized Estimating Equation analysis			
outcome	OR	95% CI	p-value
Remission DAS28-CRP <2.6	0.724	0.604 to 0.867	<0.001
Occurrence hospitalizations	3.725	2.136 to 6.494	<0.001

RDCI continuous

Linear mixed model analyses			
outcome	Beta	95% CI	p-value
HAQ	0.039	0.019 to 0.059	<0.001
DAS28-CRP	0.089	0.048 to 0.129	<0.001
PCS of SF-36	-1.122	-1.847 to -0.398	0.002
MCS of SF-36	-0.606	-1.212 to 0.000	0.050
Generalized Estimating Equation analysis			
outcome	OR	95% CI	p-value
Remission DAS28-CRP <2.6	0.895	0.824 to 0.972	0.008
Occurrence hospitalizations	1.459	1.274 to 1.670	<0.001

Results come from a separate model for each outcome with comorbidity status at baseline, treatment and time as predictors. Comorbidity status was assessed as either having an RDCI of ≥1 or o or by the RDCI score; HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; SF-36= Short Form 36 questionnaire; PCS= Physical Component Score; MCS= Mental Component Score; CI= Confidence Interval; OR= Odds Ratio.

Table 4: Results of the longitudinal analyses to investigate the impact of different types of comorbidity on all outcomes over 2 years.

Type of comorbidity	HAQ		DAS28-CRP		Rem DAS28-CRP<2.6	
	β	95% CI	β	95% CI	OR	95% CI
pulmonary disease	-0.04	-0.13 to 0.04	-0.04	-0.13 to 0.04	1.16	0.83 to 1.63
cardiovascular disease	-0.03	-0.09 to 0.04	-0.03	-0.09 to 0.04	0.91	0.71 to 1.18
hypertension	0.20*	0.15 to 0.26	0.20*	0.15 to 0.26	0.76	0.62 to 0.95
fracture	0.09	-0.21 to 0.39	0.09	-0.21 to 0.39	0.40*	0.24 to 0.66
depression	0.20*	0.10 to 0.30	0.20*	0.10 to 0.30	0.64	0.43 to 0.96
diabetes mellitus	0.05	-0.08 to 0.18	0.05	-0.08 to 0.18	1.03	0.67 to 1.57
malignancy	0.07	-0.09 to 0.22	0.07	-0.09 to 0.22	0.63	0.31 to 1.29
peptic ulcer or stomach disease	0.05	-0.04 to 0.13	0.05	-0.04 to 0.13	0.79	0.55 to 1.15

* Significant predictor at the <0.010 level.

Beta coefficients or odds come from a separate model for each outcome with types of comorbidity status at baseline, treatment and time as predictors. Comorbidity status was assessed as having a particular comorbidity (yes/no); HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; SF-36= Short Form 36 questionnaire; PCS= Physical Component Score; MCS= Mental Component Score; CI= Confidence Interval; OR= Odds Ratio.

Table 4 (continued):

Results of the longitudinal analyses to investigate the impact of different types of comorbidity on all outcomes over 2 years.

Type of comorbidity	**SF-36 PCS**		**SF-36 MCS**		**hospitalizations**	
	β	95% CI	β	95% CI	OR	95% CI
pulmonary disease	0.81	-2.21 to 3.82	-1.75	-4.27 to 0.76	2.25	1.13 to 4.50
cardiovascular disease	-0.45	-2.77 to 1.88	0.48	-1.46 to 2.42	1.58	0.88 to 2.82
hypertension	-4.74*	-6.76 to -2.72	0.68	-1.00 to 2.37	1.73	1.05 to 2.86
fracture	-7.52	-18.42 to 3.38	3.68	-5.39 to 12.75	2.80	0.63 to 12.54
depression	-3.35	-7.10 to 0.40	-6.94*	-10.07 to -3.82	1.46	0.54 to 3.90
diabetes mellitus	0.20	-4.28 to 4.69	-4.54	-8.27 to -0.80	1.68	0.64 to 4.44
malignancy	0.00	-5.69 to 5.70	2.01	-2.73 to 6.76	2.05	0.66 to 6.39
peptic ulcer or stomach disease	-2.08	-5.12 to 0.96	-0.42	-2.96 to 2.11	1.17	0.58 to 2.35

* Significant predictor at the <0.010 level.

Beta coefficients or odds come from a separate model for each outcome with types of comorbidity status at baseline, treatment and time as predictors. Comorbidity status was assessed as having a particular comorbidity (yes/no); HAQ= Health Assessment Questionnaire; DAS28-CRP= Disease activity score based on 28 joints with C-reactive protein; SF-36= Short Form 36 questionnaire; PCS= Physical Component Score; MCS= Mental Component Score; CI= Confidence Interval; OR= Odds Ratio.

DISCUSSION

Our data demonstrated a high prevalence of comorbidities, already at diagnosis of RA, before treatment initiation, with nearly half of patients in our sample having at least one clinically important comorbidity. We found that this burden of comorbidity, was significantly related to worse functionality, worse disease control and worse physical health related quality of life as well as to the occurrence of more hospitalizations. The use of intensive treatment regimens and applying the treat-to-target principle did apparently not counterbalance this effect of comorbidity on outcomes.

Physical function was impacted by comorbidity, with a mean difference in HAQ scores over time of 0.215 in patients having comorbidities compared to patients without, which reflects the minimal clinical important difference (MCID) for HAQ at the individual level. Impact of having a comorbidity on functionality was also shown by a decrease in physical health related quality of life of 3.1 over 2 years, which is above or near reported MCIDs of 2.5, 3.0 or 5.0 points for the PCS at the individual level (20). Therefore, the demonstrated impact of comorbidity on functionality can be considered clinically meaningful.

Having comorbidities in the early disease stage was also related with higher disease activity over 2 years after treatment initiation, even when adjusted for possible confounders. Patients with comorbidities had over time 28% decreased odds of achieving remission according to DAS28-CRP, even though they were treated intensively according to the most recent guidelines for management of RA. Impact of comorbidity status at baseline seemed to be driven mainly by hypertension and depression. Finally, comorbidity status was related to a higher risk of hospitalization over 2 years.

The prevalence of relevant comorbidities at baseline within our cohort confirms a high comorbidity burden, already at disease onset, as reported also in other early RA cohorts. (1,6,21–23). However, comparing prevalence rates directly between cohorts remains challenging because of differences in populations, methods of collection, registration of comorbidities, study design, and use of other comorbidity indices. Comorbidity prevalence measured by RDCI in a UK cohort of early RA patients from the Royal College of General Practitioners Research and Surveillance

database (RCGP), was higher (mean 1.63; patients with ≥1 RDCI 66%) than in our cohort (mean 0.84; patients with ≥1 RDCI 44%). Patients in this UK cohort had similar patient characteristics (age and gender), but were more often smokers (current or past; 70% versus 55% in CareRA), and had more depression (28% versus 6% in CareRA).

We confirmed that the most common baseline comorbidity in early RA is hypertension as in other cohorts, including the ESPOIR cohort in which the prevalence of arterial hypertension was increased in early RA compared with the general population (1,6,21–23). This is consistent with previous evidence that RA is an independent risk factor for cardiovascular diseases, and that individuals who have had RA for several years have around a two-fold higher risk for CVD compared with individuals without RA after taking account of most traditional risk factors. (24)

Our findings that comorbidity status at baseline is associated with worse functionality and disease control, already at baseline, were also demonstrated based on data from the CATCH cohort. The negative impact of comorbidity on function over time was also seen in the CATCH cohort and in the ERAS cohort (6,21). However, these studies were performed based on registries in which treatment wasn't protocolized, although the authors adjusted for type of RA treatment in their statistical analyses. The impact of comorbidity at baseline on achieving remission in early RA, which we demonstrated in CareRA was also seen in the CATCH cohort and was previously reported in established RA (10,21). However, this relation was not seen in the ERAS cohort (6). The fact that mental health related quality of life was not affected by comorbidity was also reported by Radner and colleagues (9).

A strength of our study is that we used data of a prospective pragmatic RCT, reflecting daily clinical practice. By randomizing treatment, we avoided that treatment allocation was influenced by having (more severe) comorbidities, thereby limiting channelling bias, in contrast to cohort studies. Moreover, contrary to classical RCTs, we did not exclude patients with important comorbidities or with very high disease activity due to less stringent inclusion criteria. Collection of comorbidities was performed by physicians and data entry was systematically monitored by comparison with the medical records. We have previously shown that the treatment schemes including glucocorticoids had similar effectiveness outcomes over time in the CareRA trial, with comparable numbers of patients needing

treatment adaptations (25). Therefore, also a potential effect of RA treatment on the impact of comorbidity on studied outcomes could be investigated and precluded. The treatment strategy applied within CareRA is in line with the latest guidelines for management of RA, enhancing relevance for daily practice. An additional strength is the evaluation of the influence of comorbidity on the cumulative burden of the different outcomes for patients over 2 years and not based on point estimates at a certain time point.

We used the RDCI, which was validated to measure more accurately the burden and prognostic impact of overall comorbidity in rheumatic diseases, based on a weighted preselection of comorbid conditions. Moreover, this index has been validated in RA to predict physical functioning measured by HAQ (26). More recently, this RDCI was proven to perform well in predicting HAQ, number of hospitalizations, as well as PCS and MCS of SF36 (15).

A limitation of our study is the limited sample size in comparison with large registries, but our study population mirrors closely an early RA population in daily clinical practice, is well characterized and confounding by indication could be avoided. It might be that not all comorbid conditions have been registered by the physician. However, all indications provided for currently taken medication were revised in search of clues for the presence of additional comorbidities.

Restoration of physical function is, next to achieving remission, one of the most important outcomes in RA since it affects patients' well-being as well as ability to work and mortality (27–29). With our findings, we are able to provide a perspective of estimated effect of comorbidity on function, even in early RA under intensive treatment. Rheumatologist should be aware of this and take into account comorbidities in their RA management plan, instead of keeping a too narrow focus on controlling RA disease activity. Future research should further elucidate the dynamics of the mutual interaction between RA disease activity and comorbidity over time and how to deal in practice with this important challenge.

In conclusion, we demonstrated a negative effect of having comorbidities at disease onset of RA on the evolution of disease activity and disability, which could not be mitigated even with intensive treatment strategies.

SUPPLEMENTAL MATERIAL

Supplement 1a:

Results of the longitudinal analyses to investigate the impact of comorbidity status, reflected by a dichotomized RDCI as ≥1 or 0 on different outcomes over 2 years.

All participants of CareRA study n=379					
Linear Mixed Model Analyses		β	95% CI		p-value
HAQ	(intercept)	0.66	0.58	0.74	<0.001
	RDCI groups	**0.21**	**0.07**	**0.36**	**0.003**
	COBRA Classic vs TSU	-0.21	-0.30	-0.11	<0.001
	COBRA Slim high-risk vs TSU	-0.15	-0.25	-0.05	0.004
	COBRA Avant-Garde vs TSU	-0.13	-0.23	-0.03	0.018
	COBRA Slim low-risk vs TSU	-0.19	-0.31	-0.07	0.002
	time (weeks)	0.00	0.00	0.00	<0.001
	RDCI groups * COBRA Classic vs TSU	0.05	-0.12	0.22	0.542
	RDCI groups * COBRA Slim high-risk vs TSU	-0.15	-0.32	0.02	0.088
	RDCI groups * COBRA Avant-Garde vs TSU	-0.16	-0.33	0.01	0.071
	RDCI groups * COBRA Slim low-risk vs TSU	-0.02	-0.23	0.18	0.816
DAS28-CRP	(intercept)	3.29	3.15	3.43	<0.001
	RDCI groups	**0.23**	**0.13**	**0.32**	**<0.001**
	COBRA Classic vs TSU	-0.41	-0.57	-0.25	<0.001
	COBRA Slim high-risk vs TSU	-0.35	-0.51	-0.20	<0.001
	COBRA Avant-Garde vs TSU	-0.42	-0.58	-0.26	<0.001
	COBRA Slim low-risk vs TSU	-0.42	-0.61	-0.23	<0.001
	time (weeks)	-0.01	-0.01	-0.01	<0.001
SF-36 PCS	(intercept)	30.46	28.05	32.88	<0.001
	RDCI groups	**-3.19**	**-4.84**	**-1.55**	**<0.001**
	COBRA Classic vs TSU	1.75	-1.04	4.54	0.220
	COBRA Slim high-risk vs TSU	2.31	-0.51	5.12	0.108
	COBRA Avant-Garde vs TSU	3.18	0.35	6.00	0.028
	COBRA Slim low-risk vs TSU	5.37	1.94	8.80	0.002
	time (weeks)	0.09	0.07	0.11	<0.001

SF-36 MCS	(intercept)	51.41	49.39	53.44	<0.001
	RDCI groups	**-1.64**	**-3.02**	**-0.26**	**0.020**
	COBRA Classic vs TSU	0.24	-2.10	2.57	0.842
	COBRA Slim high-risk vs TSU	-0.45	-2.80	1.91	0.710
	COBRA Avant-Garde vs TSU	-3.05	-5.42	-0.68	0.012
	COBRA Slim low-risk vs TSU	0.10	-2.77	2.96	0.948
	time (weeks)	0.02	0.01	0.04	0.009
Generalized Estimating Equations Analysis		OR	95% CI		p-value
Remission DAS28-CRP<2.6	(intercept)	0.51	0.38	0.68	<0.001
	RDCI groups	**0.72**	**0.60**	**0.87**	**<0.001**
	COBRA Classic vs TSU	1.12	0.81	1.54	0.505
	COBRA Slim high-risk vs TSU	1.07	0.77	1.49	0.671
	COBRA Avant-Garde vs TSU	1.20	0.87	1.67	0.268
	COBRA Slim low-risk vs TSU	1.38	0.92	2.05	0.117
	time (weeks)	1.01	1.01	1.02	<0.001
Occurrence hospitaliza-tions	(intercept)	0.01	0.00	0.02	<0.001
	RDCI groups	**3.73**	**2.14**	**6.49**	**<0.001**
	COBRA Classic vs TSU	1.20	0.43	3.31	0.732
	COBRA Slim high-risk vs TSU	1.00	0.37	2.75	0.996
	COBRA Avant-Garde vs TSU	1.00	0.35	2.84	0.993
	COBRA Slim low-risk vs TSU	0.96	0.31	3.00	0.944
	time (weeks)	1.01	1.00	1.02	0.003

Note: Coefficients stem from linear mixed models with either HAQ, DAS28-CRP, SF-36 PCS or SF-36 MCS as dependent variables, or from Generalized estimating equation models with occurrence of remission according to DAS28-CRP or of hospitalizations during 2 years as dependent variable; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score using 28 joints and CRP; SF-36: 36-item Short Form Health Survey; SF36 PCS: physical component scale of SF36; SF36 MCS: mental component scale of SF36; 95% CI: confidence intervals. OR: odds ratio.

Supplement 1b:

Results of the longitudinal analyses to investigate the impact of comorbidity status, reflected by the RDCI score on different outcomes over 2 years.

All participants of CareRA study n=379					
Linear Mixed Model Analyses		β	95% CI		p-value
HAQ	(intercept)	0.69	0.63	0.76	<0.001
	RDCI	**0.04**	**0.02**	**0.06**	**<0.001**
	COBRA Classic vs TSU	-0.16	-0.24	-0.08	<0.001
	COBRA Slim high-risk vs TSU	-0.19	-0.27	-0.11	<0.001
	COBRA Avant-Garde vs TSU	-0.17	-0.25	-0.09	<0.001
	COBRA Slim low-risk vs TSU	-0.18	-0.28	-0.09	<0.001
	time (weeks)	0.00	0.00	0.00	<0.001
DAS28-CRP	(intercept)	3.30	3.16	3.43	<0.001
	RDCI	**0.09**	**0.05**	**0.13**	**<0.001**
	COBRA Classic vs TSU	-0.39	-0.55	-0.23	<0.001
	COBRA Slim high-risk vs TSU	-0.33	-0.49	-0.17	<0.001
	COBRA Avant-Garde vs TSU	-0.40	-0.56	-0.24	<0.001
	COBRA Slim low-risk vs TSU	-0.42	-0.61	-0.23	<0.001
	time (weeks)	-0.01	-0.01	-0.01	<0.001
SF-36 PCS	(intercept)	30.34	27.92	32.76	<0.001
	RDCI	**-1.12**	**-1.85**	**-0.40**	**0.002**
	COBRA Classic vs TSU	1.39	-1.40	4.18	0.328
	COBRA Slim high-risk vs TSU	1.85	-0.95	4.65	0.194
	COBRA Avant-Garde vs TSU	2.72	-0.10	5.54	0.059
	COBRA Slim low-risk vs TSU	5.16	1.73	8.60	0.003
	time (weeks)	0.09	0.07	0.11	<0.001
SF-36 MCS	(intercept)	51.38	49.34	53.41	<0.001
	RDCI	**-0.61**	**-1.21**	**0.00**	**0.050**
	COBRA Classic vs TSU	0.05	-2.29	2.38	0.968
	COBRA Slim high-risk vs TSU	-0.68	-3.01	1.66	0.570
	COBRA Avant-Garde vs TSU	-3.29	-5.65	-0.94	0.006
	COBRA Slim low-risk vs TSU	-0.01	-2.88	2.85	0.993
	time (weeks)	0.02	0.01	0.04	0.010

Generalized Estimating Equations Analysis		OR	95% CI		p-value
Remission DAS28-CRP<2.6	(intercept)	0.50	0.38	0.67	<0.001
	RDCI	**0.90**	**0.82**	**0.97**	**0.008**
	COBRA Classic vs TSU	1.08	0.78	1.49	0.648
	COBRA Slim high-risk vs TSU	1.03	0.74	1.43	0.848
	COBRA Avant-Garde vs TSU	1.16	0.83	1.61	0.380
	COBRA Slim low-risk vs TSU	1.35	0.90	2.03	0.146
	time (weeks)	1.02	1.01	1.02	<0.001
Occurrence hospitaliza-tions	(intercept)	0.01	0.00	0.02	<0.001
	RDCI	**1.46**	**1.27**	**1.67**	**<0.001**
	COBRA Classic vs TSU	1.56	0.60	4.06	0.361
	COBRA Slim high-risk vs TSU	1.33	0.51	3.48	0.565
	COBRA Avant-Garde vs TSU	1.32	0.49	3.59	0.585
	COBRA Slim low-risk vs TSU	1.12	0.38	3.33	0.842
	time (weeks)	1.01	1.00	1.02	0.004

Note: Coefficients stem from linear mixed models with either HAQ, DAS28-CRP, SF-36 PCS or SF-36 MCS as dependent variables, or from Generalized estimating equation models with occurrence of remission according to DAS28-CRP or of hospitalizations during 2 years as dependent variable; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score using 28 joints and CRP; SF-36: 36-item Short Form Health Survey; SF36 PCS: physical component scale of SF36; SF36 MCS: mental component scale of SF36; 95% CI: confidence intervals. OR: odds ratio.

Supplement 2a:

Results of the longitudinal analyses within participants treated intensively in combination with initial scheme of glucocorticoids to investigate the impact of comorbidity status, reflected by a dichotomized RDCI as ≥1 or 0 on different outcomes over 2 years.

Participants treated intensively in combination with initial scheme of glucocorticoids n=332					
Linear Mixed Model Analyses		β	95% CI		p-value
HAQ	(intercept)	0.46	0.37	0.56	<0.001
	RDCI groups	**0.19**	**0.05**	**0.33**	**0.008**
	COBRA Classic vs COBRA Slim low-risk	-0.01	-0.12	0.09	0.793
	COBRA Slim high-risk vs COBRA Slim low-risk	0.04	-0.07	0.16	0.447
	COBRA Avant-Garde vs COBRA Slim low-risk	0.06	-0.05	0.17	0.293
	time (weeks)	0.00	0.00	0.00	<0.001
	RDCI groups * COBRA Classic vs COBRA Slim low-risk	0.08	-0.09	0.25	0.370
	RDCI groups * COBRA Slim high-risk vs COBRA Slim low-risk	-0.12	-0.29	0.04	0.151
	RDCI groups * COBRA Avant-Garde vs COBRA Slim low-risk	-0.13	-0.30	0.04	0.124
DAS28-CRP	(intercept)	2.85	2.70	3.00	<0.001
	RDCI groups	**0.23**	**0.13**	**0.32**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	0.01	-0.15	0.18	0.875
	COBRA Slim high-risk vs COBRA Slim low-risk	0.07	-0.10	0.23	0.414
	COBRA Avant-Garde vs COBRA Slim low-risk	0.00	-0.16	0.17	0.968
	time (weeks)	-0.01	-0.01	-0.01	<0.001

SF-36 PCS	(intercept)	35.78	33.04	38.51	<0.001
	RDCI groups	**-3.04**	**-4.79**	**-1.28**	**0.001**
	COBRA Classic vs COBRA Slim low-risk	-3.63	-6.64	-0.62	0.018
	COBRA Slim high-risk vs COBRA Slim low-risk	-3.08	-6.10	-0.07	0.045
	COBRA Avant-Garde vs COBRA Slim low-risk	-2.20	-5.24	0.84	0.156
	time (weeks)	0.09	0.06	0.11	<0.001
SF-36 MCS	(intercept)	51.50	49.20	53.80	<0.001
	RDCI groups	**-1.96**	**-3.43**	**-0.48**	**0.009**
	COBRA Classic vs COBRA Slim low-risk	0.15	-2.37	2.68	0.905
	COBRA Slim high-risk vs COBRA Slim low-risk	-0.49	-3.02	2.04	0.704
	COBRA Avant-Garde vs COBRA Slim low-risk	-3.11	-5.66	-0.56	0.017
	time (weeks)	0.03	0.01	0.05	0.004
Generalized Estimating Equations Analysis		OR	95% CI		p-value
Remission DAS28-CRP<2.6	(Intercept)	0.74	0.55	1.00	0.051
	RDCI groups	**0.73**	**0.61**	**0.87**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	0.82	0.59	1.12	0.207
	COBRA Slim high-risk vs COBRA Slim low-risk	0.79	0.58	1.09	0.154
	COBRA Avant-Garde vs COBRA Slim low-risk	0.87	0.63	1.21	0.408
	time (weeks)	1.01	1.01	1.01	<0.001
Occurrence hospitaliza-tions	(Intercept)	0.01	0.00	0.02	<0.001
	RDCI groups	**3.60**	**2.04**	**6.36**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	1.25	0.56	2.76	0.585
	COBRA Slim high-risk vs COBRA Slim low-risk	1.03	0.47	2.26	0.934
	COBRA Avant-Garde vs COBRA Slim low-risk	1.03	0.44	2.38	0.952
	time (weeks)	1.01	1.00	1.02	0.001

Supplement 2b:

Results of the longitudinal analyses within participants treated intensively in combination with initial scheme of glucocorticoids to investigate the impact of comorbidity status, reflected by the RDCI score on different outcomes over 2 years.

Participants treated intensively in combination with initial scheme of glucocorticoids n=332					
Linear Mixed Model Analyses		β	95% CI		p-value
HAQ	(intercept)	0.50	0.42	0.57	<0.001
	RDCI	**0.05**	**0.03**	**0.07**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	0.03	-0.06	0.11	0.504
	COBRA Slim high-risk vs COBRA Slim low-risk	0.00	-0.09	0.08	0.917
	COBRA Avant-Garde vs COBRA Slim low-risk	0.01	-0.07	0.10	0.794
	time (weeks)	0.00	0.00	0.00	<0.001
DAS28-CRP	(intercept)	2.85	2.70	3.00	<0.001
	RDCI	**0.10**	**0.05**	**0.14**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	0.03	-0.14	0.20	0.714
	COBRA Slim high-risk vs COBRA Slim low-risk	0.09	-0.08	0.25	0.306
	COBRA Avant-Garde vs COBRA Slim low-risk	0.02	-0.15	0.19	0.798
	time (weeks)	-0.01	-0.01	-0.01	<0.001
SF-36 PCS	(intercept)	35.57	32.83	38.30	<0.001
	RDCI	**-1.19**	**-2.00**	**-0.37**	**0.004**
	COBRA Classic vs COBRA Slim low-risk	-3.78	-6.80	-0.76	0.014
	COBRA Slim high-risk vs COBRA Slim low-risk	-3.30	-6.31	-0.29	0.032
	COBRA Avant-Garde vs COBRA Slim low-risk	-2.45	-5.49	0.60	0.115
	time (weeks)	0.09	0.06	0.11	<0.001

SF-36 MCS	(intercept)	51.46	49.16	53.76	<0.001
	RDCI	**-0.88**	**-1.56**	**-0.19**	**0.012**
	COBRA Classic vs COBRA Slim low-risk	0.04	-2.49	2.57	0.975
	COBRA Slim high-risk vs COBRA Slim low-risk	-0.61	-3.13	1.92	0.637
	COBRA Avant-Garde vs COBRA Slim low-risk	-3.28	-5.84	-0.73	0.012
	time (weeks)	0.03	0.01	0.05	0.005
Generalized Estimating Equations Analysis		OR	95% CI		p-value
Remission DAS28-CRP<2.6	(Intercept)	0.73	0.54	0.99	0.041
	RDCI	**0.88**	**0.81**	**0.95**	**0.001**
	COBRA Classic vs COBRA Slim low-risk	0.80	0.58	1.10	0.171
	COBRA Slim high-risk vs COBRA Slim low-risk	0.78	0.56	1.07	0.124
	COBRA Avant-Garde vs COBRA Slim low-risk	0.85	0.62	1.18	0.342
	time (weeks)	1.01	1.01	1.01	<0.001
Occurrence hospitaliza-tions	(Intercept)	0.01	0.00	0.02	<0.001
	RDCI	**1.45**	**1.22**	**1.71**	**<0.001**
	COBRA Classic vs COBRA Slim low-risk	1.40	0.64	3.07	0.405
	COBRA Slim high-risk vs COBRA Slim low-risk	1.17	0.53	2.57	0.702
	COBRA Avant-Garde vs COBRA Slim low-risk	1.17	0.50	2.71	0.722
	time (weeks)	1.01	1.00	1.02	0.001

Note: Coefficients stem from linear mixed models with either HAQ, DAS28-CRP, SF-36 PCS or SF-36 MCS as dependent variables, or from Generalized estimating equation models with occurrence of remission according to DAS28-CRP or of hospitalizations during 2 years as dependent variable; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score using 28 joints and CRP; SF-36: 36-item Short Form Health Survey; SF36 PCS: physical component scale of SF36; SF36 MCS: mental component scale of SF36; 95% CI: confidence intervals. OR: odds ratio.

Supplement 3:

Results of the longitudinal analyses to investigate the impact of different types of comorbidity on all outcomes over 2 years.

All participants of CareRA study n=379					
Linear Mixed Model Analyses		β	95% CI		p-value
HAQ	(intercept)	0.67	0.61	0.74	<0.001
	pulmonary disease	-0.04	-0.13	0.04	0.318
	cardiovascular disease	-0.03	-0.09	0.04	0.445
	hypertension	**0.20**	**0.15**	**0.26**	**<0.001**
	fracture	0.09	-0.21	0.39	0.557
	depression	**0.20**	**0.10**	**0.30**	**<0.001**
	diabetes mellitus	0.05	-0.08	0.18	0.464
	malignancy	0.07	-0.09	0.22	0.398
	peptic ulcer or stomach disease	0.05	-0.04	0.13	0.313
	COBRA Classic vs TSU	-0.16	-0.24	-0.09	<0.001
	COBRA Slim high-risk vs TSU	-0.20	-0.27	-0.12	<0.001
	COBRA Avant-Garde vs TSU	-0.18	-0.25	-0.10	<0.001
	COBRA Slim low-risk vs TSU	-0.18	-0.28	-0.09	<0.001
	time (weeks)	0.00	0.00	0.00	<0.001
DAS28-CRP	(intercept)	3.27	3.14	3.41	<0.001
	pulmonary disease	-0.12	-0.29	0.05	0.156
	cardiovascular disease	0.09	-0.04	0.22	0.165
	hypertension	**0.26**	**0.14**	**0.38**	**<0.001**
	fracture	0.42	-0.18	1.03	0.171
	depression	**0.31**	**0.11**	**0.50**	**0.002**
	diabetes mellitus	0.18	-0.09	0.44	0.188
	malignancy	0.09	-0.23	0.41	0.577
	peptic ulcer or stomach disease	0.15	-0.02	0.33	0.087
	COBRA Classic vs TSU	-0.40	-0.55	-0.24	<0.001
	COBRA Slim high-risk vs TSU	-0.34	-0.49	-0.18	<0.001
	COBRA Avant-Garde vs TSU	-0.40	-0.56	-0.25	<0.001
	COBRA Slim low-risk vs TSU	-0.41	-0.60	-0.22	<0.001
	time (weeks)	-0.01	-0.01	-0.01	<0.001

SF-36 PCS	(intercept)	30.63	28.23	33.03	<0.001
	pulmonary disease	0.81	-2.21	3.82	0.600
	cardiovascular disease	-0.45	-2.77	1.88	0.706
	hypertension	**-4.74**	**-6.76**	**-2.72**	**<0.001**
	fracture	-7.52	-18.42	3.38	0.176
	depression	-3.35	-7.10	0.40	0.080
	diabetes mellitus	0.20	-4.28	4.69	0.929
	malignancy	0.00	-5.69	5.70	0.999
	peptic ulcer or stomach disease	-2.08	-5.12	0.96	0.179
	COBRA Classic vs TSU	1.64	-1.12	4.40	0.245
	COBRA Slim high-risk vs TSU	2.14	-0.64	4.92	0.130
	COBRA Avant-Garde vs TSU	2.90	0.10	5.70	0.042
	COBRA Slim low-risk vs TSU	5.29	1.87	8.72	0.002
	time (weeks)	0.09	0.07	0.11	<0.001
SF-36 MCS	(intercept)	51.21	49.20	53.22	<0.001
	pulmonary disease	-1.75	-4.27	0.76	0.172
	cardiovascular disease	0.48	-1.46	2.42	0.629
	hypertension	0.68	-1.00	2.37	0.425
	fracture	3.68	-5.39	12.75	0.426
	depression	**-6.94**	**-10.07**	**-3.82**	**<0.001**
	diabetes mellitus	-4.54	-8.27	-0.80	0.017
	malignancy	2.01	-2.73	6.76	0.406
	peptic ulcer or stomach disease	-0.42	-2.96	2.11	0.743
	COBRA Classic vs TSU	-0.15	-2.46	2.15	0.896
	COBRA Slim high-risk vs TSU	-0.60	-2.92	1.72	0.613
	COBRA Avant-Garde vs TSU	-3.00	-5.34	-0.67	0.012
	COBRA Slim low-risk vs TSU	-0.07	-2.93	2.78	0.960
	time (weeks)	0.03	0.01	0.04	0.008
Generalized Estimating Equations Analysis		OR	95% CI		p-value
Remission DAS28-CRP<2.6	(Intercept)	0.51	0.39	0.68	<0.001
	pulmonary disease	1.16	0.83	1.63	0.384
	cardiovascular disease	0.91	0.71	1.18	0.485
	hypertension	0.76	0.62	0.95	0.013
	fracture	**0.40**	**0.24**	**0.66**	**<0.001**
	depression	0.64	0.43	0.96	0.030
	diabetes mellitus	1.03	0.67	1.57	0.907
	malignancy	0.63	0.31	1.29	0.205

	peptic ulcer or stomach disease	0.79	0.55	1.15	0.217
	COBRA Classic vs TSU	1.06	0.77	1.46	0.708
	COBRA Slim high-risk vs TSU	1.00	0.73	1.38	1.000
	COBRA Avant-Garde vs TSU	1.15	0.83	1.58	0.400
	COBRA Slim low-risk vs TSU	1.38	0.93	2.03	0.107
	time (weeks)	1.01	1.01	1.02	0.000
Occurrence hospitaliza-tions	(Intercept)	0.01	0.00	0.02	<0.001
	pulmonary disease	2.25	1.13	4.50	0.021
	cardiovascular disease	1.58	0.88	2.82	0.123
	hypertension	1.73	1.05	2.86	0.033
	fracture	2.80	0.63	12.54	0.178
	depression	1.46	0.54	3.90	0.455
	diabetes mellitus	1.68	0.64	4.44	0.293
	malignancy	2.05	0.66	6.39	0.214
	peptic ulcer or stomach disease	1.17	0.58	2.35	0.661
	COBRA Classic vs TSU	1.51	0.56	4.10	0.415
	COBRA Slim high-risk vs TSU	1.25	0.45	3.48	0.676
	COBRA Avant-Garde vs TSU	1.29	0.47	3.53	0.623
	COBRA Slim low-risk vs TSU	0.99	0.32	3.05	0.989
	time (weeks)	1.01	1.00	1.02	0.003

Types of comorbidity are based on definition of RDCI: Cardiovascular disease = myocardial infarction/stroke/other cardiovascular event; Fracture = fractures of spine/hip/leg based on definition of RDCI.

Note: Coefficients stem from linear mixed models with either HAQ, DAS28-CRP, SF-36 PCS or SF-36 MCS as dependent variables, or from Generalized estimating equation models with occurrence of remission according to DAS28-CRP or of hospitalizations during 2 years as dependent variable; HAQ: Health Assessment Questionnaire; DAS28-CRP: Disease Activity Score using 28 joints and CRP; SF-36: 36-item Short Form Health Survey; SF36 PCS: physical component scale of SF36; SF36 MCS: mental component scale of SF36; 95% CI: confidence intervals. OR: odds ratio.

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GENERAL DISCUSSION

In this general discussion chapter, we will critically evaluate/discuss each chapter. Every part consists of a summary of the main findings, an interpretation of the results in the context of the literature, methodological considerations, and practical consequences for early RA management. To conclude, we discuss the overarching message of this thesis and the practical consequences for the treatment of a patient with RA in daily practice.

CHAPTER 1: EFFECTIVE TREATMENT STRATEGY FOR PATIENTS WITH EARLY RA

Summary of key findings

We demonstrated that patients with early RA, irrespective of their prognostic profile, can achieve a rapid, significant, and sustained clinical response on the long term **by reinforcing initial csDMARD therapy with a temporary step-down scheme of prednisone** and adapting treatment to a target of low disease activity. The COBRA-like schemes led to an excellent and stable disease control with more than 70% of patients having a DAS28-CRP <2.6, two and five years after treatment initiation. Additionally, improvement in physical ability was rapid and stable and progression of joint damage was limited over time. Moreover, half of all patients did not have to intensify their DMARD treatment during this 5-year period. The vast majority of patients could stop taking glucocorticoids (GCs) within 7 months with a limited chronic use of glucocorticoids in 9% at year 5. Further, overall bDMARD use was low with 20% of patients initiating a bDMARD over 5 years. These results demonstrate the effectiveness of initiating a short-term glucocorticoid scheme early in the disease course, a principle that was meanwhile adopted in the European recommendations for the management of RA [1].

The COBRA-Slim regimen, with only MTX and prednisone bridging, resulted in similar efficacy on the long term compared to csDMARD combinations with prednisone bridging **in patients with markers of poor prognosis.** Moreover, this treatment scheme demonstrated **a more favourable safety profile** and seemed better tolerated over 2 years. In the COBRA-Slim arm only patients insufficiently responding to MTX monotherapy were exposed to csDMARD combination therapy, resulting in less adverse reactions. Additionally, slightly fewer COBRA-Slim patients discontinued study treatment due to side effects. Hence, this simplified strategy with fewer drugs could avoid unnecessary overtreatment in the large majority of patients sufficiently responding [2].

Patients without markers of poor prognosis who started a **COBRA Slim regimen had better disease control and functionality over time** than patients starting MTX without glucocorticoids. This COBRA Slim treatment did not lead to more safety issues on the long term than initial MTX monotherapy without GCs. Suppression of

joint damage progression over 5 years was comparable in both good-prognosis treatment groups. However, the COBRA-Slim treatment led more rapidly to remission and improved physical ability than the more traditional step-up strategy. Furthermore, patients in TSU arm needed more glucocorticoid injections and seemingly more rapid initiation of a second csDMARD during the first 2 years. Based on these results, the COBRA Slim regimen should be considered instead of MTX monotherapy, also in patients with an assumed better prognosis.

Results into context of literature

Our results confirm the sustained effectiveness on the long term of the original COBRA scheme and of other COBRA-like remission induction schemes as also tested in the BeSt and the COBRA-Light trial [3–6]. The original COBRA scheme resulted in a similar safety profile over 11 years in comparison with initial SSZ monotherapy. The group treated with the COBRA scheme had lower mortality and similar frequencies of cardiovascular disease and osteoporosis as this SSZ group. Increases in prevalence of hypertension and diabetes in the COBRA group were compensated by a decreased prevalence of hypercholesterolaemia. Our findings confirm that the safety profile of COBRA Slim was comparable with MTX monotherapy after 2 years in CareRA considering all adverse events related to study therapy. Even a slightly better safety profile was seen in favour of the COBRA Slim in low-risk patients, based on the reported safety issues considered as clinically relevant by rheumatologist, including eventual side-effects of GCs, during the 3-year observational follow-up period in CareRA plus. Progression of joint damage was well suppressed and remained stable according to the long term follow up data of the original COBRA study after 5 years and after 11 years, as was the case in our trial after 5 years. Results of the BeSt trial showed that initial combination therapy of MTX, SSZ and prednisone resulted in sustained clinical improvement over 10 years, including well-controlled disease activity, as well as improved functional ability, supressed joint damage progression and the possibility to taper or discontinue medication in many patients. The COBRA-light trial demonstrated that early RA patients, initially treated with a combination of MTX and prednisolone bridging had similar efficacy and safety outcomes over a 4-year period compared with patients initiated on a combination of MTX, SSZ and prednisolone bridging. This protocol required the addition of etanercept (a bDMARD) in case DAS44<1.6 was not achieved. Consequently, after 1 year 29% of

patients in the COBRA-light arm had started ≥1 bDMARD, while in the CareRA trial at the year 1 visit only 7% of all participants were using a bDMARD. Moreover, the adaptation step of initiating etanercept despite being required per protocol was often not implemented in the COBRA-light trial by the treating rheumatologists or resulted in limited additional benefit. In comparison, the adaptation scheme we used in the CareRA trial, steering at a DAS28-CRP threshold of $\leq$ 3.2, can be considered more feasible and more cost-effective.

In contrast, the Treatment in the Rotterdam Early Arthritis CoHort (tREACH) trial concluded that triple DMARD therapy (MTX+SSZ+HCQ) was more effective than MTX monotherapy after 1 year, both in combination with bridging GCs [7]. After 2 years, there was a trend for higher frequency of achieving sustained remission in the triple therapy arm versus the MTX monotherapy arm, although not statistically significant, following a treat-to-target protocol with initiation of a TNF blocker in case DAS was >2.4 or progressive treatment tapering in case of sustained remission [8]. One potential explanation of these findings is that a less powerful (started at 15mg/day till week 4 and then tapered gradually to 2.5mg/day) and shorter (10 weeks) GC bridging scheme was used in tREACH compared to the COBRA regimens used in CareRA, which could have given insufficient time for MTX to reach its full therapeutic efficacy. However, it is possible that a small subgroup of patients would benefit more from initial csDMARD combination, although probably at a higher risk of adverse effects. Identifying these patients remains difficult due to the lack of effective theranostic markers until today.

Methodological considerations

We did not blind allocation of initial treatment and did not formally assess patients' adherence to medication. We cannot exclude a particular preference of rheumatologists or patients for a specific treatment regimen, potentially influencing results. However, due to this pragmatic study design we were able to evaluate the effectiveness of COBRA regimens more realistically than in a blinded trial. Additionally, we left treatment at the discretion of the rheumatologist from the second year in CareRA onwards. Theoretically this could have resulted in bias in treatment decisions and therefore influenced differences in outcomes between arms. Proportions of patients who needed an intensification in their DMARD treatment during the 5 year follow up period were however comparable between

treatment regimens. It is therefore unlikely there were systematic differences in subsequent DMARD adaptations that could have influenced the comparison between treatment arms in the high-risk population. We compared outcomes mainly by using the DAS28-CRP composite measure, an outcome measure known to be potentially not stringent enough to detect 'real' remission [9]. However, comparing mean disease activity, and rates of low disease activity and remission based on more stringent criteria like CDAI, SDAI and ACR-EULAR Boolean criteria yielded similar results when comparing the treatment regimens. Finally, the analyses in the group of patients without factors of poor prognosis were based on a limited population. This group of patients is however seldom looked at separately in an RCT setting, and their evaluation is rarely pre-conceptualized. Furthermore, these patients are often not treated with specific treatment regimens, although this is a prerequisite to answer legitimate strategic questions regarding this specific subpopulation.

Our results are based on a representative sample of patients with early RA in Flanders since we included a broad study population from different practices, with different levels of disease activity. We had high retention rates of patients in the long-term follow-up without selective dropouts. These features enhance the relevance and generalizability of our findings and are an indication of the applicability of the proposed strategy in practice.

Clinical implications

COBRA-Slim is an effective and safe initial treatment scheme for every patient who has been recently diagnosed with RA

Should MTX be combined with another csDMARD?

Rapid remission induction with a combination of MTX and a GCs bridging scheme including a subsequent treat-to-target approach, can lead to comparable, sustained outcomes as more complex strategies, irrespective of prognosis. Moreover, this strategy leads to a lower risk of adverse reactions including toxicities and avoids unnecessary overtreatment in patients sufficiently responding [10]. Furthermore, the COBRA-Slim strategy with its consecutive adaptation steps seems to result in biologicals being initiated at a later stage, assuming a better cost-effectiveness.

Indeed, a detailed cost-effectiveness analysis of the treatments within the CareRA trial by Pazmino et al confirmed this [11]. The combination of MTX with GCs bridging was less expensive with similar health utility than more intensive step-down combinations strategies or MTX monotherapy without GCs after 2 years. Therefore, we consider the COBRA Slim scheme to be an efficacious, safe and cost-effective treatment strategy for every patient with early RA.

Despite the high response rates, a subgroup of patients could not achieve the desired target with any of the intensive treatment regimens we tested. Since early response was previously shown to be predictive of the future course of disease activity, this could be seen as a criterion to select patients for a more rapid treatment intensification, for instance with a bDMARD or a tsDMARD [12–15]. Findings of this thesis have contributed to the idea to set up the CareRA 2020 trial which is currently being conducted by the department of rheumatology of the University Hospitals Leuven. The main objective of this multicentre RCT is to compare in insufficient responders to an initial COBRA Slim strategy the potential added benefit of a 6-months course of etanercept in the remission induction phase (first 32 weeks), versus intensification with cheaper csDMARDs as in the original COBRA Slim scheme.

Should MTX be combined with an initial GCs bridging scheme?

Although GCs are often used to treat RA, their role in the management of early RA is still debated, mainly due to the risk of toxicities with long term use of high dosages. It is clear from existing evidence that GCs are effective for reducing disease activity in patients with early RA when added to csDMARDs, at least in the short term [16–18]. The CAPRA-2 trial, performed in established RA, showed that low-dose prednisone with a modified release formulation (chronotherapy) in combination with DMARDs significantly improved disease activity after 12 weeks compared with placebo [19,20]. In the BeSt study, initial combination therapies with either csDMARDs and GCs or MTX and infliximab, provided more rapid improvement and less progression of joint damage than initial csDMARD monotherapies, although a comparable long-term clinical response was seen after 10 years [21]. Moreover, both initial combination strategies performed overall equally well, indicating that infliximab is not superior to GCs as a remission inducing agent. Results of the CAMERA-II trial in early RA indicated that using prednisone 10mg daily in addition to MTX during 2 years was more effective in reducing disease activity than MTX with

placebo, with decreasing differences over time [22]. Finally, in the BARFOT early RA study, treatment for 2-years with prednisolone of 7.5mg daily together with csDMARDs resulted in better clinical outcomes at every time point and suppressed radiographic damage after 2 years compared to csDMARDs without GCs. Based on a 4 year follow-up, patients on prednisolone had a higher probability of being in remission over the entire course of the disease [23–25]. In our own CareRA trial, patients lacking poor prognostic factors treated with COBRA Slim had a more rapid reduction in disease activity after the first 16 weeks than patients initiated on MTX monotherapy without glucocorticoids [26].

Data in this thesis indicate that the clinical benefit of a bridging scheme with GCs for patients without markers of poor prognosis persists on the long term. The treatment scheme combined with GCs led to a better controlled disease activity and improved functionality over 5 years. Patients in the COBRA slim group had higher chances of being in remission over the course of the 5-years study than patients in the TSU group. Radiographic progression was evenly well suppressed in both groups without a clear benefit of COBRA Slim. A possible reason is that progression of joint damage will be a priori limited in this population lacking markers of radiographic progression. Importantly, initiation of a bridging GC scheme did not lead to a higher incidence in known side-effects of GC.

For patients with markers of poor prognosis, we demonstrated that starting a GC scheme with a more moderate dose of 30mg instead of 60mg daily in combination with MTX resulted in comparable effectiveness after 2 and 5 years. However, the starting dose is still up for debate with investigators striving to reduce the dose further. A recent conference proceeding reported on the CORRA RCT which randomized patients with active RA (<3 years) to 2 differently dosed prednisolone bridging schemes of 12 weeks in addition to MTX starting at either 60mg daily or at 10mg daily or to MTX plus placebo [27]. Results indicated non-inferiority for structural damage for the 10mg compared to the 60mg starting dose, although disease activity was more rapidly reduced in the 60mg group with lower DAS28 scores at week 4 in this group. Speed of response is shown to be an important biomarker for better outcomes later on and is perhaps a more relevant outcome than radiographic progression. DAS 28 scores after 1 year were similar between the 10mg and 60mg groups, although the authors stated that initial advantages of the higher dosed bridging scheme may have been compromised by therapy escalations

within a treat to target setting. Another remark is that reducing the initial dose further may lead theoretically to lower chances of achieving deep remission with little or no risk of disease progression.

GCs are widely used in treatment of RA, but often not in a standardized way with varied doses and durations [28,29]. The French ESPOIR cohort reported that more than 50% of early RA patients received GCs at least once over the first 5 years [30]. Prescribing GCs solely as symptomatic treatment when needed, instead of as a remission induction scheme, deprives patients of their potential as disease-modifying therapeutics. Furthermore, considering GCs as symptomatic, as sometimes is the case in the perception of physicians and patients, may hold a risk for overconsumption on the long run. Hence, efforts to standardize GC treatment should be made, to have benefit of their added structural effect and to alter perceptions on GC.

Implementation of COBRA like schemes with glucocorticoids in daily clinical practice seems challenging and we identified barriers from the rheumatologists' perspective, such as contraindications for some patients, fear for increased risk of side effects and for patients' resistance [31,32]. Also patients fear side effects but nevertheless, results from our research group indicated that patients change their perception on temporal use of GCs when they experience beneficial treatment effects or when expected side effects don't occur, regardless of the initial dose [33]. Moreover, from a patient perspective, a rapid treatment response with relief of pain and returning to "normality" was considered the most important outcome [34]. Finally, speed of response in the first months was shown by our team to be an independent predictor of patient reported health one year after treatment initiation [35]. Therefore, implementation of an intensive strategy with GC bridging, leading to rapid response, should be strived for, in the interest of patients.

CHAPTER 2: REFINEMENT OF THIS EFFECTIVE TREATMENT STRATEGY

2.1 A first indication of which maintenance therapy is effective

Summary of key findings

We evaluated the **effectiveness of two step-down strategies for patients who achieved low disease activity** after combinational treatment with MTX and LEF. For this purpose, we used data of patients randomized to the COBRA Avant-garde arm in CareRA, who initiated a combination of MTX, LEF and a prednisone bridging and were re-randomized in case they achieved a DAS28-CRP≤3.2 at week 40 to step down either to MTX or to LEF monotherapy. The results indicated that within this setting, **it was more beneficial to step down to MTX than to LEF**. Firstly, stepping down to MTX led to numerically better clinical outcomes after 65 weeks in terms of remission and low disease activity rates. Secondly, a better drug retention rate was observed in the MTX group with 20% more patients remaining on MTX than on LEF monotherapy. Survival analysis showed that participants who stepped down to LEF discontinued their assigned monotherapy more rapidly than those on MTX monotherapy. Registered reasons for not maintaining the monotherapy which patients were randomized to, were similar, except for efficacy issues which were more often reported in the LEF monotherapy arm. Thirdly, MTX as well as LEF monotherapy was well tolerated without differences in safety profile.

Results into context of literature

To our knowledge no conclusive data exist as to which drug should be stopped preferably after reaching disease control with the combination of MTX and LEF. This was the first RCT comparing different step-down regimens after having achieved a sufficient clinical response with MTX and LEF combination therapy in early RA.

Methodological considerations

We acknowledge that the results are based on a relatively small sample size. When designing the CareRA trial, comparison of the effectiveness of stepping down to MTX or to LEF in a randomized setting was pre-conceptualized as a secondary outcome. The sample size calculation of CareRA was based upon its primary endpoint, namely

the expected proportion of patients with a DAS28-CRP<2.6 at week 16. There were 85 participants per treatment arm in the high-risk group needed to detect a difference of minimally 20% in this endpoint to demonstrated superiority with 80% power. We enrolled 93 patients in the COBRA Avant-Garde arm, of which only 59 could be re-randomized, since 14 patients didn't tolerate the combination of MTX and LEF, 10 didn't achieve low disease activity by week 40 or ultimately by week 52 and 10 patients could not be re-randomized due to practical reasons. However, this re-randomized population was well characterized and was followed up every 3months for an additional 65 weeks. Nevertheless, our results should be confirmed in larger trials, preferably in a randomized setting.

Results may have been influenced by the open-label design or by having allowed the use of background concomitant medication (NSAIDs or GCs). However, this pragmatic trial design allowed us to make observations reflecting daily practice more realistically giving a valuable insight in the effect of maintenance therapy choice. Moreover, the dose or frequency of glucocorticoids used by patients did not differ between randomization groups.

Clinical implications

Methotrexate should be preferred over leflunomide as maintenance therapy after achieving good disease control with an initial intensive combination of these two drugs

Our results provide a first indication that MTX monotherapy should be preferred on the long term to maintain disease control and avoid treatment changes after stepping down from MTX plus LEF combination therapy, which is in the interest of the patients. These findings could potentially also hold true for patients achieving low disease activity after addition of LEF to MTX monotherapy because of an initial insufficient response. Based on this trial design we could not demonstrate this, but we provide a first clue as to which DMARD could be stopped preferably in such circumstances.

Since it is recommended to consider tapering of csDMARDs in case disease is well controlled, our findings are relevant for the care of patients with RA in daily practice [1]. Reasons supportive of tapering medication include reduction in costs, patient

preference and prevention of (long-term) side effects [36]. EULAR guidelines stipulate that patients should be in persistent remission before starting drug tapering, although there is no definition available yet for the term 'persistent'. A sensitivity analysis of our study showed that 85% of the re-randomized patients had a DAS28-CRP<2.6 at the time of stepping down from combination treatment. Within this subpopulation, also numerically better efficacy outcomes were observed in the MTX group after 65 weeks. Another sensitivity analysis demonstrated that 95% of the re-randomized patients had low disease activity at the two consecutive visits preceding the stepping down from combination treatment, hence during minimally 3 months. These patients had indeed better efficacy outcomes in terms of remission rates at the end of the trial compared to the small minority of patients who were in low disease activity only at the time of re-randomization. Therefore, it seems that patients who have more sustained low disease activity are more suitable for tapering combination csDMARD therapy. The most effective criteria in terms of required degree and duration of disease control to select patients for stepping down from combination treatment, are however not yet known and need to be investigated further.

2.2 Following a treat-to-target strategy is challenging in practice

Summary of key findings

Adherence of rheumatologists to the treat-to-target (T2T) principle was evaluated at every visit of CareRA. We defined adherence as performing a dose escalation or changing/adding DMARDs in case low disease activity was not achieved. Results indicated that **applying T2T strictly during the first 2 years of treatment was challenging**, since in only half of visits theoretically requiring a DMARD adaptation, treatment was intensified. Additionally, in less than half of patients, T2T was strictly applied at all visits during 2 years of follow up. In the first study year in which treatment adaptations were stipulated by protocol, an adherence rate of 60% was observed, while in the second study year with treatment adaptations at discretion of the rheumatologists, a rate of 30% was seen. The most frequent reason not to intensify treatment, given by rheumatologists during the first study year, was that they considered the disease already well-controlled. Patients in which the T2T principle was applied strictly at all visits, had higher chances of achieving remission after 2 years than patients in which the T2T approach was not followed on several

occasions. However, chances of achieving remission were comparable between patients in which T2T was nearly perfectly applied (not applied only once) and those with perfect T2T application at every visit.

Results into context of literature

Physicians' adherence to a T2T approach or protocol has been studied and quantified in other studies, ranging from 42% to 79% [37–42]. These studies varied in definition of physicians' adherence, in the type of protocol or guideline used and in treatment approach. Based on our definition, we assessed adherence to T2T principle specifically in cases above the threshold of low disease activity, indicating a theoretical need for adaptations. The majority of studies investigating physicians' adherence considered all cases in the denominator, including those with controlled disease to assess adherence. Due to varying definitions of adherence and study designs, direct comparison of physicians' adherence levels is impeded.

In CareRA, we observed that when rheumatologists chose to overrule the T2T approach during the first weeks after treatment initiation, the most frequent explanation was that they estimated disease to be sufficiently controlled. Hence, rheumatologists didn't agree with the evaluation of disease control by the DAS28-CRP score in that particular setting. Likewise, in the DREAM study, the most frequent reason for not intensifying treatment although indicated, was that clinical remission was present according to the rheumatologist, despite a DAS28 of ≥ 2.6 [41]. These findings also correspond to results of the BeSt study, in which disagreement of rheumatologists with the DAS or the required treatment adaptation according to the protocol was identified as a risk factor for non-adherence [38].

To date, only limited studies have investigated the impact of physicians' adherence on treatment outcomes. In the NEO-RACo trial, performed in patients with early RA, good physician adherence (versus intermediate or low adherence) was associated with improved remission rates after 2 and 4 years and with decreased disease activity over time, which is in accordance with our findings [42]. Despite this, no significant effect of adherence on radiological progression or on cumulative days off work was shown in this study. Similarly, another study in an Australian early arthritis cohort by Wabe et al. demonstrated that adherence to a T2T protocol was independently associated with remission and with functional outcomes after 3 years, with only a limited effect on radiographic progression [39]. However, patients

included in these two studies have been treated very intensively with an initial triple DMARD scheme of MTX + sulphasalazine + hydroxychloroquine, supplemented in the NEO-RACo trial with prednisolone and in one arm with additional infliximab. This intensive treatment may have influenced physicians' adherence or remission rates, which challenges comparison of the findings with our results.

Methodological considerations

Our definition of physician's adherence to the T2T principle as intensifying DMARD treatment when the treatment goal (DAS28-CRP $\leq$ 3.2) had not been reached, can be considered objective, but also as very stringent, since it did not take into account justifiable reasons to not intensify treatment. Such reasons can include safety issues, patients' preference or failure to achieve the treatment goal just nearly [40,43]. There is to date no standardized approach to assess physicians' adherence, although Wabe et al proposed a system to categorize the level of physician compliance with T2T as high, medium or low, together with acceptable thresholds that predicted remission and low disease activity in patients with early RA. However, by this method e.g. not intensifying treatment in case of a severe toxicity or discontinuing all DMARDs, irrespective of disease control were considered non-compliant. This system has not been validated and the thresholds can only be used for patients treated with triple therapy, which hinders its application.

Our findings are based on data of the CareRA RCT, in which it was mandatory to measure disease activity regularly by the DAS28-CRP score. However, assessing disease activity regularly seems to be common practice in Belgium, probably mainly because this effort is compensated by an additional financial incentive for rheumatologists, which can be charged up to twice a year and is paid by social security. Nevertheless, measuring disease activity at every visit, might not be commonly performed in every practice due to lack of time, or lack of confidence in or of understanding of composite scores and the T2T principle [44]. We could not evaluate (the effect of) these barriers to the implementation of a T2T strategy in the CareRA study as this was not foreseen in the trial design. However, this was further explored in a separate qualitative study performed in patients participating to the CareRA study [31,45].

Our T2T approach was based on reaching the target of low disease activity based on a DAS28-CRP<3.2. We could have chosen to treat aiming at a stricter target of remission. However, an analysis of the BeST and IMPROVED trial showed that adherence to a DAS steered treatment protocol in early RA was less maintained if the target was remission [46]. Additionally, in the COBRA-light trial, the predefined target of remission (DAS44<1.6) led to high numbers of patients requiring a treatment adaptation, but participating rheumatologists often didn't adhere to the protocol, by not prescribing initiation of etanercept [47]. Therefore, our target was set not too low and may have avoided adherence problems.

Clinical implications

'Application of the treat to target principle when indicated still seems challenging in early RA patients during the first two year after treatment initiation'

The findings on physician's adherence may be of relevance and generalizable to clinical practice since we used data from a pragmatic, prospective trial, in a well characterized study population, treated according to current recommendations. Moreover, we were able to get a valuable insight into why T2T is (not) applied, since reasons not to intensify treatment during the first year had to be provided by rheumatologists by protocol, based on a predefined checklist. This method may be less prone to reporting bias, than retrieving reasons from medical charts retrospectively.

The majority of patients within our trial achieved low disease activity and didn't need treatment intensification, probably because they all received effective initial treatment schemes. However, in those patients not achieving low disease activity, it seemed to be more challenging to apply the T2T principle strictly during the first 2 years of treatment, irrespective of type of treatment strategy. Application of T2T guidance strictly was associated with higher remission rates. Whilst it is intuitive to state that higher physician adherence will lead to better treatment outcomes, an exact cause-effect relationship could not be demonstrated, due to the potential effect of various other factors on this relationship. Rheumatologists' adherence was in our cohort associated with remission rates independently of factors known to

potentially influence chances at remission, such as serology status and baseline disease activity. Also, the possibility that more responsive disease, providing fewer opportunities for non-adherence, rather than a higher adherence level led to better outcomes, was explored in a sensitivity analysis in patients with more difficult-to-treat disease. In this subpopulation, very strict application of T2T was still associated with higher remission rates. However, the relationship between physicians' adherence and clinical outcomes is complex and likely to be influenced by other factors affecting achievement of remission. Furthermore, stating that T2T should always be applied without restriction, could also lead to a risk for overtreatment in certain cases and hence increased occurrence of (dose related) DMARD side effects.

Based on our empirical experiences, applying T2T blindly in patients with problems other than remaining disease activity still leads too often to the prescription of a consecutive series of drug intensifications, while they can sometimes benefit more of appropriate non-pharmacological care. In this respect, a more flexible tight control can be advocated for, which states that decisions to adapt treatment should not be made blindly based on ambiguous or too ambitious target measures, but should be based on the individual clinical picture [48,49]. This implies taking into consideration the degree of improvement in case the target is nearly fulfilled, and safety issues when deciding the need/possibility to intensify treatment. Moreover, other valuable treatment alternatives for DMARD changes should be examined, including intra-articular glucocorticoid injections, temporary NSAIDs, physiotherapy, psychological counselling and surgery. Finally, treatment adaptations should be based on shared decision making with patients, taking into account their preferences. Just listening to the patient before making decisions can improve dramatically the direct relationship between adherence to the treat to target principle and favourable outcomes.

There have been some initiatives aiming to improve adherence to T2T [50,51]. The TRACTION randomized trial investigated the effects of an educational program on the implementation of T2T [51]. The intervention consisted of a learning collaborative and aimed at teaching sites T2T principles, developed by an expert faculty, through face-to-face meetings, monthly webinars and site-specific progress calls. This educational collaborative improved the implementation of T2T, measured by verifying whether 1) a disease activity target was specified 2) RA disease activity was recorded by a recommended measure, 3) shared-decision making was

performed and 4) treatment decisions were based on the target and disease activity, or reasons were provided why T2T was not adhered to. The results of this study could form the base to develop such an educational program for application in daily care of RA in Belgium.

Improving adherence to T2T is however challenging and depends on overcoming several obstacles. A commonly reported barrier to adjusting treatment is patient preference or also called patients' resistance to modify therapy when indicated [37,52]. This indicates the need for shared decision making, which is also one of the core principles within the T2T paradigm. Important to take into account in this respect is that patients and physicians approach disease activity and the corresponding need for treatment changes differently, with for example patients giving more importance to pain and physicians to swollen joints [53–56]. Patient's reluctance to change their treatment is related to concerns regarding side effects, costs of medication and care and fear of losing control over their disease. Besides this, patients might also settle with their state of disease or level of disease activity instead of choosing to change treatment at the cost of potential safety issues [53]. Overcoming this patient reluctance is challenging for care providers and should focus on improving communication between patients and their physicians [56,57]. Indeed, previous work of our study group indicated the need for additional information from patients' perspective, with the physician as the most important source for this information, especially during the first months after treatment initiation [33]. Making healthcare professionals aware of the need to address their patients' concerns, can improve their trust relationship and the shared decision-making process, as well as eventually adherence to T2T principle.

Another frequently documented barrier to T2T adherence, is that an elevated disease activity score does not always reflect high RA disease activity [52]. The DAS28-CRP score is one of the most commonly used composite measures in Europe and helps to keep track of disease activity and to react promptly against remaining disease activity. However, this instrument is considered to be imperfect for this purpose since it is less reliable in patients with low disease activity due to its sensitivity to small changes in CRP and in patients' assessments of global health, when joint counts are low [58,59]. Therefore, we should probably expand the information to base our decisions on, by taking additional outcomes, relevant to patients, into account. Recent work from our study group explored the added value

of including outcomes of pain, fatigue and physical function on the evaluation of disease state, since these add valuable patient specific information. By including these outcomes to the standard components of disease activity scores, a more patient-centred estimation of disease burden could be obtained [60]. Making use of a more holistic evaluation of disease activity may improve proper steering of pharmacological treatment, with the overarching goal of improving patients' global health related quality of life.

CHAPTER 3: IMPACT OF COMORBIDITIES

Summary of key findings

We evaluated the prevalence of comorbidities in patients recently diagnosed with RA, before initiation of DMARD treatment. We demonstrated that even in this early phase of the disease there is a **high prevalence of comorbidities** with nearly half of patients in our sample having at least one comorbidity. The development of comorbidities may be related directly or indirectly to the presence of RA, since a higher prevalence was found in cohorts of patients with early RA compared to the general population [61–63]. Furthermore, this high prevalence can be considered clinically important since we considered the presence of **specific "relevant" comorbidities**, as selected by the RDCI [64]. These comorbidities are considered to be important due to their impact on relevant outcomes for RA including functional disability, direct medical costs, work disability, disability considered by social security, hospitalization and death.

Additionally, we investigated whether having comorbidities at baseline would impact treatment response in DMARD naïve patients, treated with intensive remission induction schemes. Having a comorbidity and the degree of comorbidity before treatment initiation was significantly related to **worse functionality, worse disease control and worse physical quality of life as well to occurrence of more hospitalizations.** This effect of comorbidity on treatment response, could apparently not be mitigated by using intensive treatment regimens and applying the treat-to-target principle. The mean differences in functionality and in physical-health-related quality of life over 2 years of treatment between patients with and without comorbidities was in the order of magnitude of differences considered as clinically

important at the individual level. Additionally, patients with comorbidities had lower chances of achieving remission over time, which is the currently recommended goal of treatment. Moreover, this difference in outcomes was apparent at several time points over a longer period of follow up, and not only at one cross-sectional time point. Furthermore, this impact of comorbidity on important outcomes was seen in a crucial phase of the disease according to the window of opportunity theory. For all of the above reasons, comorbidity status at disease onset should be considered as an important aspect of the management of early RA.

Results into context of literature

A high comorbidity burden already at disease onset, demonstrated by a high prevalence of relevant comorbidities at baseline within our cohort, was also reported in other early RA cohorts [61–63,65,66]. Our results confirmed that the most common baseline comorbidity in early RA is hypertension as in other studies in early RA, including the ESPOIR cohort in which the prevalence of arterial hypertension was increased in early RA compared with the general population [61–63,65,66]. However, it is challenging to compare prevalence rates directly between studies, because of differences in populations, methods of collection, registration of comorbidities, study design, and use of other comorbidity indices.

We have confirmed results from other studies on the ERAS and in the CATCH cohort regarding the association between comorbidity status and worse functionality at baseline and over time in patients with early RA [61,65]. The negative impact of comorbidity status on chances of achieving remission, shown in CareRA, was also observed in the CATCH cohort, as in other studies in patients with established RA [65,67]. However, no relation was seen between comorbidity and disease activity in the ERAS cohort [61]. These observational studies were performed based on registries and without protocolized treatment although they adjusted for type of RA treatment in their statistical analyses [61,62]. However, these observational studies could have suffered from channeling bias, with those patients having (more severe) comorbidities receiving more intensive treatment. Additionally, results obtained within these cohorts could have been influenced by reporting bias for comorbidities, as mentioned in the RCGP cohort, since the investigators had to rely on accurate recording of disease by clinicians at participating centers, which might have led to an underestimation of comorbidities [62].

Methodological considerations

Compared to the large registries which studied the prevalence and impact of comorbidities in early RA, the CareRA study had a limited sample size. However, our study contained a representative sample of the RA population in Flanders from different types of practices and was well characterized based on several demographic and clinical variables measured over time. It might be that not all comorbid conditions have been registered by the rheumatologist, nor did we use a formal tool to assess presence of specific comorbidities. However, since we used data of an RCT, collection of comorbidities by physicians was systematically monitored by comparison of all data entries with the medical records. Additionally, all indications reported for currently taken medication were revised for the presence of comorbidities.

Clinical implications

Comorbidities should be screened for and managed already at disease onset since they affect clinical outcomes despite intensive treatment of RA

Our results can be generalized to clinical practice because we used data from a prospective pragmatic RCT. Firstly, we did not exclude patients with important comorbidities and included patients with a heterogeneous disease activity profile and from several rheumatology practices. Therefore, our study population mirrors closely a real-life population with early RA. Secondly, patients were treated with intensive treatment strategies, in line with the latest international guidelines for management of RA of 2019, enhancing relevance for daily practice [1].

We demonstrated that the impact of comorbidities on the studied outcomes could not be counterbalanced by intensive treatment. Since we randomized treatment, we could limit channeling bias, in contrast to cohort studies. Moreover, because of the similar effectiveness of the treatment schemes including glucocorticoids in terms of disease activity, functionality and quality of life over time, a potential modifying effect of treatment on the impact of comorbidity could be precluded [68,69]. This shows that even though patients with early RA are intensively treated with a combination of csDMARDs and a remission induction scheme of GC, including a

treat-to-target approach, their treatment outcomes are still influenced by their comorbidity status at treatment initiation.

With our findings, we confirm that comorbidity adds to the burden of RA by its impact on clinically important outcomes. Impairment of physical ability, or not achieving remission affect patients' well-being as well as their ability to work and mortality [70–73]. Therefore, the focus of caring for patients with newly diagnosed RA should not only be on controlling disease activity, but also on the management of comorbidities. Since many comorbidities are amenable to preventive and therapeutic measures, they should be detected and taken care of at an early stage, in order to reduce their impact on the outcomes in RA.

However, globally there is still a considerable scope for improvement of the management of comorbidities in RA with a wide variability between countries in compliance with recommendations for preventing and managing comorbidities [74,75]. An initiative of the European League Against Rheumatism (EULAR) has proposed points to consider for reporting of, screening for and preventing of six selected comorbidities (ischemic cardiovascular diseases, infections, malignancies, gastrointestinal diseases, depression and osteoporosis). The task force composed three overarching principles: The first one states that comorbidities, such as the 6 selected ones, should be carefully assessed and managed in patients with chronic inflammatory rheumatic diseases. Secondly, all clinicians including health professionals such as nurses, treating general practitioners and rheumatologists and patients through self-administered questionnaires and self-management programs play a key role in the screening and detection of comorbidities. Thirdly, Comorbidities should be subject to a systematic, standardized periodical review for patients with a chronic inflammatory rheumatic disease. Moreover, 15 points to consider for comorbidities were formulated, organized per selected comorbidity [76]. More specifically, for cardiovascular disease, it was recommended to document their history, risk factors, together with a HEART-SCORE index and cardiovascular treatment. The HEART-SCORE gives an estimation of the 10-year risk of fatal cardiovascular disease, taking into account measures of total cholesterol, gender, smoking status, age, and systolic blood pressure [77]. For depression it was agreed that its history, current depression and prior screening for depression should be documented, as well as current treatments for this condition. These overarching principles and points to consider are a valuable source of inspiration to develop a

feasible care program for patients with early RA taking comorbidities into account, which should be implemented in the clinic.

Although this EULAR task force gave guidance on how to report and collect comorbidities in a standardized way, no indications were given on the management of the selected comorbidities or risk factors. Reasons given were that it is not clear who should be responsible for the management of such comorbidities, and that management may depend on the country. An initiative was undertaken in France by Gossec et al to implement the EULAR points to consider in a national context and to develop management recommendations for comorbidities, from a rheumatologist perspective [78]. This resulted in a pragmatic document for collection and management of the selected comorbidities, to be used by the rheumatology team in hospitals or in private practice. Recommendations for management by the rheumatology team entailed physical examination (such as blood pressure), prescription of screening procedures, and interpretation of results to refer to appropriate other health professionals in a timely manner. This pragmatic document clearly guides the rheumatology team in how to deal with comorbidities, and although some of these recommendations on management are country specific, many could be applied in Belgium as well.

However, application of these recommendations in practice remains challenging due to time constraints of rheumatologist to monitor patients frequently or intensively. The COMEDRA trial evaluated whether a nurse-led consultation program had a beneficial impact on the management of comorbidities in a randomized setting [79,80]. The intervention in the comorbidity arms comprised detection by a nurse of the presence of pre-existing comorbidities, of risk factors and of the implementation of the recommendation for detection (e.g. yearly evaluation of cardiovascular risk factors) or management (e.g. lipid-lowering therapy for hypercholesterolemia) of specific comorbidities. When a risk factor or non-optimal management was detected, the nurse explained the patients the interest of proper management and advised them to visit their general practitioner and/or rheumatologist, who were also informed by the nurse. This nurse-led program led to an improved screening and management of comorbidities at 6 months with an increase of 78% in the number of actions for treating or detecting comorbidities taken by the patient's general practitioner or rheumatologist. Additionally, it was shown that this nurse intervention led to an improvement of 33% in a newly developed comorbidity

prevention an screening score compared to baseline [80]. The authors stated that this provides evidence that involving a rheumatology nurse in the multidisciplinary rheumatology team can improve comorbidity screening and management. However, when assessing the added benefits of such an intervention, one should rather take into account more objective outcomes like blood pressure or cholesterol levels. In our opinion, a multidisciplinary approach with the help of specialist nurses, but also by working closely together with general practitioners in first line can help to develop global care programs for RA patients, hereby addressing the need to manage comorbidities. However, it remains to be proven if we can alter the effect of comorbidities on the disease course of RA by implementing such care programs.

OVERALL CONCLUSION AND PRACTICAL CONSEQUENCES FOR EARLY RA CARE

This doctoral thesis gives indications as how to manage care for a patient who has been recently diagnosed with RA. The different studies performed during this PhD project investigated the optimal initial treatment scheme, effectiveness of different maintenance therapies, applicability of treating-to-target, and impact of comorbidities on treatment response. The results provide directions to improve pharmacological treatment and global management of early RA, with the overall aim to optimize patients' health related quality of life.

Chapter 1

In the first chapter, we concluded that an initial combination of MTX and a GCs bridging scheme (COBRA Slim) including a subsequent treat-to-target approach, is an efficacious, safe and cost-effective treatment strategy for every patient with early RA. Since this regimen with fewer drugs led to comparable outcomes as more complex regimens on the long term, but with a more favourable safety profile, its application may avoid unnecessary overtreatment in patients sufficiently responding. Indeed, one should bear in mind that treating patients with RA intensively is paramount, but that using 'more drugs' is not always leading automatically to 'more effective treatment' [10].

A second conclusion, based on results of the first chapter, was that reinforcing MTX with an initial bridging scheme of GCs led to a persistent clinical benefit compared to MTX without GC, in patients without markers of poor prognosis. Therefore, we advocate for a standardized implementation of an initial GC bridging scheme for all patients with RA, irrespective of their prognosis. However, glucocorticoids are often perceived and used as merely symptomatic treatment, both by physicians and patients, which may hold a risk for overconsumption on the long run and deprives patients of their potential as disease-modifying therapeutics. Hence, efforts to standardize GC treatment should be made, meaning that dosage and timing should be protocolized. Moreover, it is important to explain to patients that glucocorticoids are potent and therefore also potentially harmful drugs which are ideal for temporary use as part of the initial treatment scheme because they induce prompt symptomatic relief and rapid and profound disease modification.

Chapter 2

Based on findings of the first part of the second chapter, we concluded that it was more beneficial to step down to MTX than to LEF for patients having achieved good disease control with an initial combination of these two drugs and a GCs bridging scheme. Stepping down to MTX led to a better drug retention with 20% more patients remaining on MTX monotherapy, resulted in numerically better clinical outcomes after 65 weeks and was equally well tolerated. In the LEF monotherapy arm, more efficacy issues were reported as reason for not maintaining the assigned monotherapy, whereas other reasons were evenly balanced. Therefore, we provided a first indication that MTX monotherapy should be preferred on the long term to maintain disease control without further treatment changes after stepping down from MTX plus LEF combination therapy. This can be of importance to patients, since having a rapid but also persistent clinical response is shown by our research group to lead to better psychosocial functioning later on [35]. These findings could also hold true for patients achieving low disease activity after addition of LEF to MTX monotherapy because of an initial insufficient response, although we were unable to formally demonstrate this, based on this trial design. However, we provided a first clue as to which DMARD could be stopped preferably in such circumstances.

In the second part of the second chapter, we concluded that applying T2T strictly during the first 2 years of treatment appeared to be challenging, since in only half of visits theoretically requiring a DMARD adaptation, treatment was intensified. Application of T2T guidance strictly at every visit was associated with higher remission rates after 2 years, although an exact cause-effect relationship could not be demonstrated, due to the potential effect of various other factors. Stating that T2T should always be applied without restriction, could lead to a risk for overtreatment with increased number of DMARD related side effects in certain cases. Therefore, we advocate for a flexible tight control, whereby decisions to adapt treatment should be based on patients' particular clinical state. This implies taking into consideration targets relevant to patients, the degree of improvement in case the target is nearly fulfilled, safety issues, and valuable treatment alternatives, including intra-articular glucocorticoid injections, temporary NSAIDs, physiotherapy, psychological counselling and surgery. Moreover, decisions to adapt treatment should be made in consultation with patients, based on their preferences. This is crucial, since patient's preference is reported to be a very common barrier to adjust

treatment when indicated. Informing physicians of the need to address their patients' concerns, and of the need to implement the T2T principle by for example educational programs, may eventually improve its application in daily practice.

Chapter 3

Results of the third chapter led to the conclusion that almost half of early RA patients had at least one clinically important comorbidity at disease onset and that having comorbidities was associated with worse functionality and disease activity over 2 years. This effect of having comorbidities at disease onset could not be mitigated by using intensive treatment regimens and applying the treat-to-target principle. Therefore, we confirm that comorbidity adds to the burden of RA by its impact on clinically important outcomes. Consequently, the focus of caring for patients with newly diagnosed RA should not only be on controlling disease activity, but also on the management of comorbidities. Since many comorbidities are amenable to preventive and therapeutic measures, they should be detected and taken care of at an early stage, in order to reduce their impact on the outcomes in RA. In our opinion, a multidisciplinary approach with the help of specialist nurses, but also by working closely together with general practitioners in first line can help to develop global care programs for RA patients, hereby addressing the need to manage comorbidities. However, it remains to be proven if we can alter the effect of comorbidities on the disease course of RA by implementing such care programs.

Key messages for care of patients with early RA

- COBRA-Slim is an effective and safe initial treatment scheme for every patient who has been recently diagnosed with RA
- Methotrexate should be preferred over leflunomide as maintenance therapy after achieving good disease control with an initial intensive combination of these two drugs
- Application of the treat to target principle when indicated still seems challenging in early RA patients during the first two year after treatment initiation
- Comorbidities should be screened for and managed already from disease onset since they affect clinical outcomes despite intensive treatment of RA

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SUMMARY

SUMMARY

Introduction

Rheumatoid Arthritis (RA) is an autoimmune-induced inflammatory disease with a worldwide prevalence of about 5 per 1000 adults. This chronic systemic disease is characterized by inflammation of mainly the small joints of hands and feet with pain, swelling and stiffness. If insufficiently treated, this inflammatory process can lead to worse physical functioning, impaired work and social participation and eventually joint damage through loss of articular cartilage and bone erosions. It is crucial to start an effective treatment in patients with RA as soon as possible to reach the target of remission or at least low disease activity. Treatment should be rapidly adapted in case the target is not yet met, according to the "treat to target" principle.

Objectives

This PhD research project is based on data of the 2-year Care in early RA (CareRA) trial and the 3-year observational CareRA plus follow-up study. The overall objective of this thesis was to evaluate the long-term effectiveness of intensive treatment strategies used in CareRA, in order to define an optimal approach for treating patients with early RA. In this perspective, the efficacy, safety, sustainability of treatment response and need for treatment adaptations, associated with these regimes, were assessed up until 2 and 5 years after treatment initiation. Additionally, the applicability of these regimens in clinical practice was investigated, by addressing the following questions: whether presence of significant comorbidities would affect outcomes, which maintenance therapy should be used once patients reach a sufficient clinical response and to what extent do rheumatologists adhere to these strategies in a setting close to daily clinical practice.

Results

The first chapter explored the effectiveness of initial treatment strategies for patients with early RA on the long term. We concluded that an initial combination of methotrexate (MTX) and a glucocorticoids (GCs) bridging scheme (COBRA Slim) including a subsequent treat-to-target approach, can lead to a good and sustained disease control on the long term, irrespective of patient's prognosis. This COBRA Slim regimen resulted in comparable outcomes after 2 and 5 years as more complex

regimens, and showed a more favourable safety profile. Therefore, this strategy with fewer drugs may avoid unnecessary overtreatment in patients sufficiently responding. Furthermore, the COBRA-Slim strategy with its consecutive adaptation steps seemed to result in biologicals being initiated at a later stage, assuming a better cost-effectiveness, which was confirmed in a separate cost-effectiveness analysis by our research group. Therefore, the COBRA Slim scheme was considered as an efficacious, safe and cost-effective treatment strategy for every patient with RA.

In the first part of the second chapter we explored how we could further refine the optimal treatment strategy for early RA, by investigating the effectiveness of different maintenance therapies once patients achieved a well-controlled disease state. Firstly, we compared the effectiveness of stepping down treatment to either MTX or to leflunomide (LEF) in a randomized setting, in patients who achieved low disease activity after an initial combination of MTX, LEF and a GCs bridging scheme. Our results indicated that within this setting, it was more beneficial to step down to MTX than to LEF, since this maintenance therapy led to numerically better clinical outcomes after 65 weeks, had a better retention rate with 20% more patients remaining on MTX monotherapy and was tolerated equally well. These findings could also hold true for patients achieving low disease activity after addition of LEF to MTX monotherapy because of an initial insufficient response, although we were unable to formally demonstrate this based on this trial design.

In the second part of the second chapter, we evaluated to what extent rheumatologists adhered to the treat-to-target (T2T) approach within the treatment strategies studied. We defined adherence as performing a dose escalation or changing/adding DMARDs in case low disease activity was not achieved. Results indicated that applying T2T strictly during the first 2 years of treatment was challenging, since in only half of visits theoretically requiring a DMARD adaptation, treatment was intensified. The most frequent reason not to intensify treatment, given by rheumatologists during the first study year, was that they considered the disease already well-controlled. Strict application of T2T guidance at every visit was associated with higher remission rates after 2 years, after adjusting for factors known to potentially influence chances at remission. However, an exact cause-effect relationship could not be demonstrated, due to the potential effect of various other factors. Furthermore, stating that T2T should always be applied without restriction, could also lead to a risk for overtreatment in certain cases and hence increased

occurrence of (dose related) DMARD side effects. Therefore, we advocate for a flexible tight control, which states that decisions to adapt treatment should not be made blindly based on ambiguous or too ambitious target measures but should be based on the individual clinical picture.

In the third chapter, we evaluated the prevalence of comorbidities in early RA patients before initiation of DMARD treatment and the impact of comorbidities on treatment response. We demonstrated that even in this early phase of the disease there was a high prevalence of comorbidities with nearly half of patients in our sample having at least one clinically relevant comorbidity. Additionally, we showed that having a comorbidity, but also the degree of comorbidity before treatment initiation was significantly related to worse functionality, worse disease control and worse physical health related quality of life as well as more hospitalizations. This effect of comorbidity on treatment response, could apparently not be mitigated by using intensive treatment regimens and applying the treat-to-target principle. Because of this impact of comorbidity on clinically important outcomes, the focus of caring for patients with newly diagnosed RA should not only be on controlling disease activity as soon as possible, which is necessary for all patients, but also on the management of comorbidities. Since many comorbidities are amenable to preventive and therapeutic measures, they should be detected and taken care of at an early stage, in order to reduce their impact on the outcomes in RA.

Conclusion

This doctoral thesis gives indications on how care for patients with early RA can be improved. Firstly, an initial combination of MTX and a GC bridging scheme led to sustained effectiveness and was well tolerated in patients with early RA. Secondly, stepping down treatment to MTX instead of to LEF was more beneficial in patients who achieved a good disease control after an initial intensive combination of both these drugs. Thirdly, it seems that we should be strict in our evaluation of the disease status but flexible in our approach to improve it further. And lastly, comorbidities should be screened for and managed already from disease onset since they affect clinical outcomes despite intensive treatment. These results provide directions to optimize pharmacological treatment and management of early RA, with the overall aim to improve patients' health related quality of life.

SAMENVATTING

Inleiding

Reumatoïde artritis (RA) is een auto-immuunziekte met een wereldwijde prevalentie van ongeveer 5 per 1000 volwassenen. Deze chronische systemische ziekte wordt gekenmerkt door ontsteking van voornamelijk de kleine gewrichten van handen en voeten met pijn, zwelling en stijfheid. Indien onvoldoende behandeld kan dit ontstekingsproces leiden tot een slechter lichamelijk functioneren, verminderde arbeids- en sociale participatie en uiteindelijk tot gewrichtsschade door verlies van gewrichtskraakbeen en botaantasting. Het is cruciaal om zo snel mogelijk een effectieve behandeling te starten bij patiënten met RA om het doel van remissie of op zijn minst lage ziekteactiviteit te bereiken. De behandeling moet snel worden aangepast indien het behandelingsdoel nog niet werd behaald, volgens het 'treat-to-target' principe.

Methoden

Dit doctoraatsonderzoek is gebaseerd op gegevens van de 2-jarige "Care in early RA" (CareRA) studie en van de 3-jarige observationele CareRA plus opvolgstudie. Het algemene doel van dit proefschrift was het evalueren van de effectiviteit op lange termijn van de intensieve behandelingsstrategieën die werden gebruikt in CareRA, om zo een optimale aanpak te definiëren voor de behandeling van patiënten met beginnende RA. Voor de verschillende behandelingsschema's werden de werkzaamheid, veiligheid, duurzaamheid van de behandelingsrespons en de noodzaak van aanpassingen aan de behandeling, geëvalueerd tot 2 en 5 jaar na aanvang van de behandeling. Bovendien werd de toepasbaarheid van deze regimes onderzocht in een context die dicht aanleunt bij de klinische praktijk door de volgende vragen te beantwoorden: of de aanwezigheid van significante comorbiditeiten de uitkomsten zou beïnvloeden, welke onderhoudstherapie moet worden gebruikt zodra patiënten voldoende klinische respons hebben bereikt en in hoeverre houden reumatologen zich aan deze strategieën?

Resultaten

In het eerste hoofdstuk werd de effectiviteit van initiële behandelingsstrategieën voor patiënten met beginnende RA op de lange termijn onderzocht. We

concludeerden dat een initiële combinatie van methotrexaat (MTX) en een glucocorticoïden (GCs) overbruggingsschema (COBRA Slim) inclusief een daaropvolgende toepassing van het 'treat-to-target' principe, kan leiden tot een goede en aanhoudende ziektecontrole op lange termijn, ongeacht de prognose van de patiënt. Dit COBRA Slim-schema resulteerde in vergelijkbare resultaten na 2 en 5 jaar als meer complexe behandelingsschema's en vertoonde een gunstiger veiligheidsprofiel. Zodoende kan deze strategie met minder medicijnen een onnodige overbehandeling voorkomen bij patiënten die voldoende reageren. Bovendien leek de COBRA-Slim-strategie met zijn opeenvolgende aanpassingsstappen ertoe te leiden dat biologische geneesmiddelen in een later stadium worden geïnitieerd, zodat een betere kosteneffectiviteit kan worden verondersteld, wat inderdaad werd bevestigd in een afzonderlijke kosteneffectiviteitsanalyse door onze onderzoeksgroep. Daarom kunnen we het COBRA Slim-schema beschouwen als een effectieve, veilige en kosteneffectieve behandelingsstrategie voor elke patiënt met RA.

In het eerste deel van het tweede hoofdstuk hebben we onderzocht hoe we de optimale behandelingsstrategie voor beginnende RA verder konden verfijnen, door de effectiviteit van verschillende onderhoudstherapieën te onderzoeken zodra patiënten een goed gecontroleerde ziektetoestand bereikten. Ten eerste, vergeleken we de effectiviteit van het afbouwen van de behandeling naar ofwel MTX ofwel naar leflunomide (LEF) in een gerandomiseerde setting, bij patiënten die een lage ziekteactiviteit bereikten na een eerste combinatie van MTX, LEF en een GCs-overbruggingsschema. Onze resultaten gaven aan dat het in deze context gunstiger was om over te stappen op MTX dan op LEF, aangezien deze onderhoudstherapie leidde tot numeriek betere klinische resultaten na 65 weken, een beter retentiepercentage had met 20% meer patiënten die op MTX als monotherapie bleven, en het even goed verdragen werd. Deze bevindingen kunnen ook gelden voor patiënten die een lage ziekteactiviteit bereiken na toevoeging van LEF aan MTX-monotherapie vanwege een aanvankelijke onvoldoende respons, hoewel we dit op basis van dit onderzoeksontwerp niet formeel konden aantonen.

In het tweede deel van het tweede hoofdstuk hebben we geëvalueerd in hoeverre reumatologen de treat-to-target (T2T) benadering volgden binnen de bestudeerde behandelstrategieën. We definieerden therapietrouw als het uitvoeren van een dosisverhoging of het wijzigen / toevoegen van DMARD's in het geval dat een lage

ziekteactiviteit niet werd bereikt. De resultaten gaven aan dat het strikt toepassen van T2T tijdens de eerste 2 jaar van de behandeling een uitdaging was, aangezien in slechts de helft van de bezoeken die theoretisch een DMARD-aanpassing vereisten, de behandeling werd geïntensiveerd. De meest voorkomende reden om de behandeling niet te intensiveren, gegeven door reumatologen tijdens het eerste studiejaar, was dat ze de ziekte al goed onder controle vonden. De strikte toepassing van T2T-begeleiding bij elk bezoek werd in verband gebracht met hogere remissiepercentages na 2 jaar, na correctie voor factoren waarvan bekend is dat ze de kans op remissie mogelijk beïnvloeden. Een exacte oorzaak-gevolgrelatie kon echter niet worden aangetoond vanwege het mogelijke effect van verschillende andere factoren. Bovendien zou het stellen dat T2T altijd onbeperkt moet worden toegepast, in bepaalde gevallen ook kunnen leiden tot een risico op overbehandeling en daarmee een verhoogd optreden van (dosisgerelateerde) DMARD-bijwerkingen. Daarom pleiten we voor een flexibele-strakke controle, die stelt dat beslissingen om de behandeling aan te passen niet blindelings moeten worden genomen op basis van dubbelzinnige of te ambitieuze doelstelling, maar gebaseerd moeten zijn op het individuele klinische beeld.

In het derde hoofdstuk evalueerden we de prevalentie van comorbiditeiten bij patiënten met beginnende RA vóór aanvang van de DMARD-behandeling en de impact van comorbiditeit op de respons op de behandeling. We toonden aan dat zelfs in deze vroege fase van de ziekte er een hoge prevalentie van comorbiditeiten was, waarbij bijna de helft van de patiënten in onze steekproef ten minste één klinisch relevante comorbiditeit had. Bovendien toonden we aan dat het hebben van een comorbiditeit, maar ook de graad ervan, vóór de start van de behandeling, significant verband hield met slechtere functionaliteit, slechtere ziektecontrole en slechtere lichamelijke gezondheidsgerelateerde kwaliteit van leven, evenals met meer ziekenhuisopnames. Dit effect van comorbiditeiten op de respons op de behandeling kon blijkbaar niet worden beperkt door het toepassen van de intensieve behandelingsschema's en het 'treat-to-target'-principe. Vanwege deze impact van comorbiditeiten op klinisch belangrijke resultaten, moet de zorg voor patiënten met nieuw gediagnosticeerde RA niet alleen gericht zijn op het zo snel mogelijk beheersen van de ziekteactiviteit, wat nodig is voor alle patiënten, maar ook op het management van comorbiditeiten. Aangezien veel comorbiditeiten vatbaar zijn voor preventieve en therapeutische maatregelen, moeten ze in een vroeg stadium

worden opgespoord en aangepakt worden om hun impact op de uitkomsten bij RA te verminderen.

Besluit

Dit proefschrift geeft aanwijzingen hoe de zorg voor patiënten met vroege RA kan worden verbeterd. Ten eerste was een initiële combinatiebehandeling van MTX en een GC-overbruggingsschema blijvend effectief op lange termijn en werd het goed verdragen door patiënten met beginnende RA. Ten tweede bleek het afbouwen van de behandeling naar MTX in plaats van naar LEF gunstiger bij patiënten die een goede ziektecontrole hadden bereikt na een initiële intensieve combinatie van beide geneesmiddelen. Ten derde lijkt het erop dat we streng moeten zijn in onze evaluatie van de ziektestatus, maar flexibel in onze aanpak om deze verder te verbeteren. En tot slot moeten comorbiditeiten al vanaf het begin van de ziekte worden gescreend en aangepakt, aangezien ze de klinische resultaten beïnvloeden ondanks intensieve behandeling. Deze resultaten bieden richtlijnen om de farmacologische behandeling en de aanpak van beginnende RA te optimaliseren, om zo algemeen de gezondheidsgerelateerde kwaliteit van leven van patiënten te verbeteren.

SCIENTIFIC ACKNOWLEDGEMENT

PERSONAL CONTRIBUTION

CONFLICT OF INTEREST STATEMENT

SCIENTIFIC ACKNOWLEDGEMENT

Chapter 1.1

The following authors were involved in this study: Veerle Stouten (VS), Rene´ Westhovens (RW), Sofia Pazmino (SP), Diederik De Cock (DDC), Kristien Van der Elst (KVdE), Johan Joly (JJ) and Patrick Verschueren (PV) on behalf of the CareRA study group*

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Data entry: PV and JJ were responsible for coordination of the trial and of collection of data. Data was entered by study staff of the CareRA trial and VS

Data analysis: VS was responsible for data analysis

All authors were involved in the interpretation of the data, in drafting the article, or revising it critically for important intellectual content. All authors approved the final version before publication

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Study conception and design: PV, JJ and RW designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including PV and RW recruited and enrolled patients and were responsible for daily patient management. PV, RW and VS were involved in study conception.

Data entry: PV and JJ were responsible for coordination of the trial and of collection of data. Data was entered by study staff of the CareRA plus study and VS

Data analysis: VS was responsible for data analysis.

All authors contributed to interpretation of the data. Furthermore, VS, PV, DDC and RW drafted the manuscript. DDC, SP, KVdE, DB and JJ revised it critically for important intellectual content. All authors have approved the final draft to be submitted for publication.

PERSONAL CONTRIBUTION

The following section summarizes the contribution of Veerle Stouten to this PhD thesis

Introduction and general discussion: I drafted the general introduction and the general discussion based on advice and feedback from my promoters.

Chapter 1.1: I worked previously before starting my PhD as a study coordinator on the CareRA trial, so I had the unique opportunity to become familiar into detail with its concept and conduct and I was involved in data collection. Furthermore, I was involved in data analysis and interpretation. I drafted and revised the manuscript together with Patrick Verschueren and René Westhovens.

Chapter 1.2: As study coordinator I was involved in data collection and data entry of the CareRA plus study, specifically for the site of University Hospitals Leuven. Thereafter, as PhD fellow I was involved in the coordination of the ongoing CareRA plus study, together with Johan Joly to ensure data collection and entry. I was responsible for data analysis and interpretation, together with Sofia Pazmino. I drafted and revised the manuscript based on feedback from the co-authors.

Chapter 2.1: I was involved in the data collection and performed the statistical analyses, together with Stijn Michiels. I drafted and revised the manuscript in cooperation with Stijn Michiels and based on the feedback from my supervisors.

Chapter 2.2: I was involved in the data collection and performed the statistical analysis. I drafted and revised the manuscript based on the feedback from my supervisors.

Chapter 3: I was involved in the design, collected data and performed the statistical analysis after advice from a statistician. I drafted and revised the manuscript based on the feedback from my supervisors.

CONFLICT OF INTEREST

The CareRA trial was made possible by a grant from the Flemish Governmental Agency for Innovation by Science and Technology (IWT). Patrick Verschueren holds the unrestricted Pfizer Chair for 'Early Rheumatoid Arthritis Management' at the KU Leuven and grants were also provided by the Fund for Scientific Research in Rheumatology (FWRO) and the Academic Foundation of Leuven. Leflunomide was made available for free by SANOFI Belgium without any influence on trial design. The funders of the study had no role in study design, data collection, analysis and interpretation or reporting of this study.

The authors have no conflicts of interest to disclose for the work within this PhD thesis. There was no other support from any organisation for the work of this thesis than those listed above, no financial relationships with any organisations that might have an interest in the work in the previous three years and no other relationships or activities that could appear to have influenced the work in this PhD thesis.

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CURRICULUM VITAE

LIST OF PUBLICATIONS

CURRICULUM VITAE

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Veerle Stouten was born in Bonheiden, Belgium on 2 September 1987. She is married to Mohsine Dani and mum of her 1-year old (amazing) daughter Alina.

Education

2016-present	PhD Fellow in Biomedical Sciences – University of Leuven
2009-2011	Master in Biomedical Sciences – University of Leuven Minor Research, management and communication Graduated with distinction
2009-2011	Research Tracks – University of Leuven Neurobiology, Oncology and Molecular and Cellular Medicine
2005-2009	Bachelor in Biomedical Sciences – University of Leuven
1999-2005	General High School - Sint-Theresiacollege Kapelle-op-den-Bos Graduated with distinction in Latin-Sciences

Professional experience

2016-2020	PhD Fellow at the Research Center for Skeletal Biology and Engineering – University of Leuven
2016-2020	Supervision of undergraduate students of (master thesis of Medicine, Biomedical Sciences and Pharmaceutical Sciences)
2011-2015	Clinical Research Coordinator at the Department of Rheumatology - University hospitals of Leuven
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Grants and awards

2020	European League Against Rheumatism grant to participate in e-Conference
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2017	European League Against Rheumatism travel grant
2017	Academische Stichting Leuven travel grant

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