RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/kez213

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

Veerle Stouten[1], René Westhovens[1,2], Sofia Pazmino[1], Diederik De Cock[1], Kristien Van der Elst[1,2], Johan Joly[2] and Patrick Verschueren[1,2] on behalf of the CareRA study group*

Abstract

Objectives. To investigate whether MTX should be combined with an additional DMARD and bridging glucocorticoids as initial treatment for patients with early RA to induce an effective long-term response.

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

Results. In the high-risk group 71/98 (72%) patients achieved a DAS28-CRP < 2.6 with COBRA-Slim compared with 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 with 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 with TSU.

Conclusion. 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, irrespective of patients' prognosis.

Trial registration. ClinicalTrials.gov, http://www.clinicaltrials.gov, NCT01172639.

Key words: early rheumatoid arthritis, DMARDs (synthetic), treatment, glucocorticoids, methotrexate, effectiveness

Rheumatology key messages

- Compared with DMARD combi-therapy, methotrexate monotherapy with glucocorticoid bridging (COBRA-Slim) resulted in similar two-year effectiveness.
- COBRA-Slim is an effective induction regimen, avoiding overtreatment and adverse reactions within a treat-to-target strategy.
- All patients with early RA might benefit from an initial moderately-dosed glucocorticoid bridging scheme.

[1]Department of Development and Regeneration, Skeletal Biology and Engineering Research Centre, KU Leuven and [2]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium

Submitted 23 November 2018; accepted 3 March 2019

*See acknowledgements section for a list of the CareRA study group.

Correspondence to: Veerle Stouten, Department of Development and Regeneration, Skeletal Biology and Engineering Research Centre, Herestraat 49, 3000 Leuven, Belgium.
E-mail: veerle.stouten@kuleuven.be

CLINICAL SCIENCE

Introduction

Current guidelines to treat 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 DMARD (csDMARD) 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 two-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 two-year randomized open-label pragmatic trial evaluating different treatment regimens, based on the original COBRA (Combination therapy for early RA) strategy for patients with early RA [9]. Investigators from 13 Flemish rheumatology centres (two academic centres, seven general hospitals and four 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 $<$1 year ago, were naïve to and had no contraindications for csDMARDs or glucocorticoids (Supplement 1, available at *Rheumatology* online).

Treatment protocol

Before randomization, 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, available at *Rheumatology* online). Randomization was performed via a digitally generated sequence in the electronic case report form. Patients in the high-risk group were randomized into one of three treatment arms:

COBRA-Classic
15 mg MTX weekly, 2 g sulfasalazine daily and a weekly step-down scheme of oral prednisone (60–40–25–20–15–10–7.5 mg daily).

COBRA-Slim
15 mg MTX weekly and a weekly step-down scheme of oral prednisone (30–20–12.5–10–7.5–5 mg daily).

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 daily).

Patients in the low-risk group were randomized into one of two treatment arms: COBRA-Slim; or 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, available at *Rheumatology* online). Prophylactic treatment with oral folic acid, calcium and vitamin D was prescribed. Participants received face-to-face education, printed medication schemes and standardized info-material (leaflet, DVD and website).

Response to therapy was evaluated at each visit by measuring the 28 joint DAS using CRP (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 $\leqslant$ 3.2) was not achieved. As a first step, 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 10 mg daily (Supplement 2, available at *Rheumatology* online).

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 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 ACR-EULAR Boolean criteria [10]. Additionally, physical function was assessed by the 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 three readers, retaining the mean score.

Sustainability of the initial response to therapy was analysed by the two-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 >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 end point to demonstrate superiority. Analysis of the low-risk population was exploratory.

We performed an intention-to-treat analysis including all randomized 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 week 28 and week 52 [14]. A sensitivity analysis on the population completing the two-year study was performed.

Clinical outcomes, safety and treatment adaptations were examined by χ^2, 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, 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 randomized to COBRA-Classic ($n = 98$), COBRA-Slim ($n = 98$) or COBRA-Avant-Garde ($n = 93$). Patients in the low-risk group were randomized to COBRA-Slim ($n = 43$) or TSU ($n = 47$). All randomized 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 (Fig. 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% CI -19.7, 5.8) between Slim and Classic and of 1.7% (95% CI -10.8, 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 three treatment arms at year 2. Analyses using data from participants who completed the trial showed comparable outcomes (Supplement 3, available at *Rheumatology* online).

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%) *vs* 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 with 31/41 (76%) on TSU at year 2 (Supplement 3, available at *Rheumatology* online).

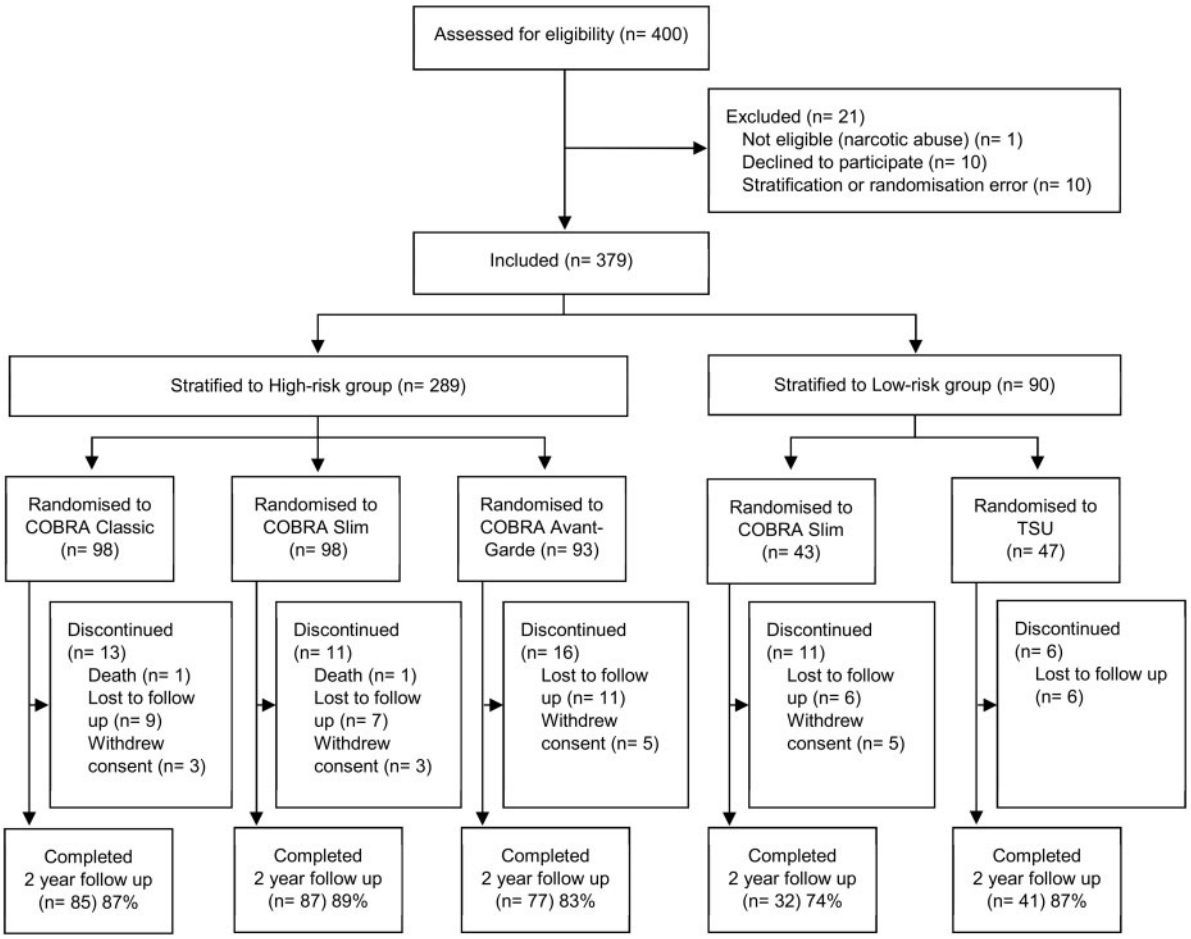
During the entire trial, 14/314 patients (4%) had a radiographic progression above the smallest detectable difference of >3.3 and the overall mean (S.D.) change in SvdH score was 0.6 (1.4). Mean SvdH progression scores did not differ between treatment arms ($P = 1.00$ in both risk groups) (Table 2) (Supplement 4, available at *Rheumatology* online).

Sustainability of treatment response

The evolution of mean disease activity and HAQ scores over the two-year period showed a similar rapid and stable response in all high-risk treatment arms (Fig. 2) with minimal changes during the second year. In the linear mixed model analyses, 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, *vs* 61% for COBRA-Slim and 61% for COBRA-Avant-Garde (log-rank; $P = 0.19$) (Fig. 3).

In the low-risk group, there were minimal changes in mean disease activity or HAQ scores during the second

Fig. 1 Flow chart of participants during the two-year trial



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

year (Fig. 2). In the linear mixed model analysis, participants on COBRA-Slim had lower DAS28-CRP scores over 2 years with a mean difference of 0.37 (95% CI 0.0, 0.7; $P = 0.04$) compared with 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; $P = 0.38$) (Fig. 3).

Treatment adaptations

At the two-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 (Fig. 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 (Fig. 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 (interquartile range) prednisone equivalent dose of 5.6 mg (3.3) daily. Almost half of those patients (30/64) were treated simultaneously with a biologic DMARD. 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 the TSU arm (22; 47%) received glucocorticoid injections compared with patients in the 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, available at *Rheumatology* online).

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

	High-risk			Low-risk	
	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/m^2	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; DAS28: DAS based on 28 joints; IQR: interquartile range; PGA: patient's global assessment; PhGA: physician's global assessment; TSU: Tight Step Up.

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, available at *Rheumatology* online). Being treated with COBRA-Slim regimen resulted in less therapy-related AEs compared with 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 AE in the High-Risk group ($P = 0.11$).

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 a 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 with 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, *vs* the other treatment arms. At the two-year visit, slightly more COBRA-Slim patients were taking a combination of csDMARDs, instead of a biologic DMARD at year 2, compared with the other arms. This trend towards a lower or delayed initiation rate of more expensive biologic DMARDs, especially during year 1, can potentially lead to a better cost

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

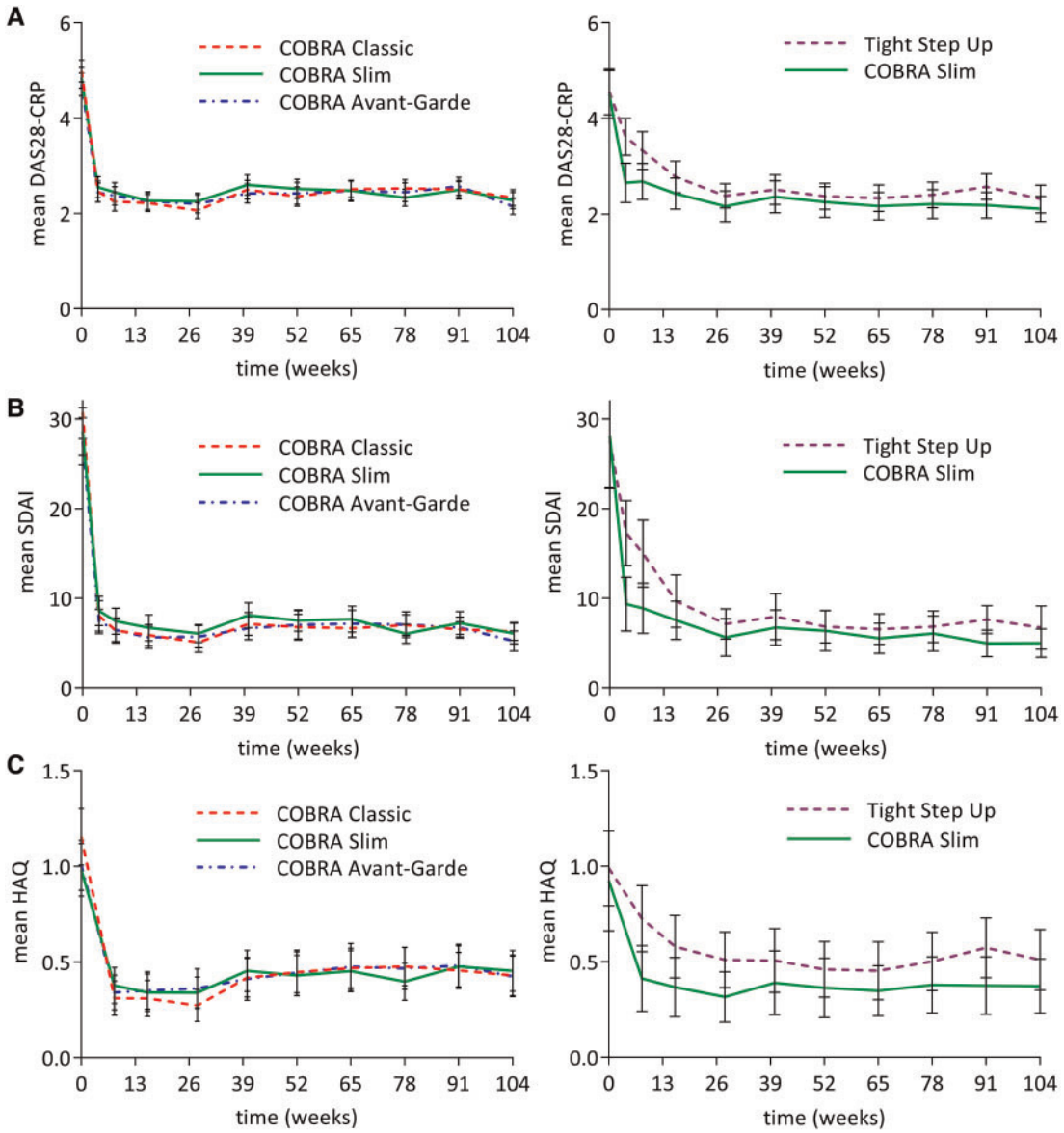
	High-risk						
	COBRA Classic *n* = 98	COBRA Slim *n* = 98	COBRA Avant-Garde *n* = 93	*P*-value	Adjusted *P*-value	Δ COBRA Slim *vs* Classic (95% CI)	Δ COBRA Slim *vs* Avant-Garde (95% CI)
DAS28-CRP <2.6	64 (65)	71 (72)	69 (74)	0.36	1.00	−7.1 (−19.7, 5.8)	1.7 (−10.8, 14.1)
DAS28-CRP ⩽3.2	86 (88)	86 (88)	85 (91)	0.65	1.00	0.0 (−9.4, 9.4)	3.6 (−5.4, 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, 0.4)	0.0 (−0.4, 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, 0.1)	0.0 (−0.3, 0.3)
Good EULAR response	81 (83)	81 (83)	73 (79)	0.70	1.00	0.0 (−10.7, 10.7)	−4.2 (−15.4, 7.1)
Moderate EULAR response	91 (93)	93 (95)	86 (93)	0.77	1.00	−2.0 (−9.5, 5.2)	−2.4 (−10.2, 4.9)
SDAI remission ⩽3.3	31 (32)	28 (29)	41 (44)	0.06	0.96	3.1 (−9.7, 15.7)	15.5 (1.9, 28.4)
SDAI LDA ⩽11	88 (90)	86 (88)	86 (93)	0.55	1.00	2.0 (−7.1, 11, 2)	4.7 (−4.1, 13.5)
CDAI remission ⩽2.8	30 (31)	29 (30)	44 (47)	0.02	0.34	1.0 (−11.7, 13.7)	17.7 (3.9, 30.6)
CDAI LDA ⩽10	88 (90)	87 (89)	83 (89)	0.97	1.00	1.0 (−8.0, 10.0)	0.5 (−8.8, 9.6)
ACR-EULAR boolean remission	21 (21)	20 (20)	21 (23)	0.94	1.00	1.0 (−10.4, 12.4)	2.2 (−9.4, 13.8)
HAQ = 0	34 (35)	34 (35)	29 (31)	0.84	1.00	0.0 (−13.1, 13.1)	−3.5 (−16.5, 9.7)
HAQ change from BL	0.7 (0.7)	0.5 (0.7)	0.6 (0.7)	0.18	1.00	0.2 (0.0, 0.4)	0.1 (−0.1, 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, 0.1)	0.0 (−0.1, 0.1)
Clinically meaningful HAQ change	71 (72)	62 (63)	64 (69)	0.38	1.00	9.2 (−3.9, 21.8)	5.6 (−7.8, 18.6)
No of X-ray pairs	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, 0.2)	−0.3 (−0.8, 0.2)
SvdH progression >SDD	3 (4)	6 (8)	3 (4)	0.45	1.00	−3.8 (−12.0, 4.1)	−3.8 (−12.0, 4.1)

	Low-risk				
	COBRA Slim *n* = 43	TSU *n* = 47	*P* value	Adjusted *P* value	Δ COBRA Slim *vs* TSU (95%CI)
DAS28-CRP remission <2.6	29 (67)	34 (72)	0.61	1.00	4.9 (−13.7, 23.3)
DAS28-CRP LDA ⩽3.2	36 (84)	41 (87)	0.64	1.00	3.5 (−11.3, 18.8)
DAS28-CRP change from BL	2.4 (1.7)	2.2 (1.9)	0.58	1.00	−0.2 (−0.9, 0.6)
DAS28-CRP change from year 1	0.1 (0.8)	0.1 (0.9)	0.61	1.00	−0.1 (−0.4, 0.3)
Good EULAR response	27 (63)	28 (60)	0.76	1.00	−3.2 (−22.4, 16.4)
Moderate EULAR response	38 (88)	37 (79)	0.22	1.00	−9.6 (−24.8, 6.2)
SDAI remission ⩽3.3	20 (47)	13 (28)	0.06	0.96	−18.9 (−36.9, 1.0)
SDAI LDA ⩽11	37 (86)	42 (89)	0.63	1.00	3.3 (−10.7, 17.9)
CDAI Remission ⩽2.8	21 (49)	13 (28)	0.04	0.68	−21.2 (−39.1, −1.2)
CDAI LDA ⩽10	37 (86)	40 (85)	0.90	1.00	−0.9 (−15.7, 14.3)
ACR-EULAR boolean remission	16 (37)	9 (19)	0.06	0.96	−18.1 (−35.4, 0.5)
HAQ change from BL	0.6 (0.8)	0.5 (0.7)	0.81	1.00	−0.1 (−0.4, 0.2)
HAQ change from year 1	0.0 (0.3)	0.0 (0.3)	0.86	1.00	0.0 (−0.2, 0.1)
Clinically meaningful HAQ change	25 (58)	26 (55)	0.79	1.00	−2.8 (−22.3, 17.1)
HAQ = 0	17 (40)	15 (32)	0.45	1.00	−7.6 (−26.4, 11.8)
No of X-ray pairs	33 (77)	41 (87)			
SvdH change from BL	0.3 (0.7)	0.5 (1.3)	0.60	1.00	0.2 (−0.3, 0.7)
SvdH progression >SDD	0 (0)	2 (5)	0.20	1.00	4.9 (−6.1, 16.1)

Data are presented as absolute number of patients (percentages) or as mean change (s.d.). *P*-values are adjusted by the Holm test to correct for multiplicity.

DAS28-CRP: DAS based on 28 joints calculated with CRP; 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); clinically meaningful HAQ change: HAQ change >0.22; No of X-ray pairs: number of available X-rays pairs at baseline and year 2 after imputation; SvdH: Sharp van der Heijde score; SDD: smallest detectable change; TSU: Tight Step Up.

Fig. 2 Clinical efficacy outcomes during 2 years of follow up

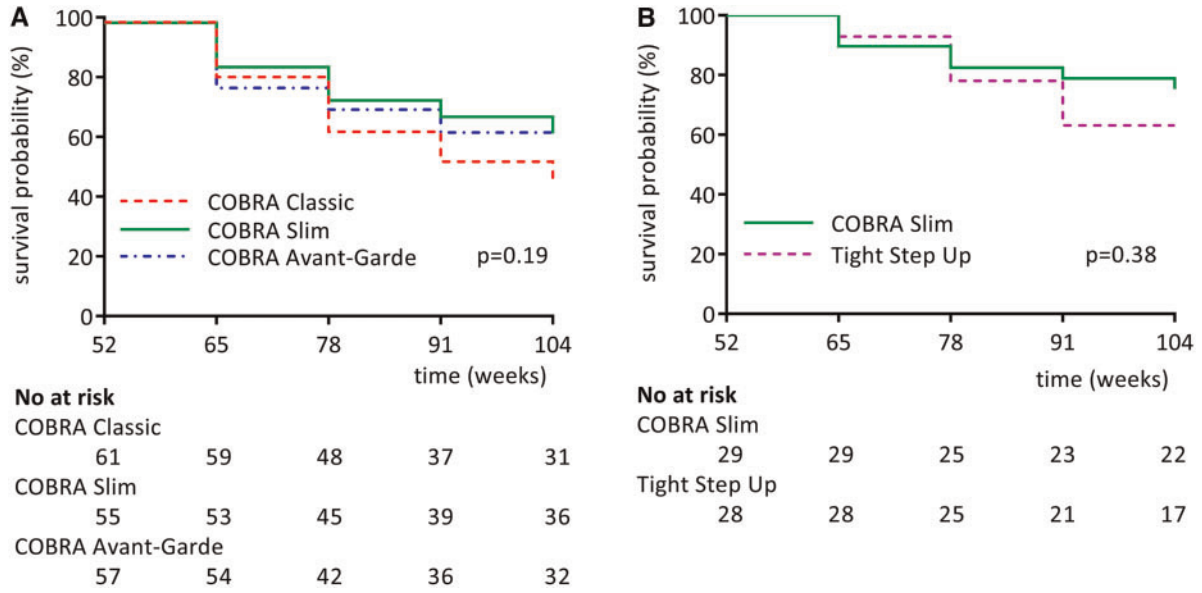


Clinical efficacy outcomes are displayed for high-risk group (left) and low-risk group (right); Error bars indicate the 95% CIs; (**A**) Mean disease activity measured by DAS28-CRP or (**B**) by SDAI; DAS28-CRP: DAS based on 28 joints calculated with CRP; SDAI: Simplified Disease Activity Index; (**C**) Mean physical function measured by HAQ.

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 fewer 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 the TSU arm needed more glucocorticoid injections and seemingly

FIG. 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.

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 end point was based on the DAS28-CRP, which might not be stringent enough, as 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.

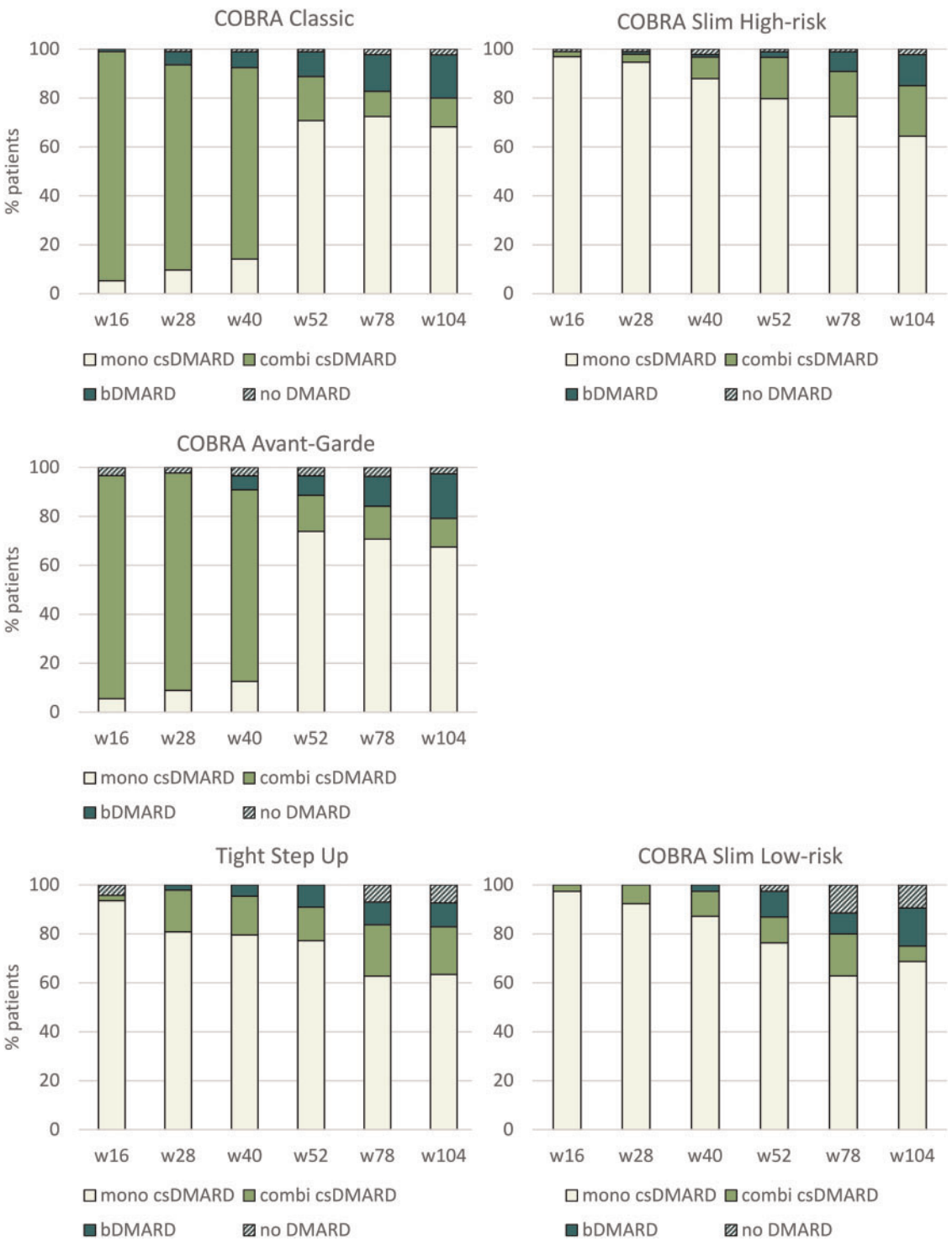
We aimed for remission but used the cut-off of low disease activity (DAS28-CRP $\leqslant$ 3.2) to decide whether to adapt treatment; this threshold was deliberately not set lower to avoid changing therapy too rapidly or too often, which might increase the risk of side effects and of rheumatologists' 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 biologic 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 with 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.

Fig. 4 DMARD treatment taken by participants during 2 years of follow up in each treatment arm



Percentages of patients calculated on patients still in follow-up at each visit. bDMARD taken with or without a csDMARD. w: week; csDMARD: conventional synthetic DMARD; bDMARD: biologic DMARD.

Acknowledgements

We would like to show our gratitude to all participating patients, as well as to the investigators and medical staff at all sites. We thank Sylvie Van Vlasselaer and all other study personnel for their contributions to the study. We would also like to thank medical student Amy Belba for her help in scoring the X-rays and statistician Anikó Lovik for her advice.

Collaborators, on behalf of the CareRA study group are as follows: Maeyaert B, De Brabanter G, Devinck M, Langenaken C, Lenaerts J, Corluy L, Remans J, Vander Cruyssen B, Ravelingien I, Van Essche E, Vandevyvere K, Durnez A, Verbruggen A, Geens E, Raeman F, Joos R, de Vlam K, Taelman V, Vanhoof J, Coppens M, Geusens P, Sileghem A, Volders P, Van Den Bosch F, Verschueren P, Westhovens R.

P.V., J.J. and R.W. designed the study protocol in collaboration with the CareRA study group. Investigators of the CareRA study group, including P.V. and R.W. recruited and enrolled patients and were responsible for daily patient management. P.V. and J.J. were responsible for coordination of the trial and of collection of data. V.S. was responsible for data analysis. All authors contributed to interpretation of the data. Furthermore, V.S., P.V. and R.W. drafted the manuscript. D.D.C., S.P., K.V.dE. and J.J. revised it critically for important intellectual content. All authors have approved the final draft for publication. P.V. and V.S. are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

The study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each participating centre (ref s51411) and all study participants gave their written informed consent before inclusion.

The authors commit to making the relevant anonymized patient level data available for a specified purpose approved by the institution and the principal investigator of the CareRA study and with a signed data access agreement.

P.V. and V.S. affirm that this manuscript is an honest, accurate and transparent account of the study being reported.

The pragmatic CareRA protocol was strongly inspired by daily interactions of the investigators with RA patients in daily clinical practice. Results of this research will be disseminated to study participants, all stakeholders and the general public in collaboration with patient organizations and the Belgian patient partners program (trained patients who educate physicians, medicine students and other health care professionals in collaboration with a rheumatologist).

Funding: This RCT was supported by a grant from the Flemish Governmental Agency for Innovation by Science and Technology (IWT). P.V. 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 had no role in study design, data collection, analysis and interpretation or reporting of this study.

Disclosure statement: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work other than those listed above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Smolen JS, Aletaha D, Barton A *et al*. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.

2 Smolen JS, Landewe R, Bijlsma J *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

3 van Nies JA, Krabben A, Schoones JW *et al*. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis 2014;73:861–70.

4 Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol 2003;21:S154–7.

5 Cush JJ. Early rheumatoid arthritis—is there a window of opportunity? J Rheumatol Suppl 2007;80:1–7.

6 Verschueren P, De Cock D, Corluy L *et al*. Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis 2017;76:511–20.

7 Verschueren P, De Cock D, Corluy L *et al*. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. Ann Rheum Dis 2015;74:27–34.

8 Verschueren P, De Cock D, Corluy L *et al*. Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. Arthritis Res Ther 2015;17:97.

9 Boers M, Verhoeven AC, Markusse HM *et al*. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine

alone in early rheumatoid arthritis. Lancet 1997;350:309–18.

10 Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity 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 2011;63(Suppl 11):S14–36.

11 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes 2003;1:20.

12 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.

13 Dempster AL, Rubin DB. Maximum Likelihood from Incomplete Data via the EM Algorithm. J R Stat Soc Series B Stat Methodol 1977;39:1–38.

14 Markusse IM, Landewe R, Wolterbeek R *et al*. Linear extrapolation of missing radiographic change scores in clinical trials does not spuriously overestimate group radiographic changes in rheumatoid arthritis. Rheumatology 2016;55:1295–300.

15 Dmitrienko A, D'Agostino RB Sr. Multiplicity considerations in clinical trials. N Engl J Med 2018;378:2115–22.

16 Verschueren P, Westhovens R. The use of glucocorticoids in early rheumatoid arthritis. Rheumatology 2018;57:1316–7.

17 Buttgereit F, Bijlsma JW. Glucocorticoids in rheumatoid arthritis: the picture is shaping up. Ann Rheum Dis 2017;76:1785–7.

18 Pazmino SS, Westhovens R, Joly J *et al*. OP0301 Two year cost-effectiveness analysis of the CareRA trial in early RA: a piggy back study. Ann Rheum Dis 2018;77(Suppl 2):197. https://ard.bmj.com/content/77/Suppl_2/197.1.

19 Landewé RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. Ann Rheum Dis 2018;77:1394–6.

20 van der Elst K, Meyfroidt S, De Cock D *et al*. Unraveling patient-preferred health and treatment outcomes in early rheumatoid arthritis: a longitudinal qualitative study. Arthritis Care Res 2016;68:1278–87.

21 Meyfroidt S, Van der Elst K, De Cock D *et al*. Patient experiences with intensive combination-treatment strategies with glucocorticoids for early rheumatoid arthritis. Patient Educ Couns 2015;98:384–90.

22 Akdemir G, Markusse IM, Goekoop-Ruiterman YP *et al*. Rheumatologists' adherence to a disease activity score steered treatment protocol in early arthritis patients is less if the target is remission. Clin Rheumatol 2017;36:317–26.

23 ter Wee MM, den Uyl D, Boers M *et al*. Intensive combination treatment regimens, including prednisolone, are effective in treating patients with early rheumatoid arthritis regardless of additional etanercept: 1-year results of the COBRA-light open-label, randomised, non-inferiority trial. Ann Rheum Dis 2015;74:1233–40.

24 den Uyl D, ter Wee M, Boers M *et al*. A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. Ann Rheum Dis 2014;73:1071–8.

25 de Jong PH, Hazes JM, Barendregt PJ *et al*. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 2013;72:72–8.