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ORIGINAL RESEARCH

Effectiveness of methotrexate and bridging glucocorticoids with or without early introduction of a 6-month course of etanercept in early RA: results of the 2-year, pragmatic, randomised CareRA2020 trial

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ABSTRACT

Objectives To investigate if patients with early rheumatoid arthritis responding insufficiently to initial methotrexate (MTX) and bridging glucocorticoids (GCs) could benefit from early but temporary etanercept introduction as a second remission-induction attempt.

Methods CareRA2020 (NCT03649061) was a 2-year, open-label, multicentre, pragmatic randomised controlled trial. Treatment-naïve patients started MTX and GC bridging (COBRA-Slim: CS). Within a time window from week (W) 8 until W32, early insufficient responders (28-joint Disease Activity Score – C-reactive Protein (DAS28-CRP) >3.2 between W8 and W32 or ≥2.6 at W32) were randomised to a Standard-CS strategy (adding leflunomide first) or Bio-induction-CS strategy (adding etanercept for 24 weeks). Additional treatment adaptations followed the treat-to-target principle. Longitudinal disease activity (DAS28-CRP) over 104 weeks (primary outcome), achievement of DAS28-CRP <2.6 28 weeks after randomisation, and biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) use at W104 were compared between randomisation groups.

Results Following CS treatment, 142 patients were early responders; 55 early insufficient responders received Standard-CS and 55 Bio-induction-CS. Superiority of Bio-induction-CS over Standard-CS could not be demonstrated (ß=−0.204, (95% CI −0.486 to 0.078), p=0.157) for the primary outcome. More patients on Bio-induction-CS achieved DAS28-CRP <2.6 at 28 weeks after randomisation (59% (95% CI 44% to 72%) vs 44% (95% CI 31% to 59%) in Standard-CS) and they were treated less frequently with b/tsDMARDs at W104 (19/55, 35%) compared with Standard-CS (29/55, 53%).

Conclusion Half of the patients responded well to initial COBRA-Slim induction therapy. In early insufficient responders, adding etanercept for 6 months did not improve disease control over 104 weeks versus adding leflunomide first. However, temporary introduction of etanercept resulted in improved disease control early after randomisation and less patients on b/tsDMARDs at W104.

Trial registration number NCT03649061.

CTR pilot approval Belgium S59474, EudraCT number: 2017-004054-41.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Some patients with early rheumatoid arthritis (RA) have an insufficient response to initial remission-induction with methotrexate (MTX) and bridging glucocorticoids (GCs), risking unfavourable long-term outcomes.

⇒ The place and ideal timing of temporary biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) use as a potential second remission-induction attempt in the early disease phase is not yet clear.

INTRODUCTION

Treatment for rheumatoid arthritis (RA) has clearly improved with the increasing availability of drugs with different modes of action and the adoption of a treat-to-target (T2T) strategy aiming for remission or at least low

WHAT THIS STUDY ADDS

⇒ A treat-to-target (T2T) strategy starting with early introduction of 24 weeks etanercept was not superior in terms of disease control over 2 years in early insufficient responders to MTX with GC bridging.

⇒ Although with this T2T strategy patients achieved DAS28-CRP (28-joint Disease Activity Score – C-reactive Protein) <2.6 more rapidly compared with adding leflunomide first, more participants of the latter group obtained a DAS28-CRP <2.6 at week 104, although at the expense of more b/tsDMARD use.

⇒ Early insufficient responders did not reach the same level of disease control as early responders irrespective of the allocated T2T strategy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This trial not only confirms the effectiveness of initial MTX with GC bridging in patients with early RA but also highlights that an insufficient response to such a remission-induction regimen predicts a more difficult to manage disease course even with b/tsDMARD use in a T2T setting.

⇒ The optimal place of b/tsDMARDs in the early RA treatment algorithm remains unclear, but long-term clinical and economic CareRA2020 data could provide further insight.

disease activity.[1 2] The currently recommended initial treatment for early RA according to the European Alliance of Associations for Rheumatology (EULAR) consists of a conventional synthetic disease-modifying antirheumatic drug (csDMARD), usually methotrexate (MTX), combined with temporary glucocorticoids (GCs).[1] Such a remission-induction strategy aims to promptly control disease activity within a 'window-of-opportunity', improving long-term outcomes in terms of disease control, radiographic progression, functionality, and even fatigue and self-efficacy.[3–8] The CareRA trial demonstrated that approximately 70% of patients reached 28-joint Disease Activity Score – C-reactive Protein (DAS28-CRP) <2.6 after the initial 16 weeks of treatment with MTX and a step-down GC scheme (COBRA-Slim, CS).[9] However, some patients did not achieve sufficient disease control, necessitating treatment adaptations according to the treat-to-target (T2T) principle. EULAR recommends starting biologic or targeted synthetic (b/ts) DMARDs in patients insufficiently responding to initial treatment in the presence of poor prognostic factors (eg, presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA), erosions, high swollen joint count). Adding csDMARDs first may be considered in patients with good prognosis, but this recommendation warrants more research.[1] However, in many countries, reimbursement criteria require trial of a second csDMARD first, independently of prognostic factors.[1 10] Although bDMARDs combined with MTX are not recommended as first-line treatment for early RA, due to a lack of superiority compared with MTX plus GCs in terms of disease control and a problematic cost-utility,[11 12] a temporary bDMARD course in the early disease stage might be sufficient to consolidate long-term disease control.[13 14] Therefore, these fast-acting drugs could potentially be used as a second remission-induction attempt. While bearing in mind that bDMARD discontinuation is not favourable and seldom successful in established RA,[15] results of the OPTIMA trial seem to indicate that there might still be a possibility to use these drugs temporarily in the early phase of the disease.[16] Fortunately, the CareRA trial demonstrated that insufficient responders to conventional remission induction can be identified as early as 8 weeks after treatment initiation enabling early intervention with a second remission-induction attempt.[9 17] Moreover, EULAR recommends to adapt treatment if no improvement is obtained after 3 months, or the target is not reached after 6 months.[1] Timely upscaling of treatment within the time window between 3 and 6 months could potentially allow more patients to benefit from the window-of-opportunity, aiming for favourable long-term outcomes, and possibly reducing the long-term b/tsDMARD need in these patients, leading to societal cost-savings. Therefore, we aimed to investigate whether providing insufficient responders to the initial remission-induction regimen with a temporary course of a tumour necrosis factor inhibitor (TNFi) could be beneficial, taking a societal perspective.

METHODS

Study design

The 'Care in early Rheumatoid Arthritis 2020' (CareRA2020) trial was a prospective, 2-year, multicentric, open-label, pragmatic, investigator-initiated, randomised controlled trial (RCT). Patients were included in 19 centres across Belgium (seven university hospitals, nine general hospitals and three private practices).

Patients

Patients were eligible if they had a recent RA diagnosis (≤1 year) according to the American College of Rheumatology (ACR)/EULAR 2010 criteria, were DMARD-naïve and at least 18 years old. Main exclusion criteria were contraindications for MTX, leflunomide, TNFi or GC, recent GC use and underlying conditions which would place the patient at an unacceptable risk according to the investigator's opinion. Detailed inclusion and exclusion criteria can be found in online supplemental file S1. All participants provided written informed consent (ICF).

Randomisation and procedures

All patients started the initial COBRA-Slim remission-induction regimen, consisting of MTX 15 mg/week (oral) combined with a step-down prednisone scheme (30–20–12.5–10–7.5–5 mg oral prednisone daily). Every prednisone dose was maintained for 7 days, except for 5 mg, which was continued until week (W) 28, and then further tapered to 2.5 mg/day for 2 weeks before stopping completely. Patients received prophylactic treatment with folic acid, calcium and vitamin D. From W4 onwards, if the DAS28-CRP ≤3.2 target was not met, treatment was

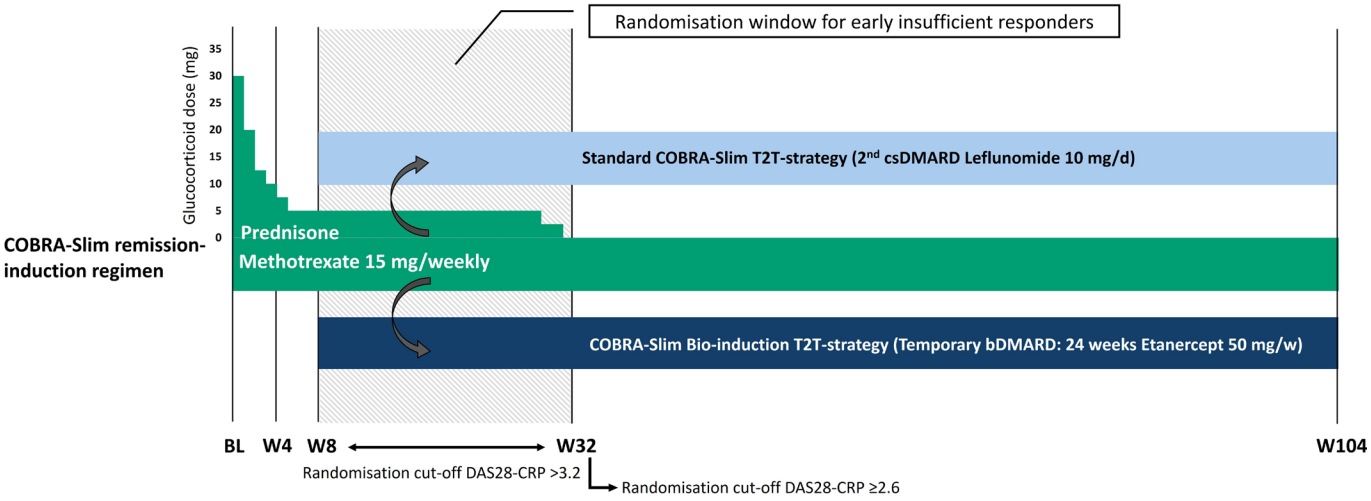

Figure 1 Study design of the CareRA2020 trial. In case of an insufficient response to initial treatment, the first adaptation was increasing methotrexate to 20 mg/week. Patients for which this was still not sufficient (=early insufficient responders) were 1:1 randomised during a time window between W8 and W32 (=randomisation window) to a T2T strategy starting with either the addition of leflunomide 10 mg/day orally (=Standard-CS strategy), or a second remission-induction attempt with 24 weeks of etanercept 50 mg/week subcutaneously (=Bio-induction-CS strategy). All adaptations were triggered by a DAS28-CRP >3.2 except for W32, where a DAS28-CRP ≥2.6 was applied. During the trial, treatment was further adapted according to the T2T principle. b, biologic; BL, baseline; cs, conventional synthetic; d, daily; DAS28-CRP, 28-joint Disease Activity Score – C-reactive Protein; DMARD, disease-modifying antirheumatic drug; T2T, treat-to-target; W, week; w, weekly.

adapted. The first adaptation was increasing the MTX dose to 20 mg/week (oral or subcutaneous). Patients were classified as 'early insufficient responders' if the target of DAS28-CRP ≤3.2 was not met, despite MTX increase, between W8 and W32, or if DAS28-CRP <2.6 was not achieved at W32, irrespective of the MTX dose (online supplemental file S2). Subsequently, early insufficient responders were 1:1 randomised during the randomisation window between W8 and W32 to a T2T strategy starting with either the addition of leflunomide 10 mg/day orally (Standard-CS strategy), or a second remission-induction attempt with 24 weeks of etanercept 50 mg/week subcutaneously (Bio-induction-CS strategy). Randomisation was stratified according to baseline DAS28-CRP, randomisation moment and RF/ACPA seropositivity using the minimisation technique including a random element, which ensured allocation concealment.[18] After 24 weeks, etanercept was stopped in Bio-induction-CS (figure 1).

During the trial, the T2T principle was further applied: if patients failed to achieve or did not maintain DAS28-CRP ≤3.2, treatment was adapted. Adaptation steps followed the Belgian reimbursement criteria, which means that patients needed to have an insufficient response to at least two csDMARDs, or had a documented toxicity, before they were eligible for b/tsDMARD reimbursement. The treatment adaptation steps were defined in detail in online supplemental file S3. Intramuscular or intra-articular GC injections were allowed, except before W8 and within 4 weeks preceding a study visit. Intra-articular injections could be administered maximally every 8 weeks. Non-steroidal anti-inflammatory drugs and analgesics were allowed at the discretion of the treating physician.

Patients were examined at screening, baseline, W4, W8, W16, W24, W32, W40, W52, W64, W78, W91 and W104. Additionally, randomised patients were assessed 8, 16, 24 and 28 weeks after randomisation, albeit that these visits mostly coincided with the predefined study visits. If deemed necessary, patients could be seen on optional in-between visits. During the COVID-19 outbreak, physical study visits could be replaced by telephone visits. However, in case of suspected need for treatment adaptation, a physical visit was required. Demographic information, comorbidities and clinical parameters were collected. Among others, patients completed the following patient-reported outcomes (PROs): Patient Global Assessment of disease activity (PGA), Visual Analogue Scale (VAS) for pain and fatigue, Health Assessment Questionnaire (HAQ) and Rheumatoid Arthritis Impact of Disease (RAID) (online supplemental file S2). Radiographs of hands and feet were obtained at baseline, W24, W52 and W104, and collected for central reading. At every visit, patients were questioned regarding medication use and (serious) adverse events ((S)AEs). Only (S)AEs related to RA, RA treatment or events of interest were recorded.

Patient and public involvement

As recommended by EULAR, two patient experts were involved in this trial.[19] After an introduction on the trial's rationale and content, they revised the protocol and ICF. One patient expert also participated in trial steering committee meetings, provided feedback on results and revised the manuscript.

Outcomes

This manuscript presents the primary, main secondary and key clinical outcomes of the CareRA2020 trial. To

evaluate the effectiveness of the second remission-induction attempt, we chose a pragmatic perspective which considered the speed and persistence of response, as well as the flare rate in the two randomisation arms. Therefore, the primary outcome was to compare in an early RA population with insufficient response to the initial CS-remission-induction regimen, the effectiveness of early introduction of 24 weeks of etanercept versus addition of leflunomide as first step in the further T2T strategy, based on the area under the curve (AUC) of DAS28-CRP over the total trial duration (104 weeks).

The main secondary outcome was to investigate if early introduction of 24 weeks of etanercept would result in improved disease control during the first 28 weeks after randomisation compared with addition of leflunomide, based on proportion of patients achieving DAS28-CRP <2.6.

Additional clinical outcomes were the proportion of patients obtaining DAS28-CRP <2.6 at W104, the 104-week AUC according to different disease activity scores: DAS28-Erythrocyte Sedimentation Rate (ESR), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and DAS28-CRP AUC from randomisation until 28 weeks later. Moreover, the proportion of patients achieving a good (DAS28-CRP ≤3.2 and DAS28-CRP reduction >1.2) or moderate EULAR response (DAS28-CRP reduction >1.2 or DAS28-CRP ≤5.1 and DAS28-CRP reduction between 0.6 and 1.2), the proportion achieving DAS28-CRP ≤3.2, DAS28-CRP change and functionality based on HAQ were determined at W104 and 28 weeks after randomisation. Radiographic progression based on the modified Sharp van der Heijde (SvdH) score at W52 and W104 (change from baseline, proportion having a change above the smallest detectable change (SDC[20]), and cumulative probability plot), DMARD use, GC use and proportion of patients with (S)AEs were assessed. All (S)AEs were coded according to the MedDRA dictionary (V.25.1).

Statistical analysis

CareRA2020 was conceived as a superiority trial comparing the Bio-induction-CS strategy versus the Standard-CS strategy in early insufficient responders to MTX plus GC bridging. A superiority design was chosen because we assumed Bio-induction-CS would be more effective and considered that it would be justifiable to invest in more costly bDMARDs earlier in RA treatment only when the effect of such an approach was superior compared with the current standard of care. Data from the prior CareRA trial were used for the sample size calculation.[7 9] In total, 82 early insufficient responders completing the trial were needed to demonstrate superiority with 86% power at a significance level of 0.05 (two-sided), assuming a clinically relevant difference of 20% in mean DAS28-CRP AUC over 104 weeks with Bio-induction-CS strategy compared with the DAS28-CRP AUC observed with Standard-CS strategy (351±103) in early insufficient responders of CareRA. As we did not find a predetermined minimal clinically important difference for evaluation of the AUC of DAS28-CRP over time, we empirically chose a 20% threshold.[21 22] A 21% dropout rate was expected during the 2-year trial.[7] Subsequently, we aimed to randomise 104 early insufficient responders, which would also be sufficient to demonstrate superiority for the main secondary outcome with a power of 87%. For the primary outcome, the method of Bell *et al*[23] was used to compare DAS28-CRP AUC over 104 weeks between randomisation groups based on a linear mixed model with DAS28-CRP as outcome and random intercepts per patient including an interaction effect between randomised treatment and time, adjusted for baseline DAS28-CRP, randomisation timepoint and ACPA/RF-seropositivity (yes/no), on an ITT population and, subsequently, on a per-protocol (PP) population. The ITT population consisted of all randomised patients, irrespective of whether they received the allocated treatment. The PP population included all randomised patients that followed the initial CS-remission-induction regimen and received the required treatment adaptations according to the protocol. Analysis of the main secondary and clinical outcomes was performed on the ITT population. The main secondary outcome was studied via a binomial generalised linear mixed model for repeated measures of achieving DAS28-CRP <2.6 from randomisation until 28 weeks later, with adjustment for baseline DAS28-CRP, randomisation moment and RF/ACPA seropositivity. Formal hypothesis tests were only carried out for the primary and main secondary outcome, with a significance level of 0.05. For the additional outcomes, 95% CIs were reported. Data from early responders were listed separately from the two randomisation groups. Radiographs were scored chronologically by two independent, experienced readers (RW, MK) based on the SvdH method.[24] Readers were blinded to the participant's clinical information and group allocation. Inter-reader reliability was excellent for SvdH status scores (intraclass correlation coefficient 0.96 (95% CI 0.96 to 0.97)), and moderate-to-good for the change in SvdH scores over 2 years (0.71 (95% CI 0.60 to 0.79)) using two-way mixed effects models and 'average of K readers' unit. Analyses were based on the mean score of both readers. Radiographic data were imputed using linear extrapolation[25] and were presented as mean and SD, and median and IQR.[26] All other missing data were multiply imputed by chained equations (classification and regression trees, m=100). Analysis was carried out in each imputed database, whereafter the results were pooled using Rubin's rules.[27] Analyses were performed with R V.4.2.3. The trial is registered at ClinicalTrials.gov: NCT03649061 (online supplemental file 2).

RESULTS

Participants

In total, 284 patients were screened between 12 June 2018 and 29 June 2020, and 276 patients were included in the

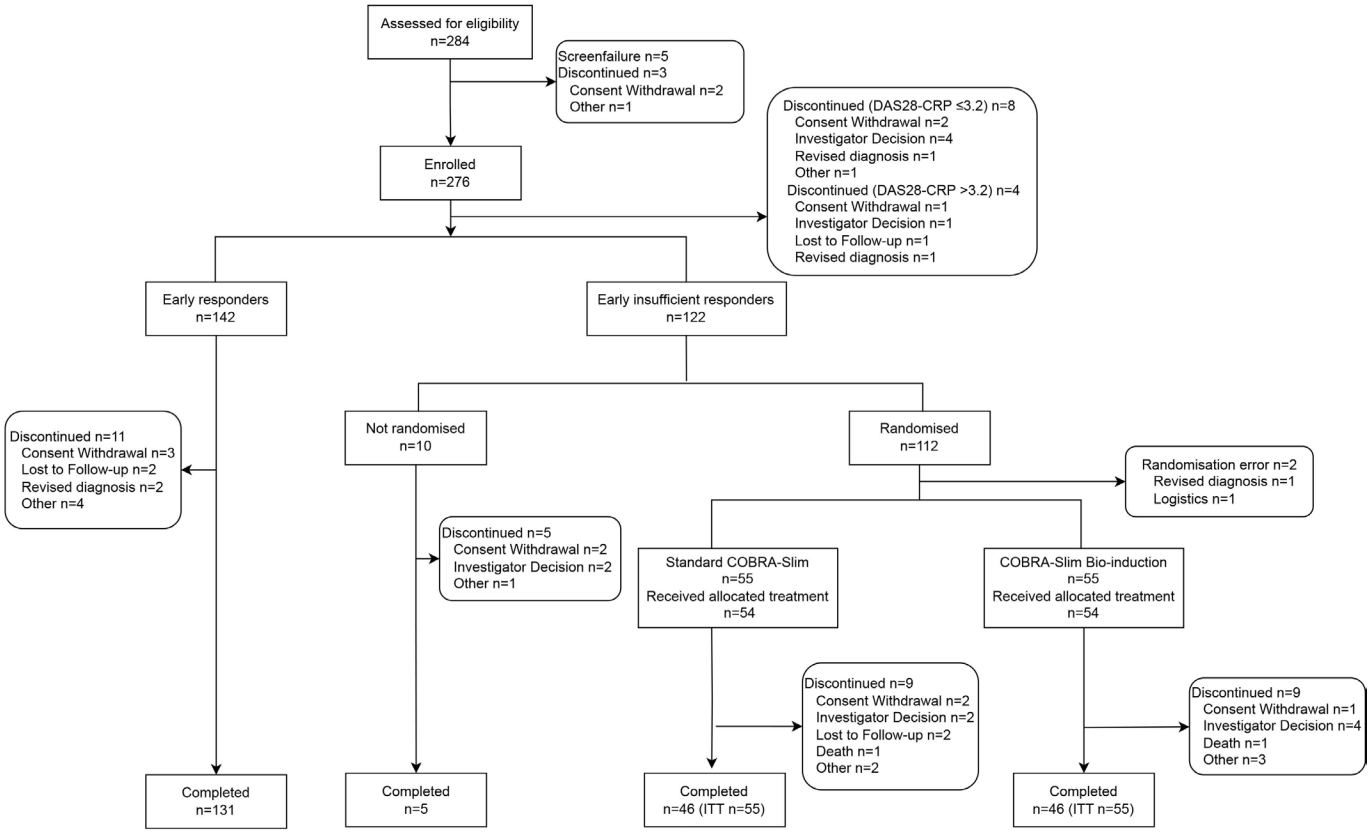

Figure 2 Patient disposition during the CareRA2020 trial. Patients were classified as 'early insufficient responders' when they did not achieve DAS28-CRP ≤3.2 from W8 onwards until W32, despite MTX dose increase to 20 mg/week, or DAS28-CRP <2.6 at W32 independently of MTX dose increase. Early insufficient responders were 1:1 randomised to either Standard COBRA-Slim or COBRA-Slim Bio-induction. DAS28-CRP, 28-joint Disease Activity Score – C-reactive protein; ITT, intention-to-treat; N, number.

CareRA2020 trial (figure 2). Twelve patients dropped out before their response to the initial CS-remission-induction regimen could be determined. Of the remaining patients, 142 out of 264 (54%) were classified as early responders, and 122 out of 264 (46%) were early insufficient responders. Ten early insufficient responders were not randomised based on the investigator's decision, and two randomisation errors occurred. Hence, 55 early insufficient responders were randomised to Standard-CS and 55 to Bio-induction-CS. Most patients were randomised at W8 or W32, and the distribution of randomisation timepoints was comparable between the two groups (online supplemental file S4). In both randomisation groups, 9 out of 55 (16%) patients dropped out, which was the case for 11 out of 142 (8%) early responders during the 2-year trial. Discontinuation reasons are presented in the patient disposition figure (figure 2). Baseline demographic and clinical characteristics are presented in table 1. Most patients (68%, 188/276) were female with a mean±SD age of 53.7±13.6 years at baseline and median symptom duration of 5 months. The randomised patients had a slightly higher baseline DAS28-CRP compared with early responders. At randomisation, the characteristics of Standard-CS and Bio-induction-CS were well balanced (online supplemental file S5).

Longitudinal effectiveness over 104 weeks

Mean (95% CI) DAS28-CRP AUC was 300.7 (282.3 to 319.1) and 297.4 (277.1 to 317.7) for Bio-induction-CS and Standard-CS, respectively. The linear mixed model could not demonstrate superiority of the Bio-induction-CS strategy compared with the Standard-CS strategy in terms of disease control over 2 years (ß=−0.204, 95% CI −0.486 to 0.078, p=0.157; interaction effect ß=0.006, 95% CI 0.002 to 0.010, p=0.002; ITT analysis). For early responders, the mean (95% CI) DAS28-CRP AUC was 205.5 (198.0 to 213.1). Comparable trends in the 2-year AUC scores of DAS28-ESR, SDAI and CDAI were found for the ITT population (online supplemental files S6 and S7). The PP analysis showed similar results for DAS28-CRP over 2 years for Bio-induction-CS compared with Standard-CS (ß=−0.243, 95% CI −0.625 to 0.139, p=0.212; interaction effect ß=0.010, 95% CI 0.006 to 0.014, p<0.001) (online supplemental file S6).

Disease activity decreased rapidly after baseline in both early responders and randomised groups, resulting in 77% (71% to 82%) of patients obtaining DAS28-CRP <2.6 at W104 (figure 3, online supplemental file S8). However, after randomisation, early insufficient responders never reached the same level of disease control as the early responder reference population.

Table 1 Baseline demographic and clinical characteristics of the patients in the CareRA2020 trial

	Standard COBRA-Slim (n=55)	COBRA-Slim Bio-induction (n=55)	Early responders (n=142)
Demographical variables			
Sex (female)	75% (41)	69% (38)	67% (95)
Age (years)	53.4±13.1	52.5±12.9	54.9±13.9
BMI (kg/m^2)*	26.6±5.5	26.9±5.7	25.9±4.3
Smoking status (ever)	60% (33)	65% (36)	45% (64)
Alcohol intake (yes)	44% (24)	47% (26)	52% (74)
Symptom duration (months)	3.0 (2.0–6.0)	4.0 (2.0–6.0)	5.0 (3.0–9.0)
Disease duration (days)	7.0 (2.5–20.0)	7.0 (2.5–19.5)	8.0 (1.0–21.0)
Employed before symptom onset (yes)	62% (34)	67% (37)	57% (81)
Employed at screening (yes)	40% (22)	42% (23)	42% (60)
RF and/or ACPA positivity	76% (42)	75% (41)	76% (108)
RF positivity	64% (35)	58% (32)	67% (95)
ACPA positivity	67% (37)	60% (33)	71% (101)
Comorbidities at screening (yes)	75% (41)	80% (44)	65% (93)
Erosions present†	15% (8)	18% (10)	28% (40)
Baseline SvdH score‡	0.0 (0.0–1.8)	0.0 (0.0–2.3)	0.0 (0.0–2.5)
Clinical variables			
DAS28-CRP	5.4±1.1	5.2±1.3	4.7±1.3
DAS28-ESR	5.8±1.1	5.6±1.4	5.1±1.4
SDAI	34.7±13.6	33.0±15.6	28.6±14.5
CDAI	31.9±12.6	30.3±13.7	26.9±13.4
Tender joint count (0–68)	16.4±9.5	16.3±10.6	12.1±8.3
Swollen joint count (0–66)	12.5±7.0	11.2±8.2	10.4±7.0
PGA (0–100 mm)	66.6±23.1	65.0±21.7	55.8±22.5
VAS Pain (0–100 mm)	66.4±22.2	63.8±23.3	57.1±24.2
VAS Fatigue (0–100 mm)	62.4±26.5	57.7±26.4	51.2±27.1
PhGA (0–100 mm)	59.3±20.8	55.6±21.0	51.3±19.0
ESR (mm/hour)	37.7±28.0	34.6±27.8	28.8±20.7
CRP (mg/L)	27.7±32.4	27.0±45.6	17.1±23.9
HAQ score (0–3)	1.6±0.6	1.5±0.8	1.1±0.8
RAID score (0–10)	6.5±2.0	6.1±2.3	5.0±2.4

Data are expressed in proportions % (n), mean±SD or median (IQR) based on their distribution.
Symptom duration: period in months between onset of symptoms and baseline; disease duration: period in days between diagnosis of RA and baseline.
HAQ score was corrected for help from another person, aids and devices.
*Two patients had a missing weight at baseline. The missing data were imputed with the weight at screening or at the week 4 visit.
†According to local reading.
‡According to central reading.
ACPA, anti-citrullinated protein antibody; BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire score; PGA, Patient Global Assessment of disease activity; PhGA, Physician Global Assessment of disease activity; RAID, Rheumatoid Arthritis Impact of Disease questionnaire; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SvdH, Sharp van der Heijde; VAS, Visual Analogue Scale.

After stopping etanercept, a DAS28-CRP increase was noticed, contributing to lower DAS28-CRP <2.6 rates in Bio-induction-CS (55%) compared with Standard-CS (69%) at W104 (figure 3, table 2). Similarly, more patients (77%) in Standard-CS obtained a good EULAR response at W104 compared with Bio-induction-CS (62%). Proportions of patients with a moderate EULAR response at W104 were high in both randomisation groups (95% and 89% in Standard-CS and Bio-induction-CS, respectively).

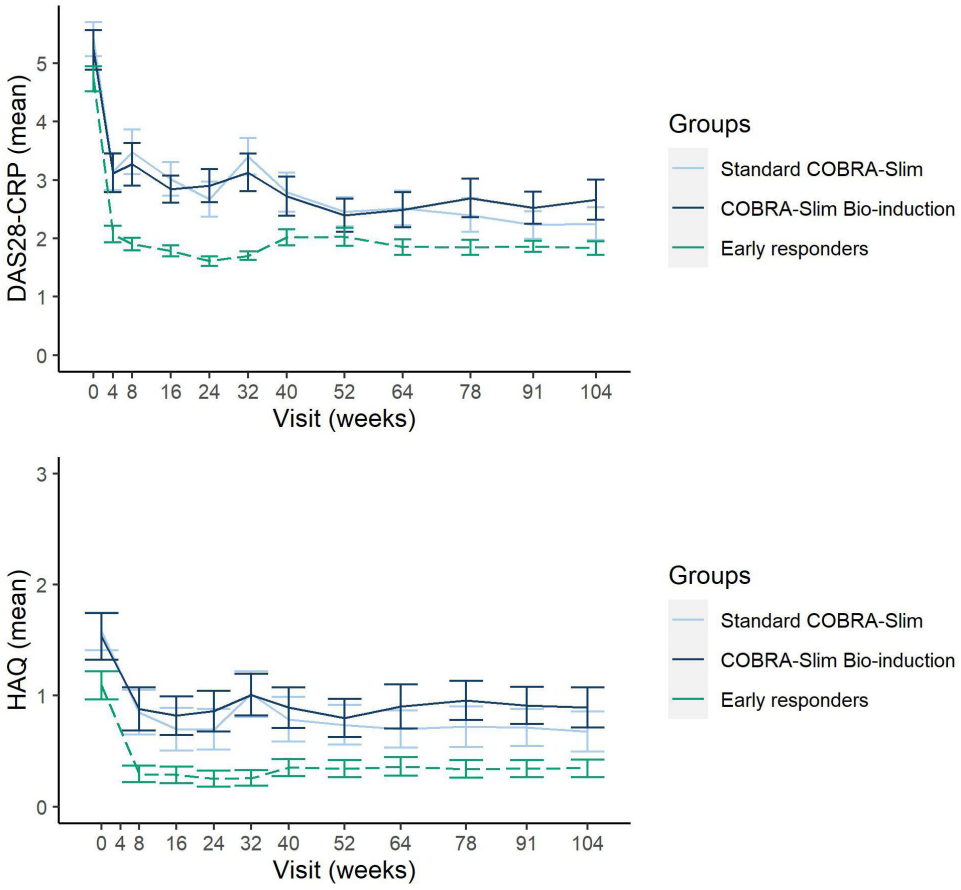

Figure 3 Evolution of disease activity, based on mean DAS28-CRP, and functionality, based on mean HAQ score, from baseline until W104 during the CareRA2020 trial. Error bars indicate the 95% CI. The early responders are shown as a reference. DAS28-CRP, 28-joint Disease Activity Score – C-reactive Protein; HAQ, Health Assessment Questionnaire.

The mean (95% CI) HAQ score at W104 was comparable between the randomisation groups (0.7 (0.5 to 0.9) and 0.9 (0.7 to 1.1) in Standard-CS and Bio-induction-CS, respectively). For the early responders, this was 0.3 (0.3 to 0.4) (table 2). Overall, the HAQ evolution mirrored the DAS28-CRP evolution during the 2-year trial (figure 3).

Radiographic progression

In total, 51 out of 55 series of radiographic images in both randomisation groups, and 141 out of 142 in the early responders were available at W52 and W104 for central reading. The median baseline SvdH score was comparable in all groups (table 1). Only minimal radiographic progression occurred after 1-year and 2-year follow-up, which was comparable in both randomisation groups (table 2, online supplemental file S9). Similarly, 6% (3/51) in both randomisation groups had a SvdH change over 2 years above 3.1 (SDC[20]). Additional information, including cumulative probability plots and early responder data, are presented in online supplemental files S9 and S10.

Initial clinical efficacy during 28 weeks after randomisation

Patients following the Bio-induction-CS-strategy had a significantly higher odds of reaching DAS28-CRP <2.6 during the first 28 weeks after randomisation compared with the Standard-CS strategy (OR 2.06 (95% CI 1.20 to 3.56), p=0.009) (online supplemental file S11). Mean (95% CI) AUC DAS28-CRP over 28 weeks after randomisation was 77.6 (72.0 to 83.2) and 89.1 (82.8 to 95.4) for Bio-induction-CS and Standard-CS, respectively (figure 4, online supplemental file S12). By 28 weeks after randomisation, more Bio-induction-CS patients achieved DAS28-CRP <2.6 compared with Standard-CS (59% and 44%, respectively, table 3). Similar EULAR responses and HAQ scores were found 28 weeks after randomisation in both randomisation groups (table 3).

Treatment adaptations according to the T2T strategy

A detailed description of the medication used in all groups can be found in figure 5. From W4 until W32 (end of randomisation window), 81% (115/142) early responders did not need DMARD treatment adaptations, and 19% (27/142) increased the MTX dose to 20 mg/week, without requiring further DMARD adaptations within the randomisation window.

All insufficiently responding patients randomised to the Standard-CS strategy, except for one, added leflunomide. Following the T2T principle, 24 out of 55 (44%) Standard-CS patients had switched to b/tsDMARD therapy by 28 weeks after randomisation. The time to

Table 2 Clinical and radiographic outcomes at the end of the CareRA2020 trial (W104)

	Standard COBRA-Slim (n=55)	COBRA-Slim Bio-induction (n=55)	Early responders (n=142)
AUC DAS28-CRP	297.4 (277.1 to 317.7)	300.7 (282.3 to 319.1)	205.5 (198.0 to 213.1)
DAS28-CRP	2.4 (2.1 to 2.7)	2.8 (2.4 to 3.1)	1.9 (1.8 to 2.0)
DAS28-CRP change from BL	−3.0 (−2.6 to −3.4)	−2.5 (−2.0 to −2.9)	−2.9 (−2.6 to −3.1)
DAS28-CRP <2.6	69% (55 to 81)	55% (40 to 68)	88% (81 to 93)
DAS28-CRP ≤3.2	80% (66 to 89)	67% (53 to 79)	95% (89 to 97)
DAS28-ESR <2.6	58% (44 to 71)	50% (36 to 64)	75% (66 to 81)
CDAI ≤2.8	29% (18 to 43)	23% (13 to 36)	58% (49 to 66)
SDAI ≤3.3	33% (21 to 47)	23% (13 to 37)	59% (51 to 67)
Good EULAR response	77% (63 to 87)	62% (48 to 75)	87% (80 to 92)
Moderate EULAR response	95% (82 to 99)	89% (77 to 95)	96% (90 to 98)
HAQ score	0.7 (0.5 to 0.9)	0.9 (0.7 to 1.1)	0.3 (0.3 to 0.4)
X-ray pairs BL – W104 (n)	51	51	141
Change SvdH BL – W104 (mean±SD)	0.7±2.1	0.8±1.7	0.8±2.0
Change SvdH score BL – W104 (median (IQR))	0.0 (0.0–0.5)	0.0 (0.0–0.5)	0.0 (0.0–0.5)
Patients with change BL – W104 >SDC (% (n))	6% (3/51)	6% (3/51)	6% (9/141)

Presented as proportion or mean and (95% CI) if not indicated otherwise. HAQ score was corrected for help from another person, aids and devices. Smallest detectable change[20] in ΔSvdH score from baseline – week 104 for the CareRA2020 trial was equal to 3.1. Good EULAR response: DAS28-CRP ≤3.2 and DAS28-CRP reduction >1.2. Moderate EULAR response: DAS28-CRP reduction >1.2 or DAS28-CRP ≤5.1 and DAS28-CRP reduction between 0.6 and 1.2. Data from early responders were reported separately from the two randomisation groups, serving only as a reference.
AUC, area under the curve; BL, baseline; CDAI, Clinical Disease Activity Index; DAS28-CRP, 28-joint Disease Activity Score – C-reactive Protein; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; HAQ, Health Assessment Questionnaire score; n, number; SDAI, Simplified Disease Activity Index; SDC, smallest detectable change; SvdH, Sharp van der Heijde; W, week.

b/tsDMARD initiation is shown in online supplemental file S13. In Bio-induction-CS, one patient never started etanercept, and all other patients started etanercept according to protocol. One patient stopped etanercept after 16 weeks due to insufficient response, and 8 out of 55 patients continued etanercept beyond the foreseen 24-week period, of whom 2 continued etanercept until the end of the trial.

At W104, csDMARD monotherapy was used in 3 out of 55 (5%) Standard-CS and 19 out of 55 (35%) Bio-induction-CS patients (figure 5). More Standard-CS compared with Bio-induction-CS patients used b/tsDMARDs (29/55 (53%) and 19/55 (35%), respectively). In early responders, 108 out of 142 (76%) used csDMARD monotherapy and their b/tsDMARD use was minimal (9/142 (6%)).

The mean (95% CI) cumulative oral GC dose during the 2-year trial (including the initial step-down GC scheme) was comparable between the randomisation groups (1893 (1568 to 2218) mg and 1777 (1497 to 2057) mg for Standard-CS and Bio-induction-CS, respectively) (online supplemental file S14). Of the patients who completed the trial, 10 out of 46 (22%) Standard-CS were using oral GC at W104 (mean dose 5 mg/day), which was less in Bio-induction-CS (6/46 (13%), mean dose 9 mg/day). Moreover, GC injections were administered in 26 out of 55 (47%, 50 GC injections) Standard-CS and 26 out of 55 (47%, 53 GC injections) Bio-induction-CS patients.

Safety

In total, 43 out of 55 (78%) Standard-CS and 47 out of 55 (85%) Bio-induction-CS patients had at least one AE. The number of AEs per patient over a 2-year duration was low: mean (95% CI) of 2.9 (2.1 to 3.8) and 3.2 (2.3 to 4.1) in Standard-CS and Bio-induction-CS, respectively (online supplemental file S15). Most frequently reported AEs were gastrointestinal disorders and infections and infestations (online supplemental file S16). In total, 7% (4/55) and 9% (5/55) patients in Standard-CS and Bio-induction-CS had at least one serious AE (SAE) (total of five and five SAEs, respectively). Two deaths, judged not to be treatment-related, occurred (Takotsubo syndrome and aortic dissection). Additional safety information, including early responder data, is presented in online supplemental files S15 and S16.

DISCUSSION

In the CareRA2020 trial, long-term effectiveness of two different T2T strategies was examined after an insufficient response to initial treatment (MTX and GC bridging), more specifically a second remission-induction

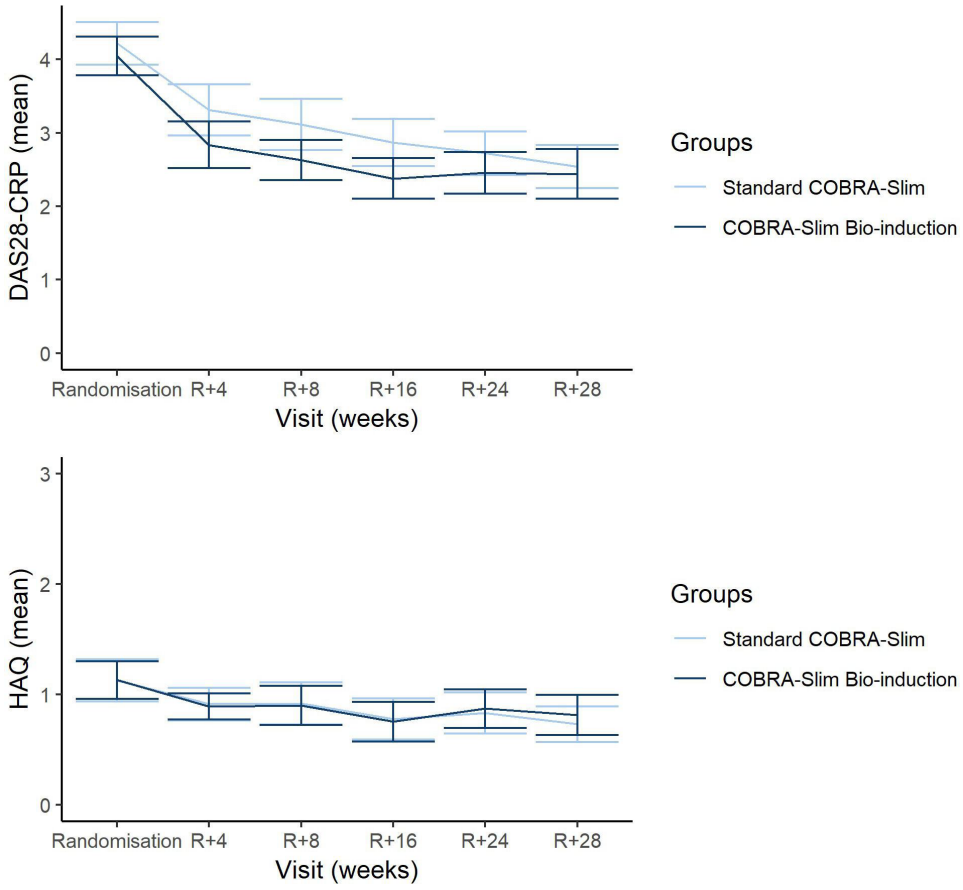

Figure 4 Evolution of disease activity according to DAS28-CRP and functionality according to HAQ, starting from the moment of randomisation until 28 weeks after randomisation. Error bars indicate the 95% CI. DAS28-CRP, 28-joint Disease Activity Score – C-reactive Protein; HAQ, Health Assessment Questionnaire; R, randomisation.

attempt consisting of 24 weeks of etanercept compared with stepping up to a second csDMARD, the current approach. Our data demonstrated that early introduction of 24 weeks of etanercept was not superior to addition of leflunomide as a first step in the T2T strategy in terms of disease control over 2 years. This could partly be explained by rapid switching to the subsequent T2T step, being b/tsDMARDs, in patients following the Standard-CS strategy. Nevertheless, more rapid disease control was achieved with 24 weeks of etanercept compared with stepping up to leflunomide, although the added value on the long-term diminished as more patients using the Standard-CS strategy achieved DAS28-CRP <2.6 at W104.

Similar to patients not achieving early DAS remission in the IMPROVED study, early insufficient responders in our trial had higher baseline disease activity, higher swollen

Table 3 Clinical outcomes 28 weeks after randomisation in the CareRA2020 trial

	Standard COBRA-Slim (n=55)	COBRA-Slim Bio-induction (n=55)
AUC DAS28-CRP	89.1 (82.8 to 95.4)	77.6 (72.0 to 83.2)
DAS28-CRP after 28 weeks	2.8 (2.5 to 3.1)	2.6 (2.3 to 3.0)
DAS28-CRP <2.6 after 28 weeks	44% (31 to 59)	59% (44 to 72)
DAS28-CRP ≤3.2 after 28 weeks	64% (49 to 77)	76% (61 to 86)
Change DAS28-CRP from moment of randomisation	−1.4 (−1.0 to −1.8)	−1.4 (−1.1 to −1.7)
Good EULAR response after 28 weeks	47% (32 to 62)	46% (32 to 61)
Moderate EULAR response after 28 weeks	74% (59 to 85)	73% (58 to 84)
HAQ after 28 weeks	0.7 (0.5 to 0.9)	0.8 (0.6 to 1.0)

Presented as proportion or mean and (95% CI). Good EULAR response: DAS28-CRP ≤3.2 and DAS28-CRP reduction >1.2. Moderate EULAR response: DAS28-CRP reduction >1.2 or DAS28-CRP ≤5.1 and DAS28-CRP reduction between 0.6 and 1.2.
AUC, area under the curve; DAS28-CRP, 28-joint Disease Activity Score – C-reactive Protein; EULAR, European Alliance of Associations for Rheumatology; HAQ, Health Assessment Questionnaire score; n, number.

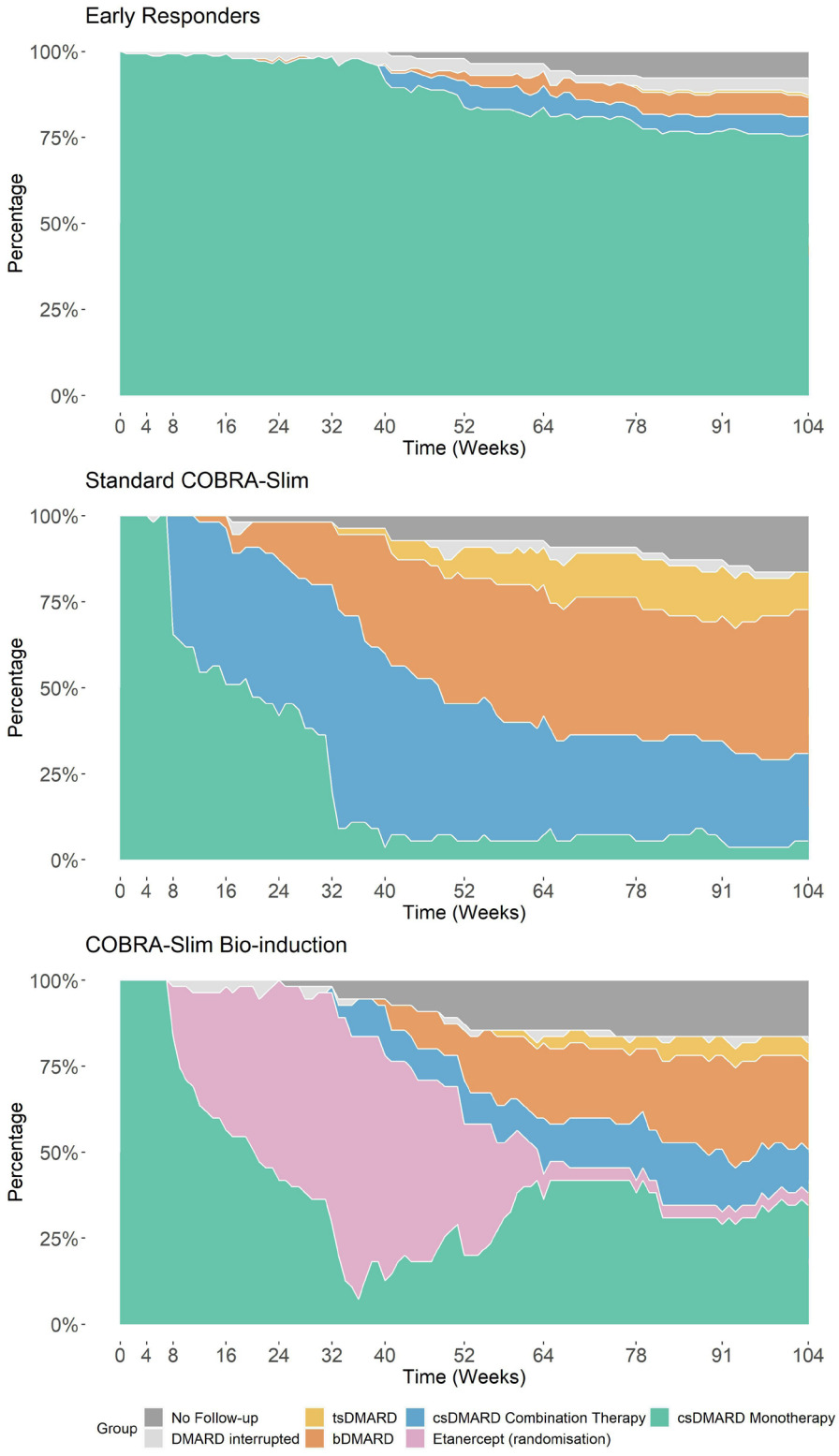

Figure 5 DMARD use during the CareRA2020 trial from baseline until week 104. 'Etanercept (randomisation)' indicates the randomised 24 weeks of etanercept. If etanercept was restarted later during the trial, this was classified as 'bDMARD'. The early responders are shown as a reference. b, biologic; cs, conventional synthetic; DMARD, disease-modifying antirheumatic drug; ts, targeted synthetic.

joint counts and higher CRP and ESR compared with the early responders.[13] In addition, a more pronounced discrepancy in the number of tender and swollen joints and a higher proportion of smokers were noted in early insufficient responders compared with early responders. By contrast, we observed no such difference for other classical markers of poor prognosis, including erosions and seropositivity. EULAR recommends to initiate

bDMARDs or tsDMARDs after an insufficient response to the first-line treatment with MTX and GC bridging in patients with poor prognostic factors.[1] Indeed, patients randomised to the Bio-induction-CS strategy had higher odds of achieving a DAS28-CRP <2.6 during the first 28 weeks after randomisation, as was expected given etanercept's faster mechanism of action. This higher rate of disease control shortly after randomisation to a TNFi was in line with the results of the IMPROVED, GUEPARD, OPERA and RACAT studies.[13 28–30] Despite rapidly obtaining disease control, just like the IMPROVED study, the CareRA2020 trial showed that a second remission-induction attempt with temporary introduction of a TNFi did not lead to superior disease control over 2 years compared with first adding csDMARDs in a T2T setting.[14]

Despite the slower initial response, more patients following the Standard-CS strategy achieved disease control at W104 compared with the Bio-induction-CS strategy. One potential explanation might be the increased long-term b/tsDMARD-use following failure of adding leflunomide in Standard-CS due to strict implementation of the T2T approach, as 44% of patients were already treated with b/tsDMARDs 28 weeks after randomisation, and this increased to 53% at W104. This higher b/tsDMARD use could indicate more effectiveness problems and side effects over time with leflunomide compared with etanercept in these early insufficient responders. Therefore, these patients seemingly tended to more rapidly cycle through the treatment adaptation steps required by the Belgian reimbursement criteria. This rapid increase in bDMARD use was also reported in the IMPROVED trial.[13 14] Another explanation for lower DAS28-CRP <2.6 rates at W104 using the Bio-induction-CS strategy could be related to the fact that the initial administration of etanercept was only temporary, since 24% of Bio-induction-CS had a DAS28-CRP >3.2 already 4 weeks after stopping etanercept per protocol. A similar increase in disease activity was noticed in the VEDERA trial after stopping etanercept at W48.[31] This reasoning was underpinned by the SWEFOT trial, which demonstrated that early introduction and continuation of infliximab yielded better disease activity outcomes compared with triple csDMARD therapy.[32] Moreover, early insufficient responders might have feared to lose disease control when stopping etanercept, inducing a nocebo response. Although we could possibly have avoided a nocebo response with the use of a double-blinded design, we opted for a pragmatic open-label trial with the potential to reflect a real-world situation in terms of patient's subjective appreciation of the treatment, for instance, preference for the newer treatment strategy as demonstrated in the BeSt study,[33] to be able to generalise the results to daily clinical practice. Another possibility would have been to taper etanercept instead of immediate discontinuation, in line with the BeSt[34] and IMPROVED trial,[14] since bDMARD tapering has been shown to result in higher chances to maintain disease control compared with immediate discontinuation.[15] However, besides the societal cost-savings, it could be argued that only prompt discontinuation truly reflects a second remission-induction attempt.

Remarkably, more patients following the Bio-induction-CS strategy were using a csDMARD combination therapy or csDMARD monotherapy compared with the Standard-CS-strategy at W104. This was in line with the results from the VEDERA trial, where patients were mainly treated with csDMARD combination therapy after stopping etanercept.[31] Although b/tsDMARD-use in Bio-induction-CS was substantially lower compared with Standard-CS at study end despite slightly higher disease activity levels, we anticipate that this proportion will increase during the observational long-term extension follow-up of this trial.

Although Bio-induction-CS resulted in rapid disease control after etanercept initiation, this effect was not observed for the HAQ scores. Possibly, the second remission-induction attempt was less effective on PROs, or these patients had already missed their window-of-opportunity.[3 4 35 36] Strikingly, despite the rapid initiation of the different treatment regimens in both randomisation groups and the T2T approach, both groups never achieved the same level of disease control as the early responders, which was also reported in the IMPROVED study.[13 14] Potentially, these early insufficient responders require prolonged etanercept treatment or a different pharmacological approach, for instance, targeted B-cell depletion.[37] Although it is generally not recommended due to higher costs and risk of overtreatment, these patients could perhaps have benefited from an even earlier introduction of a bDMARD, for instance, as initial treatment, as suggested by other research.[16 38 39] Nevertheless, pharmacological treatment alone might be insufficient to bridge the gap between early responders and early insufficient responders, and these patients might benefit from non-pharmacological complementary care.[40] Therefore, future research should identify and carefully evaluate the remaining unmet needs of these early insufficient responders, and potentially a patient-physician discordance score could be of help.[41] On the other hand, the remaining difference in level of disease control at longer term might indicate that early response to initial treatment with MTX and GC bridging defines a subgroup of patients with RA who have a milder disease course compared with insufficient responders.[14 42]

Half of the CareRA2020 participants were early responders to the initial CS-remission-induction regimen. They maintained disease control with a minimum of b/tsDMARDs and oral GCs during the 2-year trial, corroborating findings of the SWEFOT trial.[42] Moreover, we reaffirmed that an early response to initial treatment with MTX resulted in favourable long-term outcomes.[8 42 43] Compared with other recent early RA trials like NORD-STAR, our early responders obtained higher CDAI-remission rates (CareRA2020: 50% at W52 vs NORD-STAR on active conventional treatment: 39% at W48).[44] Furthermore, our findings of the

preceding CareRA trial were confirmed, namely, that responders to the CS regimen can be identified early on during the treatment course.[9] The majority (77%) of the CareRA2020 participants obtained a DAS28-CRP <2.6 at W104 with a treatment strategy consisting of the initial CS regimen followed by T2T-steered treatment adaptations.

Instead of randomising at baseline as in most RCTs, a randomisation window from W8 until W32 was used in the CareRA2020 trial. Including patients at treatment initiation allowed data collection on the dynamics of the initial treatment response before randomisation. In addition, this ensured a standardised randomised population, which facilitated the interpretation of the study results.[45] The randomisation window reflected the timelines for treatment adaptations proposed by the EULAR recommendations,[1] next to daily practice, as it attempted to protocolise the stepwise decision-making process applied in clinical practice. Moreover, previous research demonstrated that early response to remission-induction treatment is the best predictor for long-term disease control.[7] Although one might argue that MTX had not yet obtained its complete effect before randomisation in some patients, we considered the achievement of beneficial long-term outcomes an important argument for rapid treatment escalation, starting from W8 onwards, in case of insufficient response to the potent initial remission-induction regimen of MTX reinforced with GC bridging. Furthermore, GC discontinuation at W30 was the ultimate test for the stability of disease control under MTX monotherapy, since ongoing GC use could have obscured inadequate disease control. Based on this rationale, the randomisation window started from W8 and was extended until W32. Additionally, the use of a randomisation window enabled personalised treatment, considering the individual patient's disease trajectory.

In addition to the open-label design and etanercept discontinuation instead of tapering, a limitation was that medication adherence was not assessed using a drug count but was self-reported, which was in line with a pragmatic trial design. Patients were probably seen more frequently compared with current routine care, which could have impacted the outcomes. However, we believe that this approach may also be necessary for educational purposes and, if necessary, for providing additional non-pharmacological care in routine practice, especially in patients recently diagnosed and starting initial therapy. A randomisation window was incorporated in the trial design to meet patients' needs and align with clinical practice, which may have complicated the interpretation of the study results. Moreover, the use of a randomisation window implied that patients were randomised at different timepoints. Therefore, we needed a time-integrated primary outcome, for which we chose DAS28-CRP AUC over 2 years. Although this approach has been used before,[29 46 47] we acknowledge that this primary outcome is more difficult to interpret and to translate to the individual patient level compared with the classical EULAR and ACR response criteria, as well as remission and low disease activity states. Strengths of the trial were its pragmatic design and application of the T2T approach, providing insight into DMARD use and prescription patterns in a setting close to real life. For instance, not all patients and rheumatologists were in favour of stopping etanercept after 24 weeks, and 8 out of 55 patients prolonged its use. Moreover, the multicentric nationwide design is a strength. Additionally, we included an early RA population with a median symptom duration of 5 months. Early referral to rheumatologists, and subsequently early treatment initiation, could have contributed to the maintained beneficial outcomes of the early responders.

In conclusion, while a T2T strategy starting with 24 weeks of etanercept was not superior to adding leflunomide first in terms of disease control over 2 years, patients receiving 24 weeks of etanercept obtained DAS28-CRP <2.6 more rapidly after randomisation compared with Standard-CS. Additionally, more patients randomised to the T2T strategy of first adding leflunomide were using b/tsDMARDs after 2 years compared with a T2T strategy with 24 weeks of etanercept first, although this resulted in more patients achieving DAS28-CRP <2.6 at W104. Remarkably, early insufficient responders were not able to achieve the same level of disease control as the early responders, despite more b/tsDMARD use, which may indicate that they represent an RA subpopulation with a more difficult to manage disease course. The CareRA2020 trial did not completely solve the unmet need of patients responding insufficiently to conventional initial therapy for early RA, but it provides opportunities to further optimise the treatment approach in this population, for instance, by focussing on the identification of potential subgroups with different disease activity trajectories within the early insufficient responder group. A 3-year follow-up extension study is currently ongoing, which will hopefully give us more insight on the long term, including cost-effectiveness data.

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Contributors PV, JJ and RW were responsible for designing the trial. CareRA2020 study group (PV, BN, RW, JV, AS, HB, MC, PV, PG, JL, CL, FM, ldW, PD, CV, MD, BM, PR, IG, KS, KT, VT, SDR, CB, LMdB, MS, LC, MM, BA, ED, MJK, C Ribbens, C Rinkin, SH, CvF, TZ, BVC, IR, MJF, MVH, MS, MVB, BB, CN, EC, JPD, MV, VP, EVE, KD, SM, KdV, RJ, AI, EG, JV, RW, LDC, ED, JVO, IP, AM, LVP, YP, YB, GB, JPB, PM, SD, AD, MM, SA, MW, JM, LT, MS) were responsible for recruiting and following patients. PV, JJ and DB were responsible for project management of the trial. JJ and DB were responsible for data management of the trial. PV, RW, JJ, MD, EDM, SP and DB contributed to data analyses. DB, PV and RW drafted the paper. NC for the patient expertise. All authors contributed to data interpretation, revised the manuscript critically and approved the final version. PV takes responsibility for the overall content as guarantor.

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