Response to: 'Correspondence on 'Five-year treat-to-target outcomes after methotrexate induction therapy with or without other csDMARDs and temporary glucocorticoids for rheumatoid arthritis in the CareRA trial" by Jain and Dhir *et al*

We thank Dr Dhir *et al* for their kind words and would like to address some of the points raised.[1]

First, in patients without markers of poor prognosis, the COBRA-Slim scheme with methotrexate (MTX) and prednisone bridging led to a more rapid response than initial MTX monotherapy in the first 16 weeks.[2] Subsequently, remission rates did not differ until year 5, but patients starting a COBRA-Slim scheme had a lower disease activity and better functionality longitudinally over 5 years.[3–5] This long-term effect of prednisone bridging seems counterintuitive to Dr Dhir, given the results of the 'BehandelStrategieën in Reumatoïde Arthritis' (BeSt) study and the 'Treatment of Early Aggressive Rheumatoid Arthritis' (TEAR) trial, showing that long-term outcomes were essentially determined by treating-to-target.[6 7] Unfortunately, differences in design and follow-up duration hamper direct comparisons of the Care in early Rheumatoid Arthritis (CareRA) study with these trials. The 2-year TEAR trial did not include a glucocorticoid bridging scheme in its MTX step-up arms, but 40% of patients were already on low-dose oral glucocorticoids at baseline, which was prohibited per protocol in the MTX-Tight-Step-Up (TSU) arm of CareRA. Moreover, only about one in six CareRA participants used oral glucocorticoids for >6 months after the bridging period, during 5 years. Additionally, the treat-to-target algorithm in BeSt and TEAR was different from CareRA. In theory, the better outcomes on COBRA-Slim could have resulted from a stricter treat-to-target application than on initial MTX monotherapy. Therefore, we analysed rheumatologists' treat-to-target adherence in a post-hoc analysis of the 2-year CareRA trial. Adherence was defined as dose escalation or changing/adding disease-modifying antirheumatic drugs (DMARDs) in case of Disease Activity Score based on 28 joints calculated with C-reactive protein (DAS28CRP)>3.2 and was assessed at every visit. Adherence rates were calculated as a number of visits where treat-to-target was applied divided by the number of visits with a DAS28CRP>3.2. Adherence rates did not differ significantly between the COBRA-Slim and TSU regimen (63% (27/43) vs 51% (39/76); p=0.23), making it unlikely that this would explain the difference in outcomes.

We agree with Dr Dhir that our results reignite interest in the window-of-opportunity theory, because they reaffirm that an early response is essential for optimal long-term clinical outcomes. We showed this previously in an observational early rheumatoid arthritis (RA) cohort and many others confirmed this.[8–10] Recently Bergstra *et al* demonstrated that earlier treatment with fast-acting combination therapy results in better RA outcomes with higher chances to achieve sustained disease-free-remission.[11] Importantly, this window-of-opportunity also seems to exist in terms of psychosocial outcomes. Based on CareRA data, we demonstrated that patients with an early persistent response reported significantly higher vitality, better social functioning and more positive beliefs about disease consequences and treatment effect than patients with a delayed response, 1 year after treatment initiation.[12]

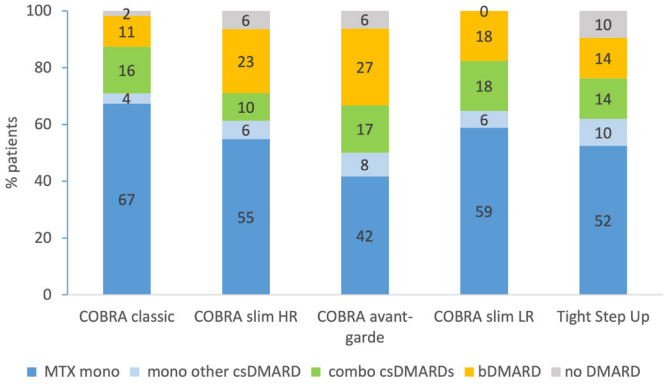

Figure 1 DMARD treatment taken at year 5. Proportion of patients on each type of treatment is provided. bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; HR, high-risk; LR, low-risk; MTX, methotrexate.

We acknowledge that the analyses in patients without factors of poor prognosis were based on a limited population. This is due to the set-up of the original CareRA trial that was powered for a superiority analysis in the more prevalent high-risk group. The patients not meeting the criteria for poor prognosis were stratified into a low-risk group on which an explorative analysis was performed. This population is seldom looked at separately in a setting of a randomised controlled trial (RCT) and many question(ed) the necessity of intensive therapies in this patient group. We attempted to bridge this knowledge gap, and our favourable results with COBRA-Slim in this subpopulation warrant further investigation in larger trials with similar intensive treatment strategies.

We deliberately chose not to include an MTX monotherapy arm in the high-risk group, because at the time of conceptualisation of CareRA, it was already clear from the COBRA and BeSt trial that intensive combination strategies were more effective. Initiating only MTX as monotherapy for patients with markers of poor prognosis would, in our opinion, have led to unnecessary delays in symptom relief and more concomitant glucocorticoids and/or analgesics use. Indeed, previous work of our group pointed towards less long-term glucocorticoid use in patients treated strategically with initial glucocorticoid bridging.[13] Therefore, we had sufficient evidence to justify glucocorticoid bridging in all treatment arms for high-risk patients in CareRA. Meanwhile, we have demonstrated that CareRA patients on initial MTX monotherapy had indeed a significantly higher risk at chronic non-steroidal anti-inflammatory drug and analgesic consumption than those treated with COBRA-Slim.[14] Moreover, according to a detailed health-economic analysis, COBRA-Slim was more cost-effective compared with MTX monotherapy with a significantly higher quality of life at a lower cost.[15]

Finally, we analysed all treatment escalations during the 2-year CareRA RCT and the 3-year observational follow-up. We considered all treatment changes independent from protocol-specified escalation steps. All treatment intensifications (switching/adding conventional synthetic DMARDs (csDMARDs) or initiating biological DMARDs were already depicted in figure 4 of the paper on the 5-year outcomes.[5] In response to Dr Dhir's question, we add treatment taken at year 5 in figure 1: 62% (125/203) were on csDMARD monotherapy.

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Contributors VS, RW, PV and DDC drafted the response letter. All authors discussed and approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The CareRA plus study was approved by the leading Ethics Committee of the University Hospitals Leuven after consulting the medical ethics committee of each participating centre (ref s53336) and all study participants gave their written informed consent before inclusion.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Stouten V, Westhovens R, Pazmino S, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2021-220857

Received 7 June 2021
Accepted 8 June 2021

Linked

► http://dx.doi.org/10.1136/annrheumdis-2021-220816

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-220857

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