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CONCISE REPORT

Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis

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ABSTRACT

Objectives To compare responses in patients with early rheumatoid arthritis (RA) initially treated with the tumour necrosis factor inhibitor (TNFi) adalimumab+methotrexate (MTX) versus MTX monotherapy who may have continued receiving MTX or switched to adalimumab rescue therapy after inadequate response to MTX.

Methods OPTIMA enrolled MTX-naive patients with active RA for <1 year. This post hoc analysis determined the proportion of patients, stratified by initial treatment, who achieved 28-joint modified Disease Activity Score based on C reactive protein <3.2, normal function and/or no radiographic progression at weeks 26, 52 and 78.

Results Significantly greater proportions of patients initially treated with adalimumab+MTX (n=466) compared with MTX monotherapy (n=460) achieved good clinical (53% vs 30%), functional (45% vs 33%) and radiographic (87% vs 72%) outcomes at week 26. From weeks 26 to 78, adalimumab rescue patients achieved similar clinical and functional outcomes versus patients initially treated with adalimumab+MTX. However, significantly more patients initially treated with adalimumab+MTX had no radiographic progression at weeks 52 and 78 versus patients initially treated with MTX (both timepoints: 86% vs 72%).

Conclusions In early RA, starting with MTX monotherapy and adding TNFi after 26 weeks yields similar longer term clinical results as starting with TNFi+MTX combination therapy but allows a small but significant accrual of radiographic damage.

INTRODUCTION

The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommend clinical remission or low disease activity (LDA) if remission is unlikely to be obtained, as the treatment goal for rheumatoid arthritis (RA).[1 2] Conventional synthetic disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (MTX), are recommended as part of an initial treatment strategy. If disease activity has not improved at 3 months, or the clinical target is not attained within 6 months and the patient has unfavourable prognostic markers, addition of a biological DMARD (bDMARD), such as a tumour necrosis factor inhibitor (TNFi), is recommended.[1 2]

This analysis evaluated the treat-to-target strategy by assessing whether patients with early RA who started on MTX monotherapy, followed by addition of adalimumab on treatment failure, had a similar or worse outcomes compared with patients who started on adalimumab+MTX combination therapy.

METHODS

Study design

OPTIMA was a 78-week, randomised, double-blind, phase 4, two-period study.[3 4] In period 1, patients received MTX monotherapy weekly or adalimumab 40 mg every other week plus MTX weekly for 26 weeks.[3] The protocol defined stable LDA as 28-joint modified Disease Activity Score based on C reactive protein (DAS28(CRP)) <3.2 at weeks 22 and 26. In period 2, patients with stable LDA continued MTX monotherapy or were rerandomised to adalimumab+MTX continuation or adalimumab withdrawal (MTX only).[4] Patients who did not achieve stable LDA in period 1 continued open-label MTX+adalimumab (adalimumab carry-on) or received open-label adalimumab added to MTX monotherapy (adalimumab rescue). All patients remained blinded to their initial treatment allocation in period 1.[4]

Post hoc populations

A 'merged adalimumab continuation' group (including the ADA continuation arm, adjusted with a scaling factor based on the total number of patients in the adalimumab continuation and adalimumab withdrawal arms, so that both arms contributed equally) was combined with the adalimumab carry-on arm, comprising the total population randomised to adalimumab+MTX at baseline (online supplementary figure 1). The MTX monotherapy and adalimumab rescue arms were combined. These two main groupings allowed comparison of the validity of the EULAR and ACR recommendations of starting with MTX monotherapy followed by addition of a TNFi in patients who do not achieve the treatment target versus starting with TNFi+MTX.

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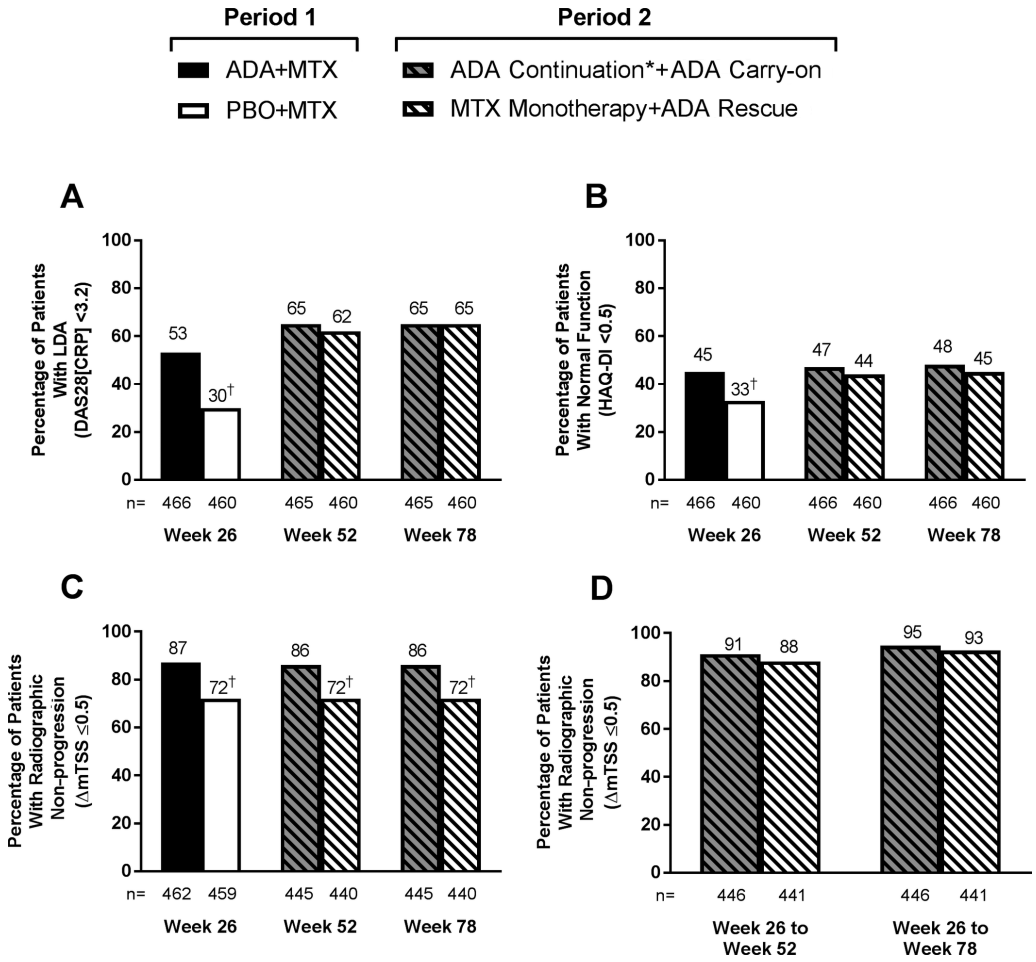

Figure 1 Percentage of patients with clinical, functional and radiographic outcomes stratified by initial treatment regimen. (A) LDA based on DAS28(CRP) <3.2 at weeks 26, 52 and 78. (B) Normal function based on HAQ-DI <0.5 at weeks 26, 52 and 78. (C) Radiographic non-progression based on ΔmTSS ≤0.5 at weeks 26, 52 and 78. (D) Radiographic nonprogression based on ΔmTSS ≤0.5 from week 26 to 52 and from week 26 to 78. *This analysis group included the ADA continuation arm (n=105) and, after scaling to yield a proportional equivalent number of patients, the ADA withdrawal arm (n=102). †P<0.001, χ^2 test. Missing DAS28(CRP) and HAQ-DI data were imputed using last observation carried forward; missing ΔmTSS data were imputed using multiple imputation. ADA, adalimumab; CRP, C reactive protein; DAS28, 28-joint modified Disease Activity Score; HAQ-DI, Disability Index of the Health Assessment Questionnaire; LDA, low disease activity; mTSS, modified total Sharp score; MTX, methotrexate; PBO, placebo.

Efficacy assessments

The main assessments were the proportion of patients who achieved DAS28(CRP) <3.2, normal function and no radiographic progression at weeks 52 and 78. Normal function was defined as Disability Index of the Health Assessment Questionnaire (HAQ-DI) <0.5 and radiographic non-progression as change in modified total Sharp score (ΔmTSS) ≤0.5. We also assessed Boolean-based remission,[5] Simplified Disease Activity Index (SDAI) remission (≤3.3), response rates for 20%/50%/70% improvements in ACR criteria and patient-reported outcomes (global assessment, pain, Functional Assessment of Chronic Illness Therapy and EuroQoL-5 dimensions).

Statistical analyses

Outcomes were assessed using the last observation carried forward method, except radiographic analyses used multiple imputation (missing values imputed in 10 steps, Markov chain Monte Carlo method).[6] Categorical outcomes were compared using the Pearson χ^2 test[4] and continuous outcomes using one-sample or two-sample t-tests.

RESULTS

As reported previously,[3] a significantly greater proportion of patients receiving adalimumab+MTX, compared with those starting on MTX only, achieved LDA, normal function and radiographic non-progression at week 26. However, after therapy adjustment at week 26 in patients who failed to attain LDA, the proportions achieving LDA at weeks 52 and 78 and normal function were similar between the groups (figure 1A,B). Results were independent of glucocorticoid use (online supplementary figure 2). Moreover, the proportion of patients with radiographic non-progression (from week 0) remained stable from weeks 26 to 52 and 78, indicating that as soon as adalimumab rescue therapy began at week 26, progression of joint damage stopped (figure 1C). Likewise, the proportion of patients with radiographic non-progression from week 26 ('reset' baseline) to week 52 or 78 was similar between the groups (figure 1D). Moreover, the proportion of MTX monotherapy responders without radiographic progression at week 26 remained stable (ΔmTSS ≤0.5: 89/109 (81.7%) at week 52, 85/109 (78.0%) at week 78). Although significantly greater proportions of patients starting with adalimumab+MTX also achieved Boolean-based remission at weeks 26 and 52 and SDAI remission at week 26 versus

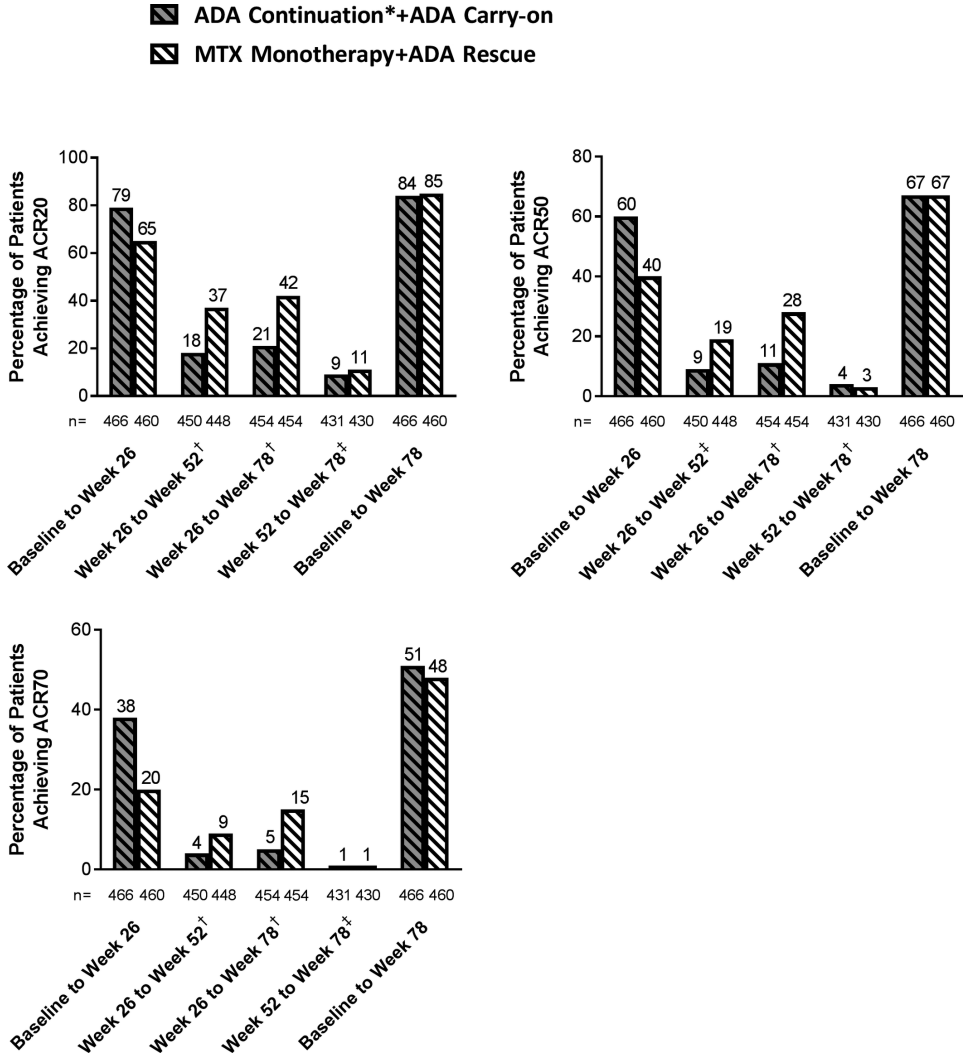

Figure 2 Response rates for patients achieving (A) 20%, (B) 50% and (C) 70% improvement in ACR criteria over the course of 78 weeks. *This analysis group included the ADA continuation arm (n=105) and, after scaling to yield a proportional equivalent number of patients, the ADA withdrawal arm (n=102). †Percentage improvement was assessed from week 26. ‡Percentage improvement was assessed from week 52. Missing data were imputed using last observation carried forward. ACR, American College of Rheumatology; ADA, adalimumab; MTX, methotrexate.

patients starting with MTX monotherapy, the differences were no longer significant subsequently (data not shown). Mean changes in clinical, functional and radiographic scores were significantly better in patients starting with adalimumab+MTX ($P<0.001$) from baseline to week 26, whereas mean changes (except radiographic scores) were significantly better in patients starting with MTX monotherapy ($P<0.001$) from week 26 to weeks 52 and 78 (ie, after possible addition of adalimumab; data not shown). Mean changes in patient-reported outcomes from week 26 to weeks 52 and 78 were similar in the two groups (data not shown).

ACR response rates from baseline to week 26 were higher on starting with adalimumab+MTX versus starting with MTX monotherapy, whereas in those starting with MTX monotherapy, the ACR rates were higher from week 26 to weeks 52 and 78 (figure 2). However, response rates were similar between groups from week 52 to week 78 or baseline to week 78.

DISCUSSION

This post hoc analysis of patients with early, active RA (disease duration: ~4 months[3]) compared 78-week outcomes in patients initially treated with MTX monotherapy, followed by addition of adalimumab if treatment target was not achieved, versus patients initially treated with adalimumab+MTX combination therapy. Patients initially treated with MTX monotherapy had similar clinical, functional and patient-reported outcomes at weeks 52 and 78 as patients initially treated with adalimumab+MTX. Although initial adalimumab+MTX combination therapy resulted in minimally superior radiographic outcomes at a group level compared with initial MTX monotherapy, these mean differences were not deemed clinically relevant because, per an established formula, this 1-point difference on the radiographic scale translates to a negligible extent of irreversible functional impairment at the group level (0.01 HAQ points).[7] Also, patients starting with adalimumab+MTX had higher ACR response rates in period 1 than patients starting with MTX monotherapy, but this pattern was reversed at week 52 when the baseline was 'reset' to week 26, so overall ACR response rates were similar by week 78. Thus, at a population level, starting with MTX monotherapy followed by addition of adalimumab in patients with early RA who did not respond to MTX within 6 months conveyed almost identical clinical, functional and quality of life (but not radiological) results at weeks 52 and/or 78 versus starting with adalimumab+MTX.

EULAR and ACR recommend starting with MTX monotherapy or MTX+glucocorticoids[1 2 8] but not with a bDMARD+MTX, in all patients with RA. In patients who do not achieve a treatment target of at least LDA and who have unfavourable prognostic factors (as in OPTIMA), adding a bDMARD is recommended. Our data fully validate this treat-to-target strategy[2] by showing that the overall population of patients starting on MTX monotherapy, over time, fared as well in clinical, functional and structural respects as those starting on adalimumab+MTX. Furthermore, among those starting on MTX monotherapy, 24% achieved stable LDA at week 26,[3] with little or no radiographic progression and mostly normative physical function thereafter; thus, the treat-to-target strategy allows for a good outcome without the need for a bDMARD, despite negative prognostic factors, and prevents overtreatment of one in four patients with active RA. Overall, by applying this strategy, approximately two of three patients with early RA achieve LDA or remission, the major therapeutic targets, within 1 year with essentially no or minimal joint damage.

To our knowledge, no previous study has addressed whether rapid addition of TNFi after MTX failure leads to different disease outcomes compared with an initial combination of TNFi+MTX. A further strength is the prospective design of this study. Limitations include the inherent bias of post hoc analyses and that the target was defined a priori as DAS28(CRP) <3.2, rather than a more stringent response. Patients were also not allowed alterations in glucocorticoids as recommended in treatment guidelines.[1 2 8] Additionally, all patients who failed to achieve a clinical target received adalimumab and MTX, without comparisons with other rescue treatment options (eg, triple DMARD therapy and another bDMARD). The adalimumab+MTX population was not treated-to-target, unlike the MTX monotherapy population, since no treatment adjustment was made in patients who did not achieve stable LDA with adalimumab+MTX at week 26. Nonetheless, many adalimumab+MTX patients had further clinical/functional improvements and maintained the halt of radiographic progression. Furthermore, treatment was switched to MTX monotherapy in a subset of patients starting with adalimumab+MTX who had LDA at weeks 22 and 26; no equivalent removal of a therapeutic component was allowed in patients starting with MTX monotherapy who achieved stable LDA. Finally, rescue therapy was open label, which could have biased patient responses, particularly for the more subjective endpoints (eg, HAQ-DI); however, the initial treatment allocation remained blinded throughout the trial.

CONCLUSIONS

Consistent with current treatment recommendations, starting with MTX monotherapy and optimising treatment by adding adalimumab after treatment failure at 26 weeks allowed patients with early RA to achieve comparable long-term clinical, functional and disease activity outcomes with patients who started with initial adalimumab+MTX combination therapy. This strategy also prevented potential overtreatment of approximately 25% of patients with early RA.

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