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# Addition or removal of concomitant methotrexate alters adalimumab effectiveness in rheumatoid arthritis but not psoriatic arthritis

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**Objective**: Randomized trials have shown that concomitant methotrexate (MTX) augments the effectiveness of tumour necrosis factor (TNF) inhibitors in rheumatoid arthritis (RA), but its benefit in psoriatic arthritis (PsA) has not been demonstrated. The goal of this study was to examine whether the impact of concomitant MTX on therapeutic outcomes in patients with PsA was similar to its effects in RA.
**Methods**: We used data from highly comparable and concurrent observational studies of patients with PsA (N = 1424) or RA (N = 3148) who initiated adalimumab therapy during routine clinical care. The 28-joint Disease Activity Score (DAS28) and patient-reported pain scores were evaluated in patients who received 24 months of continuous treatment with adalimumab monotherapy or adalimumab + MTX and in patients who initiated or stopped concomitant MTX during ongoing adalimumab therapy.
**Results**: Twenty-four months of continuous treatment with adalimumab + MTX was superior to adalimumab monotherapy in RA patients, while no significant difference was observed in patients with PsA. RA patients who added MTX during the study showed significant individual improvements in DAS28 and pain scores at 6 months after the change in therapy, while those who removed MTX had slight increases in disease activity. In contrast, in patients with PsA, neither initiation nor removal of MTX during continuous adalimumab therapy had a significant effect on therapeutic outcomes.
**Conclusion**: Addition of MTX to adalimumab confers further therapeutic benefit in patients with RA, but not in those with PsA, suggesting differences in MTX effects in these two patient populations.

Clinicaltrials.gov NCT01078090, NCT01077258, NCT01111240

The enhanced therapeutic benefit associated with the addition of methotrexate (MTX) to concomitant anti-tumour necrosis factor (TNF) therapy has been extensively documented in patients with rheumatoid arthritis (RA) (1). The mechanism of action is not well understood, but MTX may exert additional disease-modifying effects and/or reduce the formation of antibodies to TNF inhibitors, thus enhancing their therapeutic effects (1).

In psoriatic arthritis (PsA), the evidence in favour of concomitant MTX is less clear. Unlike the activity observed with MTX in RA, MTX alone did not show clinically significant effects in a placebo-controlled trial in PsA (2), and concomitant therapy with MTX does not consistently add to the therapeutic effect of anti-TNF therapy alone (3–7).

Between 2003 and 2013, long-term post-marketing observational studies of adalimumab were conducted in German patients with RA or PsA. These studies had almost identical designs and most of the clinicians involved had patients in both studies. The combination of these highly comparable studies with large numbers of patients treated in real-life situations gave us the opportunity to further explore the role of adding MTX to adalimumab in PsA compared with RA.

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## Method

### Study design

This study is a retrospective analysis of data from three multicentre, non-interventional studies that prospectively followed patients with RA (two studies; NCT01078090 and NCT01077258) (8) or PsA (one study; NCT01111240) (3) who received adalimumab therapy at the decision of and under the direction of their physician during routine clinical practice in Germany. The design, documentation, and visit intervals of these studies were identical with respect to rheumatology parameters, and most clinicians (73%) in the RA study also had patients in the PsA study. RA patients were enrolled from 2003 to 2013 and PsA patients were enrolled from 2005 to 2013.

Patients enrolled in the adalimumab non-interventional studies had a diagnosis of RA or PsA and active disease as judged by the clinician. The use of concomitant therapies, including MTX, was solely dependent on the shared decision of the patient and the clinician, and was not influenced by this retrospective evaluation. Patients receiving concomitant therapy with other disease-modifying anti-rheumatic drugs (DMARDs) instead of or in addition to MTX were excluded from these analyses. All patients were informed of the study objectives and gave written consent to their voluntary participation and the anonymous use of their personal data in statistical analyses. Because this was a non-interventional study with anonymized data sets, ethics approval was not required by German law.

Evaluations of continuous therapy included all patients who received adalimumab monotherapy or adalimumab + MTX combination therapy for 24 months and had adequately documented outcome data. Evaluations of changes in concomitant MTX therapy included patients who received stable treatment (adalimumab monotherapy or adalimumab + MTX) until at least the 6 month visit; had a recorded change in concomitant MTX therapy (addition or removal) at month 6, 12, or 18; and had adequately documented data at 6 months after the change in concomitant MTX. Only patients who changed MTX for the first time were included.

### Outcome assessments

The primary effectiveness evaluation was the 28-joint Disease Activity Score (DAS28), which reflects overall disease activity in RA (9, 10) and PsA (11, 12). Pain, the most important determinant of patient-reported global disease assessment (13, 14), was scored on a categorical scale of 0 (absent) to 10 (severe). For physical function assessments, we used the self-administered Funktionsfragebogen Hannover (FFbH) patient questionnaire, which is highly correlated with the Health Assessment Questionnaire Disability Index (HAQ-DI) (15). The FFbH questionnaire indicates the remaining percentage of patient function and is scored on a scale of 0 (total loss of functional capacity) to 100 (maximal functional capacity) (16). In PsA patients, psoriasis was assessed by body surface area (BSA) estimates (17) and by the target lesion score (TLS), which is based on assessment of prospectively defined psoriasis target lesions of at least 2 cm in width, considered to be representative of affected areas. Target lesions were assessed for severity of erythema, scaling, and infiltration on a scale of 0 (absent) to 5 (maximal expression), for a total score range of 0 (absent) to 15 (severe). Although this measure of skin disease has not been formally validated, TLS and related variations are frequently used to assess psoriasis (18), especially in patients with low BSA involvement (17), and have been included as an outcome in clinical trials of PsA and psoriasis patients (19, 20).

### Statistical analyses

Statistical analyses were performed using SAS® statistical software, version 9.4. Descriptive statistics or frequencies were computed for all data as appropriate. Missing data were not imputed. In patients on continuous therapy, between-group significance tests were performed for mean change from baseline for adalimumab therapy versus adalimumab + MTX for each disease state (RA or PsA). For analyses of outcomes in patients who changed concomitant MTX therapy, the difference between the variable at the time of change and 6 months after the change was tested against 0 with 95% confidence intervals (CIs) as determined by the one-sample t-test. Any p values ≤ 0.05 were considered significant.

## Results

### Patient characteristics

Patients enrolled in the adalimumab observational studies generally had disease of long-standing duration and moderate to high disease activity (Table 1). RA and PsA patients who stopped concomitant MTX during adalimumab therapy were younger and had a shorter disease duration than other patient cohorts.

There were no significant differences in MTX doses between RA and PsA groups during continuous therapy ($p > 0.05$ for all time-points) or at the time of addition ($p = 0.52$) or removal ($p = 0.49$) in groups that changed concomitant therapy. RA patients who added MTX did so more frequently at month 6 (44.3%) than at month 12 (33.8%) or 18 (21.9%). For PsA patients, the addition of MTX was more evenly distributed (35.7%, 35.7%, and 28.6% at months 6, 12, and 18, respectively). Among patients who stopped concomitant MTX, month 6 was the most common time-point for both RA (44.4%) and PsA (46.5%) patients; 29.9% and 26.3% of RA and

Table 1. Characteristics of the patient populations.

| | RA | | | | PsA | | | |
|---|---|---|---|---|---|---|---|---|
| | Continuous ADA mono | Continuous ADA + MTX | MTX added | MTX removed | Continuous ADA mono | Continuous ADA + MTX | MTX added | MTX removed |
| Number of patients | 1305 | 1624 | 219 | 374 | 670 | 559 | 56 | 99 |
| Gender (% female) | 79.6 | 74.4 | 80.4 | 74.3 | 44.2 | 47.6 | 40.7 | 34.7 |
| Age (years) | 55.8 ± 13.0 | 54.0 ± 12.1 | 54.6 ± 12.4 | 53.5 ± 13.4 | 49.5 ± 11.6 | 49.1 ± 11.2 | 49.7 ± 10.3 | 46.2 ± 12.7 |
| BMI (kg/m$^2$) | 26.1 ± 5.0 | 26.1 ± 4.8 | 27.0 ± 5.5 | 26.2 ± 4.8 | 27.9 ± 5.2 | 28.3 ± 5.5 | 28.8 ± 3.6 | 26.7 ± 3.8 |
| Disease duration (years)* | 12.2 ± 9.6 | 11.0 ± 8.9 | 12.4 ± 10.1 | 10.9 ± 9.3 | 10.0 ± 9.3 | 9.3 ± 7.9 | 9.7 ± 7.5 | 7.2 ± 6.7 |
| DAS28 score | | | | | | | | |
| Baseline | 5.77 ± 1.16 | 5.72 ± 1.11 | 5.97 ± 1.23 | 5.80 ± 1.17 | 4.77 ± 1.31 | 4.70 ± 1.31 | 4.27 ± 1.25 | 4.63 ± 1.29 |
| At time of MTX change | NA | NA | 4.22 ± 1.44 | 3.49 ± 1.38 | NA | NA | 3.36 ± 1.17 | 2.54 ± 1.28 |
| Pain score | | | | | | | | |
| Baseline | 6.56 ± 2.12 | 6.44 ± 2.00 | 7.10 ± 2.04 | 6.65 ± 2.04 | 5.80 ± 2.31 | 6.02 ± 2.15 | 6.17 ± 1.99 | 6.11 ± 2.42 |
| At time of MTX change | NA | NA | 4.81 ± 2.32 | 3.68 ± 2.31 | NA | NA | 4.00 ± 2.12 | 2.96 ± 2.35 |
| FFbH score | | | | | | | | |
| Baseline | 59.2 ± 22.9 | 62.8 ± 21.8 | 55.0 ± 23.2 | 59.3 ± 24.7 | 70.8 ± 21.5 | 71.2 ± 20.3 | 70.2 ± 22.0 | 75.7 ± 19.8 |
| At time of MTX change | NA | NA | 63.8 ± 24.3 | 73.3 ± 23.1 | NA | NA | 75.1 ± 20.2 | 84.8 ± 18.1 |
| BSA (% of body) | | | | | | | | |
| Baseline | NA | NA | NA | NA | 9.9 ± 8.6 | 8.7 ± 8.1 | 10.1 ± 9.4 | 9.7 ± 8.9 |
| At time of MTX change | NA | NA | NA | NA | NA | NA | 5.9 ± 10.5 | 5.0 ± 9.3 |
| TLS | | | | | | | | |
| Baseline | NA | NA | NA | NA | 6.7 ± 4.1 | 5.7 ± 4.2 | 7.1 ± 4.1 | 6.5 ± 4.2 |
| At time of MTX change | NA | NA | NA | NA | NA | NA | 3.7 ± 3.4 | 2.4 ± 3.2 |
| MTX dose (mg/week)† | NA | 15.6 ± 4.7 | 12.1 ± 4.4 | 13.2 ± 5.2 | NA | 15.8 ± 4.4 | 12.5 ± 4.9 | 12.8 ± 4.6 |

For demographic characteristics, baseline data are presented. For disease activity measures (DAS28, pain, FFbH, BSA, and TLS), baseline data are presented for all patients and data at the time of change in concomitant MTX are presented for patients who added or removed MTX. Values are presented as mean ± sd unless otherwise indicated.

* Duration of arthritis symptoms.

† Dose at time of treatment initiation for 'continuous ADA + MTX' and 'MTX added' groups; dose at time of MTX removal for 'MTX removed' group.

ADA, adalimumab; BMI, body mass index; BSA, body surface area; DAS28, 28-joint Disease Activity Score; FFbH, Funktionsfragebogen Hannover functional assessment; mono, monotherapy; MTX, methotrexate; NA, not applicable; PsA, psoriatic arthritis; RA, rheumatoid arthritis; sd, standard deviation; TLS, target lesion score.

PsA patients, respectively, stopped MTX therapy at month 12, and 25.7% and 27.3% of RA and PsA patients, respectively, stopped MTX at month 18.

### Effect of MTX during continuous treatment

In RA patients, continuous adalimumab + MTX resulted in modest but significant reductions in mean DAS28 scores at 24 months compared with continuous adalimumab alone [mean change from baseline of −2.30 (95% CI −2.38 to −2.23) vs −2.12 (95% CI −2.20 to −2.03) at month 24; p = 0.0017 for between-group comparison] (Figure 1A). In contrast, in PsA patients, the effect of continuous adalimumab + MTX on DAS28 scores was not significantly different from that of continuous adalimumab monotherapy [mean change from baseline of −2.19 (95% CI −2.35 to −2.03) vs −2.10 (95% CI −2.23 to −1.96) at month 24; p = 0.38].

A similar pattern was observed with pain (Figure 1B) and function (FFbH) (Figure 1C). For RA patients, the improvement in patient-reported pain was significantly greater in the group receiving adalimumab + MTX than in the group receiving adalimumab monotherapy [mean change from baseline of −2.85 (95% CI −2.99 to −2.71) vs −2.47 (95% CI −2.64 to −2.31) at month 24; p = 0.007], whereas the mean change in pain scores in PsA patients receiving concomitant MTX was not significantly different from that observed with monotherapy [−2.50 (95% CI −2.74 to −2.26) vs −2.72 (95% CI −2.96 to −2.47); p = 0.22]. Differences in physical function (mean FFbH scores) did not reach statistical significance, but the same overall pattern of greater improvement with adalimumab + MTX versus adalimumab monotherapy in RA patients, but not PsA patients, was observed. Differences in skin outcomes between adalimumab monotherapy and adalimumab + MTX also failed to achieve statistical significance in patients with PsA (p = 0.07 for TLS and 0.53 for BSA; data not shown).

### Effect of addition or removal of MTX

To gain a better understanding of the impact of changing MTX during ongoing adalimumab therapy, we identified patients who either stopped or initiated concomitant MTX therapy and assessed outcomes at the subsequent visit (6 months after the change). This approach had the important advantage of allowing each patient to serve as his or her own internal control: comparisons were made between individual patient scores before the change in concomitant MTX and scores after the change. In addition, these analyses allowed us to include a greater number of patients and to evaluate outcomes irrespective of the time-point of the therapeutic change.

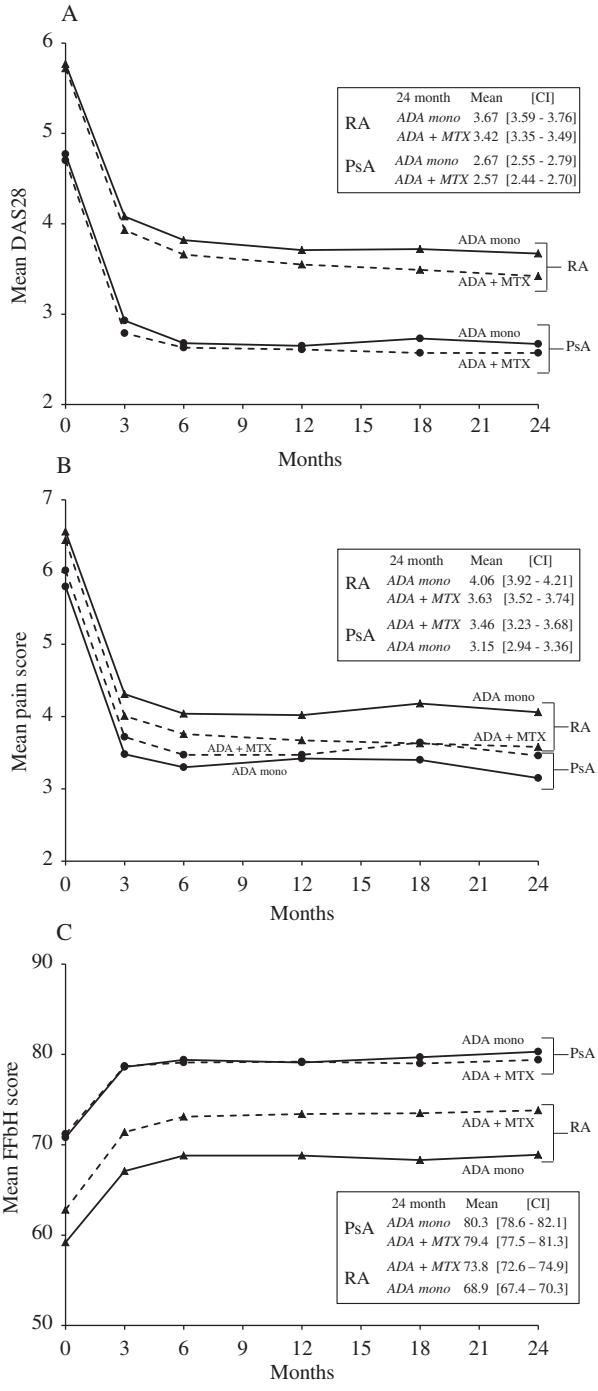
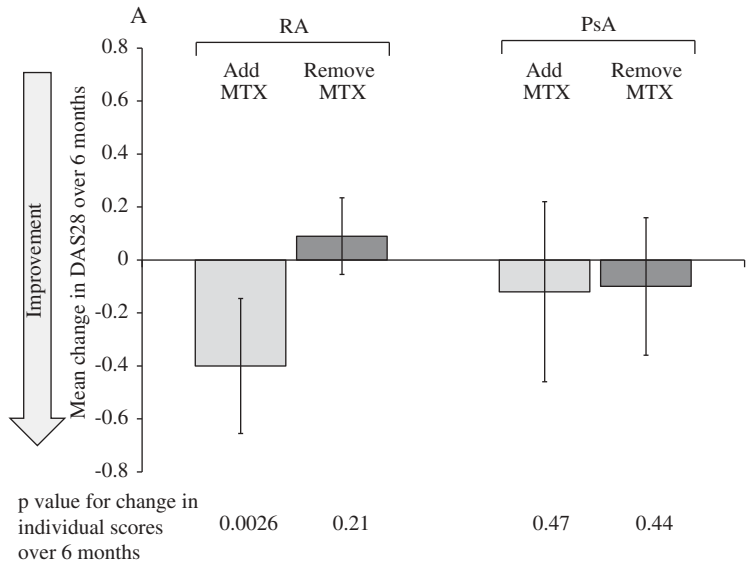
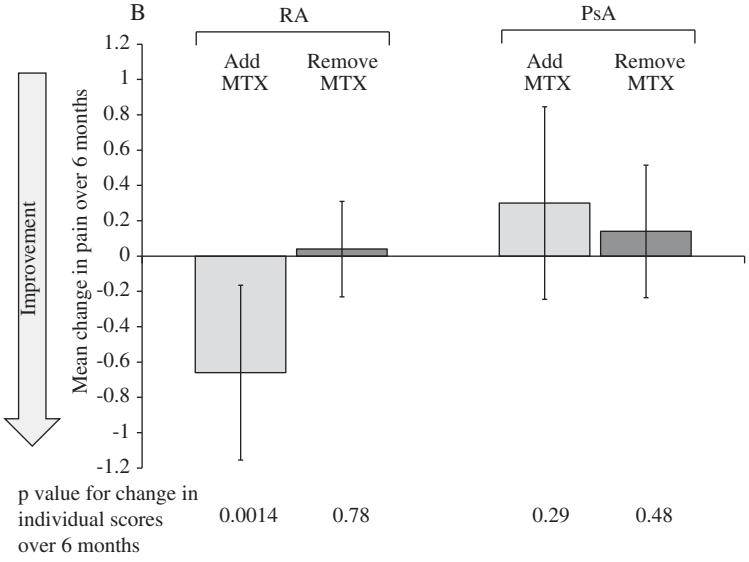



Figure 1. Effect of concomitant methotrexate (MTX) on therapeutic response in patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA). (A) Mean 28-joint Disease Activity Score (DAS28); (B) mean pain scores; and (C) mean physical function [Funktionsfragebogen Hannover questionnaire (FFbH)] scores during 24 months of continuous therapy with adalimumab (ADA) monotherapy (mono) (—) or ADA + MTX (– – –) in patients with RA (▲) or PsA (●). CI, confidence interval.

The addition of MTX to ongoing adalimumab therapy resulted in significant improvements in individual therapeutic outcomes in RA patients over the 6 month period (from the time of change to 6 months post-change), but was not associated with significant changes



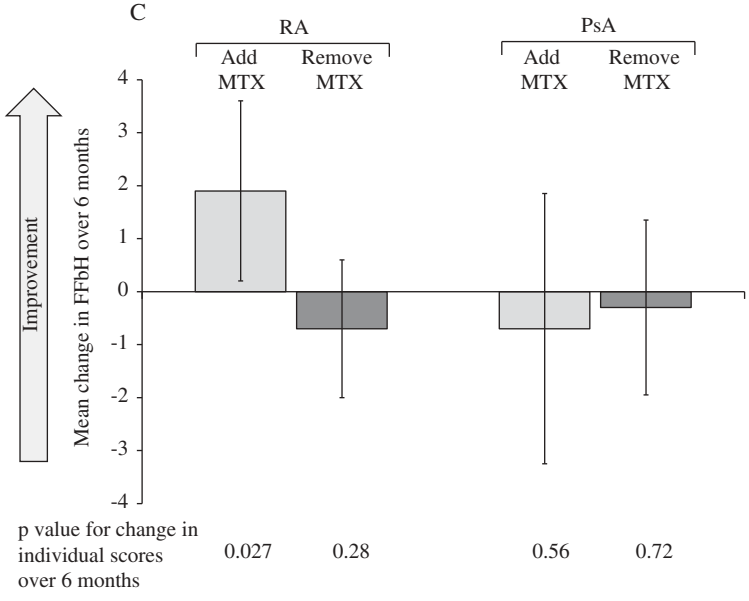




Figure 2. Effect of methotrexate (MTX) addition or removal on therapeutic responses in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). (A) Mean change in 28-joint Disease Activity Score (DAS28); (B) mean change in pain scores; and (C) mean change in physical function [Funktionsfragebogen Hannover questionnaire (FFbH)] scores between the time of therapy change and 6 months after the change (addition or removal) in MTX therapy. Capped bars indicate 95% confidence intervals. The p values were calculated using the one-sample t-test for change in individual scores over the 6 month period.

in PsA patients (Figure 2). In RA patients, adding MTX resulted in a significant reduction in mean DAS28 scores from 4.22 to 3.82 [mean difference of −0.40 (95% CI −0.65 to −0.14); p = 0.0026 for change in individual scores], while stopping MTX resulted in a slight, non-significant increase from 3.49 to 3.59 [mean difference of 0.09 (95% CI −0.05 to 0.24); p = 0.21]. In contrast, PsA patients who either added MTX or stopped MTX showed similar modest improvements in mean DAS28 scores 6 months after the change, from 3.36 to 3.24 for MTX addition [mean difference of −0.12 (95% CI −0.46 to 0.22); p = 0.47] and from 2.54 to 2.43 for MTX removal [mean difference of −0.10 (95% CI −0.36 to 0.16); p = 0.44]. Changes in pain and function assessments showed a similar pattern: mean pain and function scores improved significantly in RA patients who added MTX, but not in PsA patients. In PsA patients, neither TLS nor BSA showed significant changes following the addition or removal of MTX (data not shown).

## Discussion

The availability of data from large, highly comparable, concurrent observational studies provided an unprecedented opportunity to compare the effects of concomitant MTX in RA versus PsA during routine clinical practice. Although MTX provided significant benefits in RA patients, neither continuous therapy with concomitant MTX nor the addition of MTX to ongoing adalimumab therapy resulted in significantly improved outcomes in PsA patients.

Unlike randomized trials, patients in different therapy groups in clinical practice have often already undergone some form of selection. There are two major reasons why rheumatology patients receiving treatment with a TNF inhibitor are not treated with concomitant MTX: either they do not tolerate it, or they have milder symptoms and are not considered to need an additional agent. Given this non-randomized setting, which is potentially biased towards milder disease, the statistically significant difference between adalimumab + MTX and adalimumab monotherapy provides evidence for the additive effect of MTX during routine clinical practice in RA patients, but not PsA patients. More robust support for the differential effect of MTX in RA versus PsA was provided by analyses of patients who changed MTX during continuous adalimumab treatment. In these analyses, each patient served as his or her own internal control, thus eliminating potential issues with confounding factors inherent to between-group comparisons. These analyses showed that the addition of MTX positively impacted three different domains of importance to patients with RA: disease activity, pain, and function. The three domains are only moderately correlated with each other in patients with RA (14), so the ability of MTX to mediate improvements in all three distinct outcomes is noteworthy.

In a separate study, we evaluated the effects of adalimumab + MTX in PsA patients with or without axial disease, and found that concomitant MTX failed to confer an additional therapeutic benefit even in patients with no axial disease (6). We therefore believe it unlikely that the presence of axial disease in this population confounded our findings. It is also not likely that our results were biased by differences in treatment patterns or outcome assessments, as most clinicians were involved in both studies. However, this study was not a randomized, controlled study with blinded therapy, which may limit its interpretation.

Our study has a number of limitations, many of which are inherent to its observational design. Comorbidities may have influenced the choice of therapy and may also have affected treatment response (21). In particular, MTX may have been added to adalimumab in PsA patients to address skin involvement, thereby potentially skewing the population of PsA patients treated with adalimumab plus MTX towards those with more severe skin disease. Changes in disease activity in PsA patients may not have been adequately captured by DAS28 assessments. The DAS28 has been successfully used to assess disease activity in patients with PsA (11, 12) and was chosen as one of the analyses reported here because it was used in both the RA and PsA studies. However, this assessment does not capture the full spectrum of disease activity in patients with oligoarticular disease or skin involvement and may therefore underestimate disease activity in patients with PsA (12, 22). Because of the limitations of DAS28 in patients with PsA, we also analysed changes in pain, function, and skin outcomes. As with DAS28, the addition of MTX to adalimumab did not result in improvements in these additional measures.

The data presented here have ramifications both for the clinical management of PsA and for an understanding of the mechanism by which MTX affects disease activity in RA. From a clinical point of view, the addition of MTX to anti-TNF therapy does not seem to significantly benefit most PsA patients, and stopping concomitant MTX therapy does not appear to have a negative impact on therapeutic outcomes. Although our conclusions are by necessity limited to concomitant therapy with MTX and adalimumab, other smaller studies suggest that our findings are also likely to apply to TNF inhibitors other than adalimumab (4, 7). In particular, an analysis of biologic-naïve PsA patients (N = 519) who initiated anti-TNF therapy (adalimumab, etanercept, or infliximab) in the US Corrona registry found that time to remission was not improved with concomitant MTX compared with anti-TNF monotherapy (7). Similarly, a Norwegian registry study of patients with PsA (N = 440) found that the use of MTX in combination with various anti-TNF agents (infliximab, etanercept, or adalimumab) did not influence therapeutic outcomes at 6 months (4). Mixed results were obtained in a study of patients treated with anti-TNF therapy in the Danish DANBIO registry (N = 764). In that study, concomitant MTX at baseline was associated with

improved American College of Rheumatology 20% (ACR20) response rates after adjustment for other variables, but not with European League Against Rheumatism (EULAR) or ACR 50% (ACR50) responses (5).

Two randomized trials of TNF inhibitors (etanercept and golimumab), with or without MTX, in MTX-naïve PsA patients have been designed to address this question (23, 24). These studies are vitally needed to determine the optimal treatment in patients with early PsA. Results from the etanercept study, published in 2019, indicate that addition of MTX to etanercept did not improve overall efficacy compared with etanercept alone in MTX- and biologic-naïve PsA patients, although numerical improvements in skin endpoints in favour of the combination arm were observed (statistical significance was not evaluated) (25). However, it should be noted that a MTX-naïve patient population with a mean disease duration of 3.2 years (56% of patients had a disease duration of ≤ 2 years) is dissimilar from the PsA patients studied here, who generally had long-standing disease (mean disease duration of 7.2–-10 years) and in many cases had been treated with MTX for some time before the addition of adalimumab. It is therefore of significant interest that similar results were obtained in these very different PsA populations.

It has been hypothesized that MTX augments treatment response in PsA by improving treatment continuation, but this effect may vary among different anti-TNF agents. In the Corrona registry, overall anti-TNF persistence was similar with or without MTX; however, combination therapy did increase persistence in the subset of patients treated with infliximab (7). The Norwegian PsA registry study also found a strong effect of MTX on anti-TNF drug survival for infliximab (4), and both the Norwegian and Danish registries reported an overall improvement in anti-TNF treatment continuation in PsA patients treated with concomitant MTX (4, 5). In contrast, in our previous study of PsA patients initiating treatment with adalimumab, MTX did not appear to have an effect on treatment discontinuations (6), and concomitant DMARD use was not identified as a predictor of anti-TNF drug survival in a 2 year study of PsA patients initiating their first anti-TNF therapy (26). The role of MTX in improving treatment persistence in anti-TNF agents other than infliximab thus remains in question.

## Conclusion

Our study supports a different mechanism of action of concomitant MTX in RA versus PsA. It is possible that MTX may have a specific anti-inflammatory activity that is directed against pathogenic events occurring in RA, but not PsA, or that its suppression of the development of anti-adalimumab antibodies is more relevant in RA. It is also possible that MTX affects an inflammatory pathway that is redundant in PsA, but not in RA. There may also be additional, yet unexplored, explanations for the differential effect of MTX.

Given that the RA patient population is much larger than the PsA population and that anti-TNF agents are effective in both diseases, it is tempting to extrapolate management practices from RA to the field of PsA. Our data serve as a cautionary reminder that there are important differences between these two types of inflammatory arthritis, and that therapeutic response patterns observed in one may not be shared by the other. We hope that these findings encourage further investigations into the differential effects of MTX in RA and PsA.

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## Disclosure statement

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