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ORIGINAL ARTICLE

Treatment efficacy and methotrexate-related toxicity in patients with rheumatoid arthritis receiving methotrexate in combination with adalimumab

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ABSTRACT

Background Treatment of rheumatoid arthritis (RA) with a combination of methotrexate (MTX)+adalimumab (ADA) is more effective than ADA monotherapy. We assessed the toxicity of different doses of MTX and treatment efficacy of ADA+MTX in two trials.

Methods Data originated from CONCERTO, in patients with early RA initiating ADA+ 2.5, 5, 10 or 20 mg/week MTX for 26 weeks; and MUSICA, in patients with an inadequate response to MTX initiating ADA+ 7.5 or 20 mg/week MTX for 24 weeks. Efficacy was assessed by the American College of Rheumatology 50 (ACR50). Patient-reported MTX-related toxicity information was collected at each visit on 18 prespecified MTX-related adverse events (AE) in the MTX label.

Results In CONCERTO, ACR50 rates increased over time, ranging from 54% to 68% at week 26, while AE rates remained steady, ranging from 2.4% to 17.8% at week 26. Of 395 patients, 113 (28.6%) reported 345 MTX-related AEs, including one serious AE (SAE, excessive fatigue and/or malaise); 10 AE (in two patients) led to study discontinuation. In MUSICA, ACR50 rates increased over time, and were 32.3% and 37.5% at week 24, while MTX-related AE rates remained steady and were 6.5% at week 24. Of 309 patients, 71 (23%) reported 185 MTX-related AEs, including 5 SAEs (four infections and one fever/chills); six AE (in four patients) led to study discontinuation.

Conclusion In patients with RA initiating ADA+MTX combination, treatment efficacy was achieved and increased throughout both trials, while rates of MTX-related AEs remained steady. MTX-related AEs were observed in up to 30% of patients and most were mild. MTX was discontinued by 0.5%–1.3% of patients.

INTRODUCTION

Methotrexate (MTX) is recommended by the European League Against Rheumatism and the American College of Rheumatology (ACR) as a first-line treatment for patients with rheumatoid arthritis (RA), owing to its proven efficacy and acceptable safety profile.1 2 Patients who do not achieve adequate disease control with MTX monotherapy may benefit from...
the addition of a conventional synthetic disease-modifying antirheumatic drug (DMARD) or biologic, such as the tumour necrosis factor (TNF) inhibitor, adalimumab (ADA). Combination treatment with ADA has been shown to be more effective at reducing disease activity and the progression of radiographical damage than monotherapy with MTX or ADA. However, MTX is potentially associated with various toxicities. Gastrointestinal adverse events (AE) such as nausea, vomiting, dyspepsia, ulcers and diarrhoea are observed in up to 40% of patients, and hepatotoxicity may also occur. Higher doses of MTX (>25 mg/week) have been reported to be more toxic. It is not clear whether toxicity negatively affects efficacy outcomes, or whether higher levels of toxicity are experienced at higher levels of efficacy.

Due to a rapid decrease in serum concentrations of MTX after administration, it is difficult to predict its efficacy and toxicity. However, MTX is taken up into erythrocytes and modified by the addition of 1–5 glutamate residues. These intracellular MTX-polyglutamate (MTX-PG) derivatives remain in the blood for relatively longer, and their concentration has been reported to correlate with improved responses and lower disease activity, suggesting their potential utility as biomarkers. Concentrations of MTX-PG were also reported to correlate with increased hepatotoxicity in a longitudinal cohort study in a Japanese population.

Here, we undertook a post hoc analysis of two randomised controlled clinical trials (RCTs) of ADA in combination with MTX, in which patients were blinded to the MTX dose. We assessed the relationship between MTX-related toxicity and achieved efficacy of treatment with ADA plus MTX, and the relationship of MTX-PGs with MTX-related AEs, in two trial populations with differing RA durations and prior MTX experience (MTX-naïve and MTX-inadequate responders, both ADA-naïve).

METHODS
Patients and studies
This post hoc analysis included data from two double-blind RCTs in patients with RA: CONCERTO (NCT01185301, post-results) was a phase III trial of ADA in patients with early RA who were biologic DMARD-naïve and MTX-naïve. Patients were randomised to initiate treatment with open-label, subcutaneous ADA in combination with concurrent, double-blind, oral MTX at 2.5, 5, 10 or 20 mg/week for 26 weeks.

MUSICA (NCT01185288) was a phase IV trial of ADA in patients with moderate-to-severe RA and an inadequate response to MTX. Patients receiving ≥15 mg/week MTX for ≥12 weeks prior to the study were randomised to initiate treatment with open-label, subcutaneous ADA in combination with double-blind, oral MTX at 7.5 or 20 mg/week for 24 weeks.

Clinical assessments and statistical analysis
The efficacy of initiated ADA plus concomitant MTX treatment and MTX-related toxicity are reported by observed rates without imputation. Efficacy was assessed by a 50% improvement in the ACR core set of variables (ACR50 response rate at baseline and weeks 4, 12, 16, 20 and 24/26 (for MUSICA and CONCERTO, respectively)). For this analysis, we only considered information on patient-reported MTX-related toxicity, collected at each visit and assessed by the investigators, on the following 18 prespecified MTX-related AEs in the MTX product label: abnormal hair loss, abnormal sweating, chronic dry cough, conjunctivitis, dizziness, excessive fatigue/malaise, fever and/or chills, infection, nausea and/or vomiting, nose bleed, oral ulcers, skin pigment changes, skin rash/hives, stomach discomfort, tinnitus, unexplained visual changes, unexplained diarrhoea and unintended weight loss.

Data on other common AEs (not prespecified in the MTX label), such as thrombocytopenia, neutropaenia and abnormal liver function tests (LFT), were reported if the investigator considered them clinically relevant based on the central laboratory reports.

Logistic regression modelling was performed to determine the association of the development of MTX-related toxicity with baseline characteristics, including age, gender, 28 Joint Disease Activity Score based on C reactive protein (DAS28(CRP)) score, rheumatoid factor (RF), RA duration, MTX treatment dose and prior MTX dosage (for MUSICA only).

Measurement of intracellular MTX-PG
Intracellular erythrocyte levels of MTX-PG with chain lengths 1–5 were measured at baseline and weeks 2, 4, 8, 12, 16, 20 and 24/26 using a sensitive and selective validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) biochemical method (online supplementary methods). The mean PG1+2 (short chain), PG3 (long chain) and PG4+5 (very long chain) levels in patients who experienced or did not experience MTX-related toxicity at baseline, week 4 and week 24/26 were calculated.

RESULTS
Baseline demographics and disease characteristics
In both trials, patients had moderate-to-severe RA at baseline as indicated by mean DAS28(CRP) scores. Patients in CONCERTO had a mean disease duration of 0.32±0.5 years, and were MTX-naïve and biologic-naive (table 1). The mean duration of MTX exposure during the trial was approximately 172.2 days; for the 2.5, 5, 10 and 20 mg/week groups, the mean exposure was 167.8±38.3, 172.9±27.9, 175.1±22.3 and 172.0±27.2 days, respectively.

Patients in MUSICA had a mean disease duration of 5.3±7.6 years. Out of 309 patients, 151 (48.9%) received 15 mg/week MTX prior to study entry; 40 (12.9%) received 17.5 mg/week MTX; 118 (38.2%) received ≥20 mg/week; and 17 (5.5%) had exposure to one prior biologic DMARD. The mean duration of prior MTX exposure was 1.5±2.8 years, while the mean prior
MTX dosage was 17.3±2.3 mg/week. During the trial, the mean duration of MTX exposure was ~157.5 days and the mean duration of MTX exposure for the 7.5 and 20 mg/week groups was 157.4±30.9 and 157.6±30.7 days, respectively.

### ADA+MTX efficacy and MTX-related toxicity

In both trials, and generally for each MTX dosage group, the rate of MTX-related toxicity peaked at week 4 and remained steady thereafter, whereas the ACR50 response rate increased over time. In CONCERTO, the ACR50 response rates and MTX-related toxicity rates were in increasing trend with the MTX dosages (figure 1A). At week 26, the ACR50 response rates for the four MTX dosage groups ranged from 54% to 68%, while the MTX-related toxicity rates ranged from 2.4% to 17.8%. In MUSICA, both MTX dosage groups reported similar ACR50 response rates and MTX-related toxicity over 24 weeks of treatment (figure 1B). At week 24, the ACR50 response rates were 32.3% and 37.5% for the 7.5 mg/week and 20 mg/week MTX dosage groups, respectively, while the MTX-related toxicity rate was 6.5% for both groups.

In CONCERTO, in general across MTX dosage groups, the proportion of patients with MTX-related toxicity (white bars, figure 2A) remained steady over time, with an increase for the 20 mg/week group. Over time, the proportion of patients with an ACR50 response (black bars) increased. A small proportion of patients achieved an ACR50 response while experiencing some MTX-related toxicity (grey bars); this proportion increased slightly over time for the 20 mg/week MTX dosage group. In MUSICA, for both MTX dosage groups, a similar pattern as in CONCERTO was observed, although with a lower rate of efficacy (figure 2B).

### Time to the first ACR50 response or MTX-related toxic event

In CONCERTO, out of 388 patients with ACR50 data available, 113 (29.1%, grey line) experienced...
MTX-related toxicity at least once, and 289 (74.5%, black line) achieved ACR50 at least once (figure 3A). The mean study duration was similar for the group who developed MTX-related toxicity (n=113) and for the group that did not (n=275) (24.6 and 25 weeks, respectively). Among the 91 patients with MTX-related toxicity and available ACR50 data, 37 (40.1%) achieved ACR50 and later developed MTX-related toxicity, 15 (16.5%) had ACR50 and MTX-related toxicity simultaneously, and 39 (42.9%) developed MTX-related toxicity earlier in the study and subsequently achieved ACR50.

In MUSICA, out of 305 patients with ACR50 data available, 71 (23.3%, grey line) experienced MTX-related toxicity at least once, and 146 (47.9%, black line) achieved ACR50 at least once (figure 3B). The mean study duration was similar for the groups that developed MTX-related toxicity (n=71) and the group that did not (n=234) (22.6 and 22.5 weeks, respectively). Among the 29 patients with MTX-related toxicity and ACR50 response, 11 (37.9%) achieved ACR50 and later developed MTX-related toxicity, 6 (20.7%) had ACR50 and MTX-related toxicity simultaneously, and 12 (41.4%) developed MTX-related toxicity earlier in the study and subsequently achieved ACR50.
subsequently achieved ACR50. These results from both trials indicate that development of MTX-related toxicity did not prevent the subsequent achievement of an ACR50 response.

**MTX-PGs and MTX-related toxicity**

Levels of accumulated intracellular MTX-PGs were determined in patients with or without MTX-related toxicity. In CONCERTO, increases in PG (PG1+2, PG3 and PG4+5) were observed with time and with dose; the increase was more pronounced for the PG3 and PG4+5 than for PG1+2 (figure 4A). The pattern of PG accumulation did not differ between patients with or without MTX-related toxicity, indicating that there was no apparent correlation between the concentration of these MTX-PGs and MTX-related AEs in CONCERTO.

For patients in MUSICA, who were entering the study with MTX at ≥15 mg/week, in general, the proportions of PG did not change much over time, except for a decrease in PG3 and PG4+5 for patients on 7.5 mg/week at week 24 (figure 4B). There were no major differences in PG accumulation with time and dose.
when comparing patients with and without MTX-related AEs. The only exception was observed for patients in the 20 mg/week MTX group, where the mean PG1+2 concentration was higher at baseline for patients with MTX-related AEs than for those without. However, there were only two patients with an AE, one with a relatively high MTX PG1+2 concentration.

**MTX-related toxicity**

In CONCERTO overall, 113/395 patients (28.6%) reported 345 MTX-related AEs (table 2): 1 event was a serious AE (excessive fatigue and/or malaise), 4 events were severe AEs (three infections and one event of excessive fatigue and/or malaise in three subjects), 78 events were moderate AEs and 10 events in two subjects led to the discontinuation of study drug. The MTX-related AEs that were most frequently reported were infection, nausea and/or vomiting, abnormal hair loss and stomach pain/discomfort. The proportion of subjects who reported these MTX-related AEs was numerically higher in the 10 mg and 20 mg MTX dose groups.

In MUSICA overall, 71/309 patients (23%) reported 185 MTX-related AEs (table 2): 5 events in four patients were serious AEs (four infections and one fever and/or chill), 3 events in three patients were severe AEs (three infections), 58 events were moderate AEs, 124 events were mild AEs and 6 events in four patients led to discontinuation of study drug. The proportion of patients reporting MTX-related toxicity was comparable between the 7.5 mg MTX and 20 mg MTX groups. The MTX-related AEs that were most frequently reported by at least 3% of all patients were infection, nausea and/or vomiting, abnormal hair loss and stomach pain/discomfort.

**AE not prespecified on the MTX label**

In CONCERTO, no patients reported thrombocytopenia or neutropenia. Two patients reported abnormal LFTs, both probably related to MTX as assessed by the investigator; one patient on 20 mg MTX had a moderate non-serious AE (elevated LFT) leading to discontinuation of the study drug, and one patient receiving 10 mg MTX had a mild non-serious AE (elevated LFT) reported 37 days after study completion, which led to reduction of MTX dose.

In MUSICA, no patients reported neutropenia and one patient reported thrombocytopenia, which was considered mild by the investigator, unrelated to either ADA or MTX, and which did not lead to study discontinuation. Two patients had abnormal LFT; both were assessed by the investigator to be mild and non-serious: one patient receiving 7.5 mg MTX had an elevated LFT, which could be MTX-related or ADA-related, which led to a temporary discontinuation of study drug. The other
patient, receiving 20 mg MTX, had elevated LFT, probably unrelated to ADA, possibly related to MTX, which did not result in any changes in MTX dose.

Factors associated with development of MTX-related toxicity

In CONCERTO, compared with male patients, female patients had a higher probability of developing toxicity (OR, 95% CI 1.934 (1.064 to 3.521)). Compared with patients receiving 5 mg/week MTX, patients receiving 10 or 20 mg/week MTX were at a higher risk for developing toxicity (OR, 95% CI 2.092 (1.087 to 4.032) and 2.037 (1.063 to 3.906), respectively).

In MUSICA, younger patients were at a slightly higher risk of developing toxicity (OR, 95% CI 1.024 (1.000 to 1.048)). The mean age of patients was 54.7±13.0 years and 55.0±11.3 years for patients with and without toxicity, respectively. MTX dose, gender, disease duration and RF value were not associated with development of toxicity.

DISCUSSION

Owing to its low cost and efficacy, treatment with MTX, either as monotherapy or in combination with other DMARDs, is a mainstay of the treatment of RA. Combination therapy with MTX and anti-TNF biologics has been demonstrated to inhibit structural damage and improve disease activity to a greater extent than monotherapy with either the biologic or MTX alone.\(^3\)\(^4\)\(^5\)\(^6\) The coadministration of MTX can improve efficacy by suppressing the formation of antidrug antibodies,\(^7\) which are associated with reduced serum levels and clinical response.\(^8\)\(^9\)\(^10\) The increased efficacy could also be attributed to MTX and TNF inhibitors acting on different molecular pathways, thus providing additive effects. However, some patients may experience MTX-related toxicities, with some discontinuing MTX as a result. Here, we examined the prevalence, onset and severity of MTX-related toxicities (specified in the label) in relation to the efficacy of combination therapy with ADA+MTX, in two different trial populations: MTX-naïve patients with early RA, and patients with established RA and an inadequate response to MTX. These trials were unique in design, since the patients were blinded to the dose of MTX, and thus for instance did not know if they took 2.5 or 20 mg.

In both study populations, the majority of AEs to MTX were mild and led to discontinuation in only 0.5% (CONCERTO) or 1.3% (MUSICA) of patients. The rate of MTX-related toxic events remained steady (around 20%), while efficacy increased over time. Consistent with this observation, the proportion of patients who achieved efficacy as measured by an ACR50 response increased over time. Few patients experienced toxicity without efficacy, and in general this proportion decreased over time, concomitant with an increase in the proportion of patients who achieved efficacy.

Importantly, in both populations, efficacy was achieved despite reported MTX-related toxicity, which remained stable. Across both trials, approximately 40% of patients experienced a toxic event before achieving an ACR50 response. Of the MTX-related toxic events, infections were the most frequent. Although not specified on the MTX label, hepatotoxicity is a commonly noted MTX-related AE; however, in both trial populations included here, hepatotoxic events were infrequent (0.5% and 0.6% in CONCERTO and MUSICA, respectively) and cytopenias occurred at a low rate in CONCERTO (0.5%), and not in MUSICA. This may reflect continuous folate administration required in both trials.

In CONCERTO, but not MUSICA, there was an increased incidence of MTX-related AEs in groups receiving higher MTX doses. Efficacy showed MTX dose dependence, with the 2.5 mg dose and 5 mg MTX dose appearing to have similar efficacy, as did the 10 mg and 20 mg MTX doses.\(^13\) In MUSICA, ACR50 as well as ACR20/70 responses, were numerically slightly higher for the 20 mg/week MTX group.\(^14\)

MTX is modified in bone-marrow erythrocytes, by the addition of glutamate moieties to form chains of 1–2 (short chain), 3 (long chain) or 4–5 (very long chain) PG derivatives.\(^9\)\(^10\)\(^11\) These intracellular MTX-PG derivatives persist long after the decrease of serum levels of MTX, and have been shown to be associated with treatment efficacy in RA.\(^10\)\(^11\)\(^12\)\(^13\) In CONCERTO, but not MUSICA, there was a dose-dependent increase in MTX-PG1+2, 3 and 4–5. Preliminary analysis (not shown) demonstrated that weight was not a significant covariate for the accumulation of MTX-PG1+2 in either trial. In a Japanese cohort, MTX-PG accumulation was shown to be dependent on body mass index rather than body weight.\(^15\) MTX-related toxicity did not appear to be driven by MTX-PG, in patients from either trial, as indicated by the similar pattern of PG accumulation in patients who experienced or did not experience MTX toxicity. However, it is possible that the MTX-PG is not the sole contributor to MTX-related AEs. In MUSICA, the apparently higher MTX-PG1+2 levels at baseline for the 20 mg/week MTX group in patients with AEs compared with patients without AEs was due to one of the two patients in this group having a relatively high MTX PG1+2 concentration, contributing to the high mean MTX PG1+2 for this group.

MTX-related toxicity and ADA+MTX treatment efficacy showed similar patterns in both the early and established RA populations examined here. We used the ACR50 response, which indicates a substantial improvement over baseline, to measure efficacy. An inherent limitation is that due to the lack of monotherapy comparator arms, AEs due to ADA cannot be separated from those due to MTX alone, and the 6-month period over which both populations were assessed for toxicity and efficacy is relatively short. As opposed to CONCERTO, patients included in MUSICA were already treated with MTX and thus represent a selected group who had not experienced intolerance to MTX. Additionally, the mean disease duration for patients in MUSICA and CONCERTO was 5.3 years and 0.3 years, respectively. These differences in study design and disease duration may explain why toxicity was observed in the same proportion in 7.5 mg/week and
20mg/week in MUSICA, whereas toxicity occurred in a higher proportion among patients receiving the highest doses of MTX in CONCERTO (online supplementary figure 1). Although the route of administration has been reported to impact the tolerability of MTX, patients in both studies included here only received orally administered MTX, so this could not be evaluated. As opposed to a clinical setting with most likely, lower drug adherence, all the patients in this analysis were enrolled in a clinical trial, which may have contributed to a cleaner safety profile for MTX. Conversely, target dosing is often achieved more rapidly in a trial versus clinical setting, which may have accentuated some minor MTX-related AEs. The observations in MUSICA are possibly closer to a real-world clinical setting, where ADA plus MTX combination treatment is not administered to MTX-naive patients. Monotherapy versus combination therapy with MTX has been studied for biologics with other mechanisms of action. Patients with early RA receiving abatacept plus MTX had greater benefits than those on MTX monotherapy, with a similar safety profile. In MTX-inequate responders receiving tocilizumab (TCZ) plus MTX experienced a similar level of disease control but reported more events of elevated liver transaminases versus patients receiving TCZ monotherapy.

In summary, treatment with MTX, especially in combination with TNF inhibitors, offers many benefits over monotherapy. Our study shows that significant MTX-related toxicity was low, did not preclude the development of a clinical response to ADA+MTX treatment and did not appear to be driven by MTX-PGs. In patients with both early and established RA, most MTX-related toxic events were mild and remained at steady rates while efficacy continued to increase. Overall, out of 704 patients in the two studies, only 6 (<1%) discontinued due to MTX toxicity.

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