Worldwide treatment opportunities of rheumatoid arthritis

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CHAPTER 4

Similar Short Term Clinical Response to High versus Low Dose Methotrexate in Mono- and Combination Therapy in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Aiming at rapid decrease of disease activity, there has been a trend to start with higher doses of methotrexate (MTX) in newly diagnosed rheumatoid arthritis (RA) patients, both as monotherapy and in combination with other antirheumatic drugs. We aimed to study the relationship between clinical response and MTX-dose as mono- or combination therapy in early RA patients.
Methods: DMARD naive early RA-patients from a large international observational database, the METEOR database, were selected if MTX was part of their initial treatment. Patients were divided into 4 groups: MTX monotherapy, MTX + csDMARDs, MTX + glucocorticoids or MTX + bdMARDs. MTX-dose was dichotomized: low dose ≤10 mg/week; high dose ≥15 mg/week. Linear mixed model analyses for DAS, DAS28 and HAQ were performed for each medication group, with MTX-dose and time as covariates. Outcomes were assessed from baseline until 3-6 months follow-up. Associations were adjusted for potential confounding by indication by propensity score (PS) modelling.
Results: For patients starting MTX monotherapy (n=523), MTX + csDMARDs (n=266) or MTX + glucocorticoids (n=615), the PS-adjusted effects of MTX-dose (high versus low) on DAS, DAS28 and HAQ were small and not clinically meaningful. Patients starting MTX + bDMARDs were disregarded due to low numbers (n =11).
Conclusions: In newly diagnosed RA-patients, no clinical benefit of high over low initial MTX-doses was found for MTX monotherapy or for MTX combination therapy with csDMARDs or glucocorticoids.

BACKGROUND

Methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA). Current recommendations for MTX monotherapy suggest to initiate 15 mg/week orally, and escalate with 5 mg/month to 25-30 mg/week or the highest tolerable dose.[1, 2] No specific recommendations exist for MTX used in combination with other antirheumatic drugs (glucocorticoids, csDMARDs and/or biological DMARDs (bDMARDs)). Many studies have shown faster reduction of disease activity, quicker improvement in physical functioning and less radiographic damage progression on MTX combination therapy than on MTX monotherapy.[3-6] It is questionable whether a higher initial MTX-dose in combination with other effective medication is more effective than lower initial MTX-dose regarding short-term results. The CONCERTO study compared four treatment arms with different MTX-doses (2.5, 5, 10 or 20 mg/week) in combination with adalimumab 40 mg/2 weeks in early RA-patients.[7] More patients achieved Disease Activity Score 28 (DAS28) low disease activity or remission with increasing MTX-doses over 26 weeks. However, radiographic progression and Health Assessment Questionnaire (HAQ) scores were similar in the various arms. Proportions of patients achieving low disease activity or remission were similar in the MTX 10 and 20 mg/week arms.
Recently, a meta-regression analysis of trials in recent onset RA-patients showed that higher initial MTX-doses were not associated with better short term clinical outcomes, neither for MTX monotherapy, nor in combination with bDMARDs or glucocorticoids.[8] In the current study we aim to assess the influence of MTX-dose on disease outcomes and physical functioning in an international cohort with real-life data. We hypothesized that in patients with newly diagnosed RA the initial MTX-dose as monotherapy or in combination with other csDMARDs, bDMARDs or glucocorticoids will not determine short-term outcomes.

METHODS

Data selection

Data from the international, observational METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology) database were used, which has been described previously.[9] For the current study, we selected all DMARD-naive early RA-patients with symptom duration <5 years, with ≥1 follow-up visit after 3-6 months. At both baseline and follow-up visits, patients had to have at least one of the following outcome measures: DAS, DAS28, ESR, CRP or HAQ. MTX had to be part of the initial treatment, (as monotherapy or in combination with other csDMARDs/bDMARDs/glucocorticoids). Variation in dose was allowed (e.g. step-up MTX-dose or step-down prednisone dose) but

no change in medication type was allowed between initial treatment and follow-up visit after 3-6 months. Since the METEOR database consists of observational data gathered in clinical practices, irregular time intervals between follow-up visits exist and number of follow-up visits differ per patient. Therefore, the last visit within 3-6 months after treatment initiation meeting all in- and exclusion criteria was defined for each patient, and all follow-up visits between baseline and this last follow-up visit were selected. In order to take into account step-up dosing schedules, the MTX-dose prescribed at the final visit before 3 months follow-up was used.

Statistical analysis

Patients were analysed in four groups, based on initial MTX-strategy: 1) MTX monotherapy, 2) MTX+other csDMARDs, 3) MTX+glucocorticoid (+/- additional csDMARDs) or 4) MTX+bDMARD (+/- additional csDMARDs). Missing data were imputed using multivariate normal multiple imputation (30 cycles). Linear mixed model (LMM) analyses were performed to assess the effectiveness of MTX-dose on the outcome measures DAS, DAS28 and HAQ, within the 4 groups. To account for irregular time intervals, random intercept and slope were added to each model, with 'independence' covariance matrix. MTX-dose was dichotomized ('low dose' ≤10 mg/week; 'high dose' ≥15 mg/week). Time in days between baseline and each follow-up visit was added as continuous variable. Differences in environmental and patient characteristics may affect the initial MTX-dose, and therefore may have caused confounding by indication. To adjust for potential confounding, a propensity score (PS) was calculated in the imputed dataset, using multiple probit regression analysis based on observed baseline patient and environmental characteristics[10]. Several PS models were tested and compared regarding best data fit, in all 30 imputations. Representing the probability of receiving an intervention given observed baseline variables, the PS was then added as covariate adjustment to the LMM analyses. Details regarding the PS are described in online Supplementary file 1. All LMM analyses were performed with and without PS, to see whether confounding by indication was present. All analyses were performed using STATA SE 14 (StataCorp LP).

RESULTS

From the METEOR database, 1438 patients (3193 visits) were selected: 523 patients (1120 visits) started MTX monotherapy, 266 patients (581 visits) started MTX+csDMARDs, 615 patients (1416 visits) started MTX+glucocorticoids and 11 patients (26 visits) started MTX+bDMARD (figure 1). Detailed information regarding concomitant treatment is presented in online supplementary file 2. Patients originated from 20 different countries,

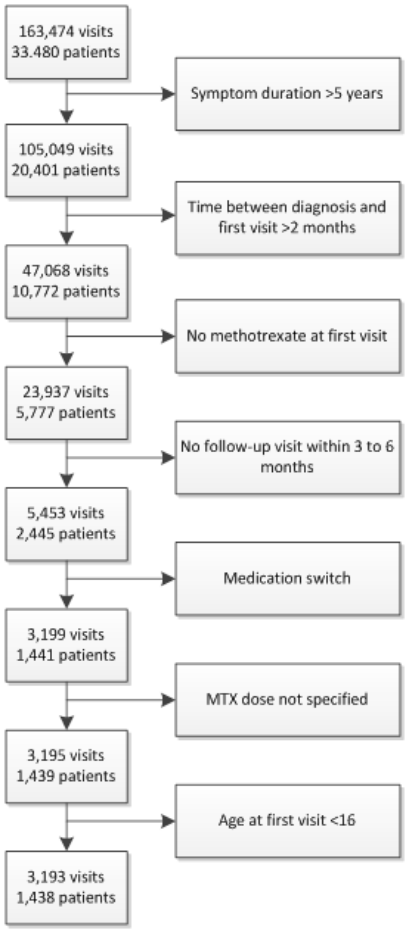

Figure 1. Flow chart of the patient selection.

with 94% of data originating from India, South-Africa, Portugal, the Netherlands, the United States, Ireland and Mexico. Too few patients started MTX+bDMARDs to perform meaningful analyses. In addition, 23 patients (50 visits) who started MTX 12.5 mg/week (the intermediate dose) were disregarded. Baseline characteristics of the other patients are shown in table 1. There was a trend over time to start higher MTX doses (online supplementary file 3).

Since physicians were free to choose their own disease activity measure, DAS and DAS28 based on ESR were missing in 40% and 35% of all visits, respectively. However, in only 4% of all visits no official disease activity measure was available and in only 0.3% of all visits no disease activity measure component was available.

In table 2, the PS-adjusted and unadjusted coefficients for the association between initial MTX-dose and outcomes within 3-6 months follow-up are presented, stratified

per treatment group. For patients starting MTX monotherapy, MTX+csDMARDs or MTX+glucocorticoids, the PS adjusted effects of MTX-dose (high vs low) on DAS, DAS28 and HAQ were small and not clinically meaningful. For example, in the MTX monotherapy group, β (95% CI) for outcome DAS was 0.070 (-0.15;0.29), indicating an increase in DAS of 0.070 for a high versus a low MTX-dose.

The unadjusted main associations between MTX-dose and outcomes were often in opposite direction and/or much larger than the PS adjusted associations, suggesting that confounding by indication indeed plays a role and that it has been (at least partly) corrected for by adjusting for the PS. Two sensitivity analyses were performed: one excluding the country which added most patients to the analyses (India) and one excluding all patients with a symptom duration >2 years, both resulted in similar outcomes (data not shown).

Table 1. Baseline characteristics per treatment group, non-imputed data. Data per number of patients are means (SD), unless indicated otherwise.

	MTX monotherapy (n=523)		**MTX+csDMARDs (n=266)**		**MTX+glucocorticoids (n=615)**	
	n		n		n	
Age at first visit *(years)*	522	47.9 (13.1)	264	44.6 (10.9)	479	48.3 (14.8)
Gender *(% female)*	520	78	266	83	609	81
Body Mass Index	281	26.6 (6.7)	184	27.6 (6.3)	272	27.2 (6.0)
Symptom duration at diagnosis *median (IQR)*	451	365 (169-731)	266	730 (365-1095)	482	458 (181-1095)
Rheumatoid factor *(% positive)*	511	77	263	84	585	81
ACPA *(% positive)*	300	72	98	85	342	76
Erosions present *(% positive)*	305	40	62	55	293	52
ESR	462	56.5 (33.0)	241	69.3 (31.7)	543	59.5 (35.5)
CRP	415	33.1 (33.9)	219	40.3 (35.5)	515	37.7 (37.1)
HAQ	439	1.0 (0.6)	249	1.1 (0.6)	506	1.3 (0.7)
DAS	314	3.7 (1.2)	189	4.0 (0.96)	347	3.9 (1.2)
DAS 28	340	5.7 (1.5)	192	6.2 (1.2)	415	6.0 (1.5)
MTX-dose *(% high dose)*	523	28	266	14	615	46
Follow-up duration *(days)*	523	134 (28)	266	135 (28)	615	139 (31)

Table 2. Unadjusted and propensity score adjusted results of the linear mixed model analyses to investigate the effectiveness of high versus low methotrexate doses on disease activity (DAS and DAS28) and physical functioning (HAQ), stratified per medication group.

Methotrexate monotherapy (n patients=522, n visits=1090)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	0.070 (-0.15; 0.29)	0.12 (-0.19; 0.43)	0.060 (-0.09; 0.21
MTX-dose group unadjusted	-0.63 (-0.79; -0.47)	-0.90 (-0.13; -0.67)	0.16 (0.055; 0.26)
Methotrexate+csDMARDs (n patients=262, n visits=567)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	0.051 (-0.23; 0.33)	0.024 (-0.37; 0.42)	-0.0058 (-0.20; 0.19)
MTX-dose group unadjusted	-0.18 (-0.44; 0.072)	-0.28 (-0.63; 0.072)	0.092 (-0.085; 0.27)
Methotrexate+oral glucocorticoid (+/-csDMARDs) (n patients=615, n visits=1403)			
	DAS β (95% CI)	**DAS28 β (95% CI)**	**HAQ β (95% CI)**
MTX-dose group PS adjusted	-0.047 (-0.26; 0.16)	-0.16 (-0.44; 0.12)	-0.028 (-0.16; 0.11)
MTX-dose group unadjusted	-0.42 (-0.56; 0.28)	-0.74 (-0.93; -0.55)	0.13 (0.045; 0.22)

DAS=disease activity score, HAQ=Health Assessment Questionnaire, PS=propensity score, 95% CI=95% confidence interval. MTX-dose group is a binary variable with low dose ≤10 mg/week and high dose ≥15 mg/week. Time is modelled in days between the baseline visit and each follow-up visit. Low dose is the reference category.

DISCUSSION

In this study based on daily practice treatment decisions in newly diagnosed RA-patients, we did not find a clinical benefit of high over low MTX starting doses in monotherapy or in combination with csDMARDs or glucocorticoids: high initial MTX-doses did not result in greater improvement in DAS, DAS28 or HAQ compared to low initial MTX-doses. Co-medication with csDMARDs or glucocorticoids did not influence this effect. In an earlier metaregression analysis we showed that also in clinical trials there was no early clinical benefit of a high over a low MTX starting dose.[8]

We found a trend over time in daily practice to start higher MTX doses. In particular patients receiving co-medication with glucocorticoids as initial treatment were prescribed higher MTX doses, possibly as the rheumatologist estimated their RA to be more severe. Although we used PS to adjust for baseline differences that may have influenced treatment decisions of the rheumatologist as well as outcomes, intangible or unmeasured baseline differences may still affect the results.

We assessed response to treatment within 3-6 months, since current recommendations

advise a treat-to-target strategy, in which medication is intensified or changed as soon as possible if treatment is not effective. The more rapid onset of action of glucocorticoids as co-treatment may mask any effect of the initial dose of slow acting MTX.[3, 11] As demonstrated in clinical trials, this appears also to be true for initial treatment with bDMARDs and MTX, but as this is a rare initial treatment in daily practice, we were unable to investigate this further. However, also for MTX monotherapy a higher dose was not more effective than a low dose. The most likely explanation is in the pharmacokinetics of MTX, where a stable availability of active MTX-polyglutamates seems independent of the weekly MTX dose.[12]

This study has potential limitations. The effect of MTX-dose was assessed within 3 subgroups depending on presence and type of co-medication, but within each group, variations in type, number and dose of additional drugs in individual patients could influence efficacy. However, previous clinical trials have shown comparable disease outcomes of various combination therapies and dosing schedules for many drugs are fixed.[13, 14] We dichotomized MTX-dosages, and defined MTX >15 mg/week as 'high' dose, which is used in current recommendations, but is still an arbitrary cut-off. Results might have been slightly different with other cut-offs. In addition, MTX was mostly administered orally, and uptake can vary between individuals. We have no further data on number and timing of patients who might have switched to subcutaneous treatment. Results might have been different for subcutaneous administration of MTX. Moreover, although we are unware of any evidence that the response to methotrexate could differ between the countries included in the analysis, we took into account a potential influence of country on our outcomes and adjusted for potential country differences by adding country to the propensity score.

Since real-world data were used, no formal procedures were taken to control the quality of clinical assessments, which may have led to more noise compared to clinical trial data. However, our data are in line with previous findings.[8]

CONCLUSION

In conclusion, these real-world data show that in newly diagnosed RA-patients, a higher MTX-dose with or without other csDMARD or glucocorticoids does not result in better clinical efficacy after 3-6 months compared to a low dose. This seems to contradict a general trend over time to start higher MTX-doses. Without apparent early benefit, higher initial MTX-dosages may introduce more side effects which may jeopardise drug retention. However, since side effects were not measured in the METEOR database, we could not assess this. On the other hand, starting a low MTX-dose may induce delays in suppression of disease activity and in the introduction of additional therapies, as previously up to 23%

of patients required higher dosages and up to 56% did not achieve low disease activity on MTX.[15] For the moment, our results suggest that although for MTX monotherapy there may be other considerations, rheumatologists should consider a low instead of a high initial MTX-dose, in particular when prescribed in combination with other csDMARDs or glucocorticoids, and further modify treatment according to a treat-to-target protocol.

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