Worldwide treatment opportunities of rheumatoid arthritis

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CHAPTER 3

Meta-regression of a dose-response relationship of methotrexate in mono- and combination therapy in DMARD naive early rheumatoid arthritis patients

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ABSTRACT

Objective: To investigate a possible short term dose-response relationship of initial treatment with methotrexate in monotherapy and combination therapy in recent onset rheumatoid arthritis (RA) patients.
Methods: A systematic literature search was performed on trials and cohorts including early, Disease Modifying Antirheumatic Drugs (DMARD) naive RA patients, treated with methotrexate, with data on clinical results within 6 months from treatment start. Cohen's effect sizes were calculated for the HAQ, ESR/CRP and/or DAS/DAS28 in 4 treatment groups: methotrexate monotherapy, or methotrexate in combination with synthetic (cs)DMARDs, biologic (b)DMARDs or glucocorticoids. Random-effects meta-regression analyses were performed for each outcome, with treatment group as predictor corrected for baseline HAQ or disease activity and assessment point.
Results: Thirty-one studies including 5589 patients were included. The meta-regression did not support higher effectiveness of increasing methotrexate dose in monotherapy. The number of treatment groups using combination therapy with csDMARDs was too small to perform meta-regression analyses.
In combination therapy with glucocorticoids a higher methotrexate dose was associated with higher (worse) outcome HAQ, but not with DAS/DAS28 or ESR/CRP. In combination therapy with bDMARDs a higher methotrexate dose was associated with higher outcome HAQ and DAS/DAS28, but not with ESR/CRP. All effect sizes were small.
Conclusion: In DMARD naive early RA patients who start methotrexate, either as monotherapy or in combination with bDMARDs or glucocorticoids, a higher initial dose of methotrexate was not associated with better clinical outcomes. This finding suggests that there is little short term gain from starting with high compared to low methotrexate doses.

INTRODUCTION

Methotrexate (MTX) is recommended and widely used as the drug of first choice in the treatment of newly diagnosed rheumatoid arthritis (RA) patients, either as monotherapy or in combination with other drugs, because it is (cost)effective and has an acceptable safety profile[1-3]. Although several mechanisms of action have been proposed, the exact mechanisms of action of MTX in reducing inflammation in RA patients are unknown[4, 5]. In the early trials MTX was used as subcutaneous injection in patients with severe RA refractory to other available medications such as non-steroidal anti-inflammatory drugs[6, 7]. In later years, the importance of initiating early antirheumatic treatment has become apparent [8, 9] and methotrexate was used in earlier disease stages. Initially, MTX was used as monotherapy in low dosages only (7.5-15 mg/week), as a precaution against possible side effects. Current recommendations are to start MTX in a dosage of 15 mg/week orally, escalating with 5 mg/month to 25-30 mg/week or the highest tolerable dosage[1, 3, 4].

Since it was shown that the safety profile of MTX is acceptable in most RA patients[10], higher initial MTX dosages were used in recent trials (20-30 mg/week)[11, 12]. Higher dosages have been reported to be more effective than lower dosages of MTX, although the number of adverse events also slightly increased[4, 12, 13].

Despite the reputation of high effectiveness of MTX, up to 75% of DMARD naive patients (depending on the outcome definition) do not reach a state of low-disease activity within 3 to 6 or even 12 months after starting MTX monotherapy in dosages of 20-25 mg/week[1]. Therefore, the effectiveness of MTX in combination with several other drugs has been investigated, including other conventional synthetic (cs)DMARDs and/or prednisone (or other corticosteroids) or biologic (b)DMARDs. These combination therapies have been shown to be superior to MTX monotherapy in reducing disease symptoms more rapidly and preventing radiographic damage in more patients[9, 14-16]. However, some combination therapies may also lead to more adverse reactions than MTX monotherapy[17, 18]. Specific recommendations regarding the MTX dosage when used in combination with other (types of) medication do not exist. Recently there is a trend in trials investigating combination therapy with bDMARDs – and possibly in daily practice too – to start MTX at the same high dosages as recommended for MTX monotherapy in order to decrease disease activity as quickly as possible[9, 11, 14, 19, 20]. Yet, it might still be that in the first 6 months of treatment, in combination with other drugs there is little additional benefit of higher doses of MTX compared to lower doses[21]. The CONCERTO study[22] recently investigated the effects of starting with various dosages of initial MTX (2.5, 5, 10 or 20 mg/week) in combination with adalimumab 40 mg/2 weeks. A statistically significant positive dose-response between MTX dose and number of patients reaching DAS28 low disease activity or remission was found over 26 weeks. However, among

patients on 10 mg or on 20 mg MTX per week, the proportion who achieved low disease activity or remission was similar. Also radiographic progression and HAQ were similar in all 4 MTX dosage groups.
We have conducted a systematic review of multiple trials and cohorts, in order to investigate the short term dose-response relationship of MTX in monotherapy and in combination therapy in DMARD naive early RA patients.

PATIENTS AND METHODS

Systematic search strategy
A literature search was performed with the help of a trained librarian in the following databases at February 27, 2015: Pubmed, Embase (OVID-version), Web of Science, COCHRANE, CENTRAL, CINAHL, Academic Search Premier and Science Direct. A separate literature search for meeting abstracts was performed in the databases Embase and Web of Science.

The search consisted of the combination of four subjects:

- Methotrexate
- Rheumatoid arthritis
- Drug administration and dosage
- Start of treatment

To optimize resemblance with daily practice, rheumatoid arthritis was defined by a clinical diagnosis of RA, and undifferentiated arthritis with a clinical suspicion of RA. In the majority of studies, the patients also fulfilled the current classification criteria for RA. The same query was applied in all databases, taking into account the terminological and technical differences between these databases. Various synonyms and related terms for all subjects were used. The exact search queries for each database can be found in online supplementary file 1.

Study selection
The following inclusion and exclusion criteria were used for study selection:

- Patients should have a clinical diagnosis of recent onset rheumatoid arthritis or undifferentiated arthritis with a clinical suspicion of RA
- Patients should be DMARD naïve
- MTX should be part of the first treatment strategy, either as monotherapy or in combination with other antirheumatic drugs (“combination therapy”).
- The exact dosage of all study medications should be described.

- Study results within 6 months after treatment start should be described.
- The study results should include measures of treatment effects.

One reviewer (SAB) selected articles for inclusion by title and abstract reading of each article. Abstracts and articles not written in English were translated if possible. A full-text assessment was performed when further information was required to determine whether an article met the inclusion criteria.

Data extraction

Relevant data regarding the outcome measures was extracted from each article. If necessary, authors were contacted to provide additional results. A quality assessment of each study was performed[23] and presented in online supplementary file 2. This quality assessment had no consequences for in- or exclusion of individual study results in the analyses.

Based on the availability of data and the sensitivity of the outcome measures to assess disease activity, the Health Assessment Questionnaire[24] (HAQ), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), disease activity score[25] (DAS) and DAS28[26] (either based on ESR or CRP, both based on 4 components) were chosen as main outcome measures. For each of these outcomes a lower value indicates or is fitting with a lower disease activity or functional ability. Means and standard deviations (SD) were extracted. If these were not available, mean and SD were estimated from median and range.[27] If data were only reported in graphs, data were extracted using Web Plot Digitizer version 3.9.[28] Only if means and SD could not be extracted from the article and authors could not provide the data, the study was excluded.

For each study it was determined at which time point the outcome measures were provided prior to a possible treatment change (this excludes a dose escalation protocol for the same medication). If the MTX dosage was increased within 6 weeks of treatment start, the final dosage was presented.

Data analysis

Cohen's effect size (ratio of mean change in score and baseline SD) and the corresponding standard errors and 95% confidence intervals were calculated for each treatment group. An effect size of 0.2 was considered small, an effect size of 0.5 was considered moderate and an effect size of 0.8 was considered large. In order to analyze the effect of MTX dose on disease activity, multivariate random-effects meta-regression analyses were performed with HAQ, ESR/CRP or DAS/DAS28 as outcomes. Unstructured variance-covariance matrices were used. Models were estimated using restricted maximum likelihood. If models did not converge, the multivariate method of moments procedure was used[29]. The meta-regressions were based on the effect sizes and variances (=squared standard errors) of the included treatment groups. Since effect sizes were calculated and ESR and

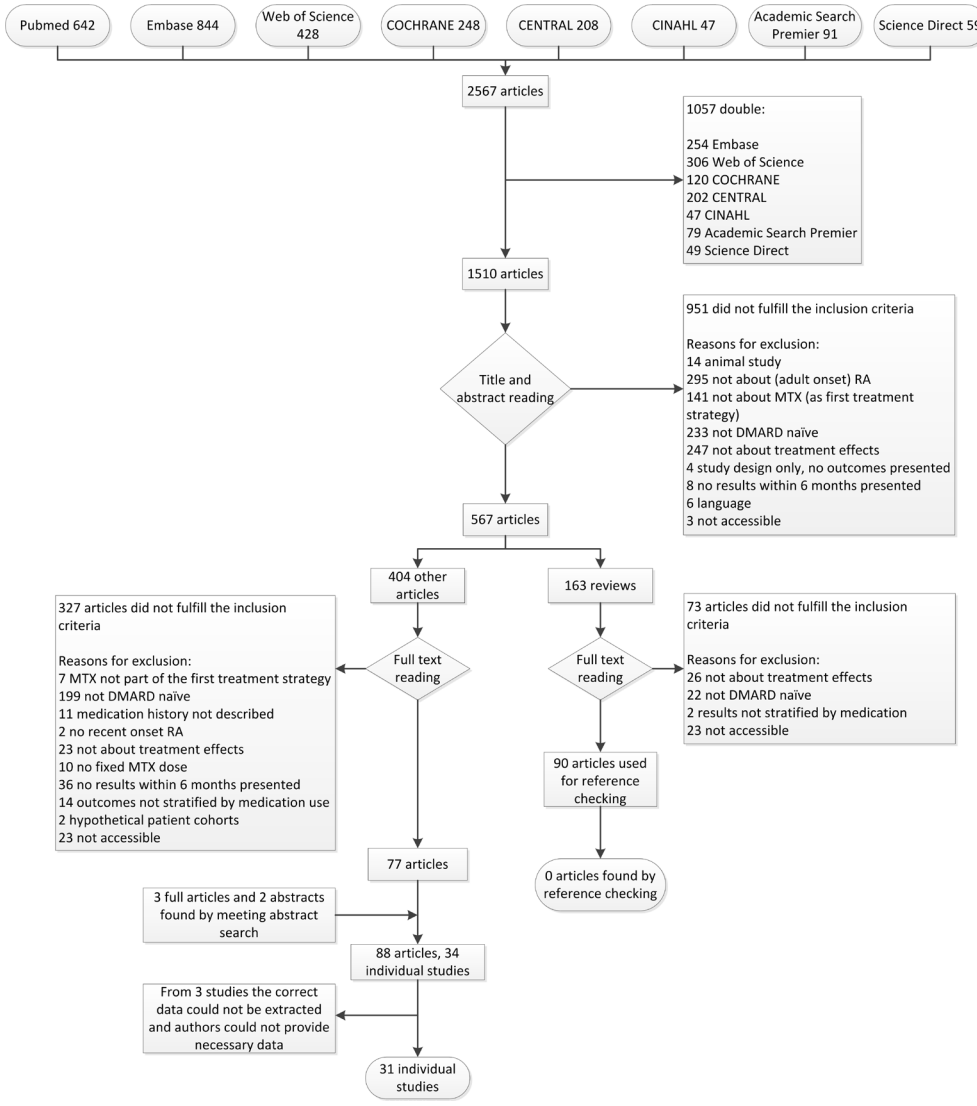

Figure 1: flow diagram of the research article selection procedure

CRP both measure similar constructs, the results for the ESR and CRP were combined in one meta-regression. The same applies to the DAS and DAS28. For the multivariate meta-regression analyses treatment groups were categorized in different medication strategies: 1) MTX monotherapy, 2) MTX in combination with other csDMARDs, 3) MTX in combination with a glucocorticoid (with or without csDMARDs) and 4) MTX in combination with a bDMARD (with or without csDMARDs). If two or more treatment groups fell in the same medication strategy, the results of these treatment groups were combined by taking

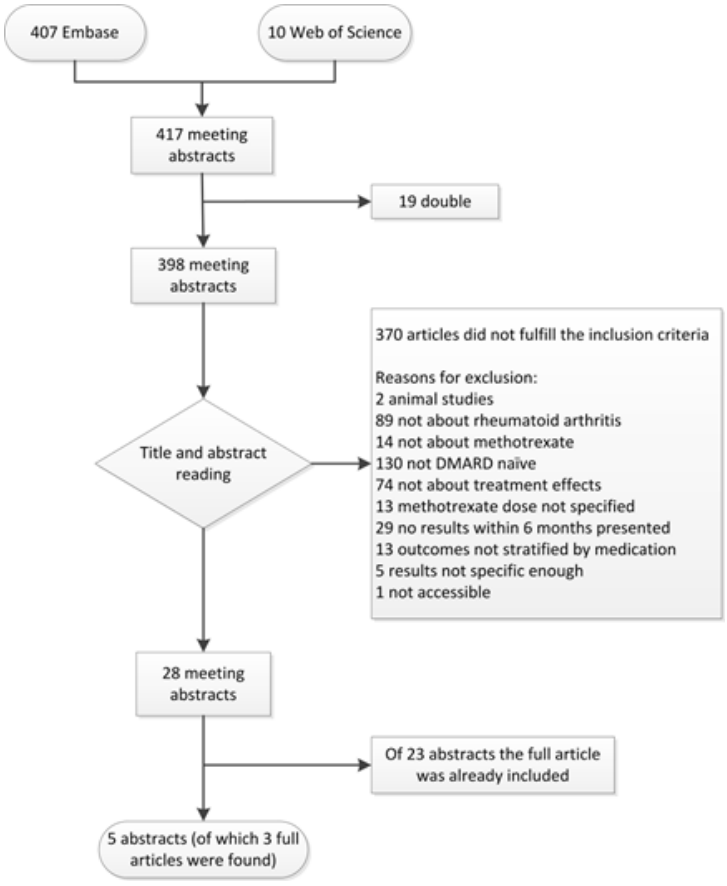

Figure 2: flow-diagram of the meeting abstract selection procedure.

the mean weighted by the sample sizes. Thus, each study could give up to at most 4 effect sizes and corresponding variances, which can be viewed as components of a 4-dimensional multivariate outcome which were analyzed by multivariate meta-regression using the program mvmeta of Stata. MTX dose was added as predictor to the model, together with the time point of assessment in months and the baseline HAQ, ESR/CRP or DAS/DAS28, in order to correct for the different follow up durations of the included studies and the baseline physical functioning or disease activity. Baseline ESR/CRP and DAS/DAS28 values were standardized by calculating [(mean at baseline minus cut-off value) / baseline standard deviation] in order to make values at baseline comparable. Cut-off values for DAS and DAS28 were remission (1.6 and 2.4 respectively) and for ESR and CRP no inflammation (25 and 10 respectively). The coefficient for MTX dose reflects the change in effect size of MTX dose within a medication strategy, independent of time point of assessment and baseline physical functioning or disease activity.

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
MTX monotherapy								
CAMERA[2] *[1, 2]*	7.5	148	3 months	-0.30 (-0.22; -0.38)	-0.37 (-3.32; 2.58)			
CIMESTRA[13] *[2]*[a]	7.5	80	3 months	-0.81 (-0.95; -0.66)	-0.41 (-5.74; 4.93)			-2.20 (-2.44; -1.96)
Quinn et al.[25] *[1]*	7.5[b]	10	3 months	0.058 (-0.54; 0.66)		0.10 (-23.95; 24.15)		-0.75 (-1.56, 0.07)
Haagsma et al.*[1]*	7.5	35	3 months		-0.38 (-9.19; 8.44)		-1.11 (-1.41; -0.81)	
BeSt[1] *[1, 2]*	15	237	3 months	-0.60 (-0.52; -0.68)	-0.45 (-4.00; 3.10)		-1.20 (-1.31; -1.10)	
HIT HARD[9] *[2]*	15	85	6 months	-0.94 (-1.07; -0.80)	-1.09 (-5.25; 3.08)			-3.00 (-3.19; -2.81)
OPERA[14] *[2]*	15[c]	91	3 months	-1.10 (-1.24; -0.96)		-0.38 (-8.69; 7.94)		-2.82 (-3.03; -2.61)
PROMPT[28] *[1]*	15	55	3 months	-0.20 (-0.33; -0.06)	-0.27 (-4.14; 3.60)		-3.54 (-3.74; -3.33)	
CareRA LR[29] *[1]*	15	47	4 months	-0.60 (-0.79; -0.41)				-1.08 (-1.55; -0.61)
Haroon et al.[12] *[1]*	17.5[d]	25	4 months				-3.49 (-4.01; -2.97)	
Chara et al.[31] *[1]*[e]	20[f]	52	6 months	-0.49 (-0.63; -0.36)		-0.93 (-3.03; 1.17)		-1.43 (-1.52; -1.05)

SWEFOT[7] *[1]*	20	405	3 months	-0.73 (-0.79; -0.67)	-0.63 (-3.15; 1.90)		-1.68 (-1.78; -1.58)
Ducreux et al.[10] *[2]*	20[g]	13	6 months				-1.17 (-1.88; -0.46)
TEAR[16] *[3, 4]*	20[h]	379	3 months			-1.17 (-1.28; -1.06)	
Revu et al [19] *[1]*	20[d]	20	2 months			-10.5 (-10.60; -10.40)	
Schipper et al.[20] *[1]*	20[i]	126	3 months				-1.15 (-1.36; -0.94)
Tan et al.[21] *[1]*[f]	20[d]	69	3 months	-0.75 (-0.88; -0.63)	-2.12 (-4.67; 0.44)		-0.71 (-0.93; -0.50)
Lisbona et al.[22] *[1]*	25[j]	33	4 months	-0.45 (-0.63; -0.26)	-0.64 (-6.10; 4.82)		-0.91 (-1.46; -0.37)
CAMERA-II[8] *[2]*	30[d]	119	3 months	-0.93 (-1.04; -0.82)	-0.33 (-4.65; 3.98)		-1.23 (-1.43; -1.03)
MTX + csDMARD							
CIMESTRA[13] *[1]*	7.5	80	3 months	-0.82 (-0.98; -0.67)	-0.63 (-6.15; 4.91)		-2.07 (-2.33; -1.80)
Haagsma et al.[26] *[3]*	7.5	35	3 months		-0.31 (-10.83; 10.21)	-1.38 (-1.64; -1.11)	
MTX + 2 csDMARDs							
Proudman et al.[24] *[1]*	10[k]	139	3 months		-0.57 (-4.82; 3.68)		-1.27 (-1.48; -1.07)
Roivainen et al.[23] *[1]*	15[l]	17	2 months		-0.82 (-17.03; 15.39)		2.83 (-3.40; -2.26)

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
TEAR[16] *[2]*	20[f]	132	3 months					-1.68 (-1.86; -1.49)
MTX + glucocorticoid								
CareRA LR[29] *[2]*	15[m]	43	4 months	-0.91 (-1.10; -0.71)				-1.3 (-1.79; -0.81)
CareRA HR[30] *[2]*	15[m]	290	4 months	-0.87 (-1.01; -0.73)			-2.64 (-2.85; -2.42)	
COBRA light[4] *[1]*	17.5[n]	81	6 months	-1.13 (-1.28; -0.97)	-0.98 (-5.91; 3.95)		-3.08 (-3.26; -2.91)	
Prioreschi et al.[18] *[1]*	20[g]	18	3 months	-1.10 (-1.51; -0.70)				
IDEA[17] *[2]*	20[d]	57	6 months	-1.13 (-1.27; -0.99)				
tREACH[3] *[3]*	25[d]	97	3 months	-0.54 (-0.68; -0.41)	-0.60 (-4.78; 3.59)		-1.21 (-1.40; -1.01)	
IMPROVED[6]	25[d]	610	4 months	-1.08 (-1.13; -1.03)	-0.74 (-2.65; 1.17)		-1.87 (-1.94; -1.78)	
CAMERA-II[8] *[1]*	30[d]	117	3 months	-0.76 (-0.89; -0.64)	-0.81 (-5.34; 3.72)			-2.34 (-2.57; -2.10)
MTX + csDMARD + glucocorticoid								
COBRA light[4] *[2]*	7.5	81	6 months	-1.21 (-1.36; -1.07)	-0.63 (-6.54; 5.28)		-2.45 (-2.64; -2.26)	
COBRA[5] *[1]*	7.5	76	6 months	-1.57 (-1.72; -1.41)	-1.18 (-8.82; 6.47)			

BeSt[1] *[3]*	7.5	97	3 months	-1.16 (-1.28; -1.04)	-0.96 (-5.19; 3.26)		-2.33 (-2.47; -2.18)	
CareRA HR[30] *[1]*	15[n]	290	4 months	-1.14 (-1.28; -1.00)			-2.33 (-2.57; -2.10)	
CareRA HR[30] *[3]*	15[m]	290	4 months	-1.09 (-1.22; -0.96)			-2.00 (-2.24; -1.76)	
Verschueren et al.[11] *[1]*	15	19	4 months	-1.01 (-1.35; -0.68)				-2.10 (-2.68; -1.53)
MTX + 2 csDMARDs + glucocorticoid								
FIN-RACo[27] *[2]*	7.5	97	3 months		-1.05 (-8.82; 6.47)			
NEO-RACo[15] *[2]*	10	49	3 months	-1.03 (-1.22; -0.83)	-0.95 (-7.11; 5.21)			-3.50 (-3.78; -3.22)
tREACH[3] *[1, 2]*	25[d]	184	3 months	-0.48 (-0.61; -0.35)	-0.21 (-3.53; 3.11)		-0.99 (-1.21; -0.77)	
MTX + bDMARD								
Quinn et al.[25] *[2]*	7.5[b]	10	3 months	-1.24 (-1.78; -0.70)		-1.43 (-18.72; 15.86)		-4.21 (-4.71; -3.72)
HIT HARD[9] *[1]*	15	87	6 months	-1.49 (-1.62; -1.36)	-1.62 (-4.16; 0.91)			-4.00 (-4.17; -3.83)
OPERA[14] *[1]*	15[o]	89	3 months	-1.34 (-1.48; -1.19)		-0.67 (-8.08; 6.74)		-2.66 (-2.90; -2.42)
TEAR[16] *[1]*	20[f]	244	3 months	-1.17 (-1.28; -1.06)				-1.79 (-1.93; -1.65)
IDEA[17] *[1]*	20[d]	55	6 months	-1.33 (-1.47; -1.19)				

Table 1: overview of effect sizes for each of the main outcome measures by treatment group.

Study [treatment group]	MTX dose mg/week	No. patients	Assessment point	ΔHAQ effect size (95% CI)	ΔESR effect size (95% CI)	ΔCRP effect size (95% CI)	ΔDAS effect size (95% CI)	ΔDAS28 effect size (95% CI)
BeSt[1] *[4]*	25[p]	126	3 months	-1.07 (-1.19; -0.95)	-0.63 (-5.45; 4.20)		-1.98 (-2.13; -1.83)	
MTX + 2 csDMARDs + glucocorticoid + bDMARD								
NEO-RACo[15] *[1]*	10	50	3 months	-1.70 (-1.87; -1.53)	-1.23 (-7.33; 4.87)			-2.57 (-2.96; -2.18)

[ ] denotes treatment group in study
Reference numbers refer to Supplementary File 4.
Treatment groups within each study which received equal treatment were combined.

[a] Betamethasone injections were given each visit to each swollen joint. [b] Initial dosage 7.5 mg/week, increased to 15 mg/week at 14 weeks. [c] Initial dosage 7.5 mg/week, increased to 20 mg/week in 2 months [d] If medication increased within 6 weeks, final dosage taken as dosage. [e] Initial dosage 10 mg/week, increased with increments of 5 mg/week to 20 mg/week. [f] Results in study shown for responders [1] and non-responders [2] separately. [g] Initial dosage 15 mg/week, increased to 20 mg/week [h] Escalated to 20 mg/week, initial dosage and time to highest dose unknown.
[i] Initial dosage 15 mg/week, increased with 5 mg per month [j] Initial dosage 2.5 mg/week, increased to 20-25 mg/week, time to highest dose unknown.
[k] Difference is the fish oil dosage. [l] Exact dosage not indicated, between 7.5 and 15 mg/week. [m] If disease activity remains high, MTX increased to 20 mg/week by week 8. [n] Initial dosage10 mg/week, increased to 25 mg/week in 9 weeks [o] Initial dosage 7.5 mg/week increased to 15 mg/week after 1 month and to 20 mg/week after 2 months [p] Initial dosage 25-30 mg/week

Table 2: Meta-regression on the effect of methotrexate-dose on HAQ (n=23), DAS/DAS28 (n=25) and ESR/CRP (n=21).

HAQ		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.008	0.584	-0.035; 0.020
	Month of assessment[a]	-0.0021	0.980	-0.17; 0.16
	Baseline HAQ	-0.11	0.570	-0.49; 0.27
Combination therapy with glucocorticoids	MTX dose (mg)	0.012	0.037	0.00070; 0.023
	Month of assessment[a]	-0.033	0.380	-0.11; 0.041
	Baseline HAQ	-0.42	<0.001	-0.63; -0.21
Combination therapy with bDMARDs	MTX dose (mg)	0.042	0.007	0.012; 0.073
	Month of assessment[a]	0.094	0.430	-0.14; 0.33
	Baseline HAQ	-0.71	0.240	-1.88; 0.47
DAS/DAS28		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.042	0.170	-0.10; 0.018
	Month of assessment[a]	-0.064	0.766	-0.48; 0.35
	Baseline DAS/DAS28	-0.62	<0.001	-0.78; -0.47
Combination therapy with glucocorticoids	MTX dose (mg)	-0.0010	0.954	-0.035; 0.033
	Month of assessment[a]	-0.046	0.672	-0.26; 0.17
	Baseline DAS/DAS28	-0.91	<0.001	-1.23; -0.60
Combination therapy with bDMARDs	MTX dose (mg)	0.033	0.013	0.0070; 0.059
	Month of assessment[a]	0.10	0.503	-0.19; 0.39
	Baseline DAS/DAS28	-1.03	<0.001	-1.38; -0.69
ESR/CRP		**β**	**P**	**95% CI**
MTX monotherapy	MTX dose (mg)	-0.043	0.372	-0.14; 0.052
	Month of assessment[a]	-0.20	0.593	-0.92; 0.53
	Baseline ESR/CRP	-0.81	0.281	-2.29; 0.66
Combination therapy with glucocorticoids	MTX dose (mg)	0.00074	0.994	-0.18; 0.18
	Month of assessment[a]	-0.061	0.926	-1.34; 1.22
	Baseline ESR/CRP	-0.83	0.848	-9.32; 7.66
Combination therapy with bDMARDs	MTX dose (mg)	0.037	0.880	-0.44; 0.52
	Month of assessment[a]	-0.25	0.841	-2.66; 2.17
	Baseline ESR/CRP	0.21	0.982	-18.15; 18.57

[a]Number of months after treatment start

RESULTS

The literature search resulted in 2,567 articles and 417 meeting abstracts. After removing duplicates, 1,518 articles and 398 meeting abstracts remained. Of these, 77 articles and 5 meeting abstracts (of which 3 full text articles were available) were included, providing information on 34 separate studies. Three of these studies had to be excluded, since means and SD could not be extracted for any of the outcome measures. This resulted in 31 studies (including 1 meeting abstract) with a total of 5,589 patients, of which 2,029 patients had received MTX monotherapy, 403 patients had received combination therapy with csDMARDs, 2,496 patients had received combination therapy with glucocorticoids and 661 patients had received combination therapy with bDMARDs. Several trials in which different medication strategies were investigated in early RA patients could not be included, since not all participants were DMARD naive (e.g. the PREMIER study[30], the COMET study[19] and the OPTIMA study[31]). Figure 1 shows a flow diagram of the selection procedure of the research articles and figure 2 a flow diagram of the meeting abstract selection procedure. In table 1 an overview of the effect sizes of the disease activity outcomes per treatment group is shown. Studies are grouped by medication strategy and ordered by increasing MTX dosage. The number of patients per treatment group ranged from 10 to 610 and the MTX dose ranged from 7.5 to 30 mg/week. Results could be presented at 2, 3, 4 or 6 months. A description of the exact treatment strategies can be found in supplementary file 2. Baseline disease activity for each treatment group varied from 'moderate' to 'high disease activity' according to the DAS (means ranging from 2.7 to 5.8) and DAS28 (means
ranging from 3.4 to 7), with most patients being in high disease activity. The HAQ varied from low to moderate (means ranging from 0.75 to 1.8), with most patients having a moderate HAQ. Baseline ESR ranged from 12 to 70 mm/hour, with most treatment groups having an average ESR close to 50 mm/hour. In table 1 it can be seen that all treatment groups showed an improvement in all outcomes at all assessment points, except for 1 small study, which showed small positive effect sizes for the HAQ and CRP[32]. Across all outcomes most of the effect sizes were large, with the DAS exclusively showing large effect sizes. Combination therapy with bDMARDs most often showed large effect sizes (89% large effect sizes), followed by combination therapy with glucocorticoids (87% large effect sizes), combination therapy with csDMARDs (70% large effect sizes) and MTX monotherapy (63% large effect sizes). In supplementary file 4,'bubble plots' are presented with effect sizes of the main outcome measures HAQ, ESR/CRP and DAS/DAS28 by MTX dosage. The results are grouped by the time point of assessment (in months) and medication strategy. For none of the medication groups there was a clear increase or decrease of effect size by increasing MTX dosages.
In table 2 the results of the meta-regression analyses are described for the HAQ, ESR/

CRP and DAS/DAS28, with the effect of MTX dose corrected for time of assessment (in months) and (standardized) baseline HAQ, ESR/CRP or DAS/DAS28, within the treatment strategies MTX monotherapy, combination therapy with glucocorticoids and combination therapy with bDMARDs. The effects of MTX dose within the combination therapy with csDMARDs could not be analysed because the number of treatment groups with csDMARD combination therapy was too small, and none of the studies compared csDMARD combination therapy to combination therapy with glucocorticoids.
Results for the HAQ showed that increasing MTX doses were not associated with higher efficacy in MTX monotherapy (i.e. no dose-response relationship). For the combination therapy with glucocorticoids (β= 0.012, 95% CI= 0.0007; 0.023) and the combination therapy with bDMARDs (β= 0.042, 95% CI= 0.012; 0.073) a small but statistically significant positive association was found with MTX dose. Results for the DAS/DAS28 also showed a small statistically significant positive association with MTX dose in combination therapy with bDMARDs (β=0.033, 95% CI=0.0070; 0.059), but not with glucocorticoids. Rather than denoting a better HAQ and/or DAS/DAS28 response, these results indicate a small increase in HAQ and DAS/DAS28 by increasing MTX doses for the respective combination therapy groups, although results were not clinically relevant. We did not find an association between ESR/CRP with increasing MTX dose in any of the 3 medication therapy groups.

DISCUSSION

This comprehensive meta-analysis did not provide support for starting MTX in higher dosages for DMARD naive early RA patients, neither as MTX monotherapy nor in combination with glucocorticoids or bDMARDs. In combination with glucocorticoids a higher MTX dose was even associated with a higher (instead of a lower) HAQ outcome and in combination with bDMARDs with a higher HAQ and DAS/DAS28 (but the effect sizes were only trivial).
As far as we know, this review is the first to investigate the dose-response relationship of MTX in combination therapy as initial treatment. There is a general expectation that, as in daily practice many patients require a dose increase to achieve optimal response to MTX, more patients will respond better after 3-6 months when starting on a higher rather than a lower MTX dose. A previous review [4] suggested that for MTX monotherapy a dosage of 15 mg/week escalating with 5 mg/month to 25-30 mg/week was the optimal strategy, which has consequently been implemented in current recommendations [1, 3]. The review included patients with established RA who were previously treated with other DMARDs. The aim of our study was to test the hypothesis that DMARD naive RA patients will have more clinical improvement on a higher dose of MTX than on a lower dose, not only with

MTX as monotherapy, but also with MTX as partner in combination therapy. Based on our results, we could not confirm the previously reported dose-response effect for MTX monotherapy after 3-6 months of initial treatment. It may be possible that DMARD-naive RA patients are more responsive to relatively low doses of MTX when assessed within 6 months than patients with a more advanced disease.

Recent trials have implemented the policy to start MTX in higher dosages in combination with corticosteroids or bDMARD. There is little evidence that in case of an insufficient response on MTX in combination with corticoids or bDMARDs, a dose increase in MTX will provide better outcomes. We hypothesized that the dose of MTX as partner in combination therapy with a corticosteroid or a bDMARD might not have much impact. In the CONCERTO trial[22], in MTX- naive, although potentially DMARD-treated patients, no differences in disease activity, radiographic progression or functional ability response after 6 months were found between MTX dosages of 10 or 20 mg/week in combination with adalimumab. Our results show that there is indeed no additional benefit for early response of starting with a higher rather than a lower dose of MTX in combination therapy. Although we corrected for baseline disease activity, it may be possible that the patients included in the studies with the highest starting doses had more severe disease, resulting in even higher HAQ and DAS28/DAS outcomes compared to the lower dosed studies. Another factor which could possibly influence the effect of MTX dose on disease activity is oral versus subcutaneous administration of MTX[33]. However, since subcutaneous MTX was used in only one study included in this review[34], this factor was not taken into account in the analyses. Considerations on which is the optimal starting dose of methotrexate are important because current recommendations focus on achieving early remission or at least low disease activity in all patients, as soon as possible[1]. For patients who do not achieve this within 3-6 months, tight control and treat to target strategies proclaim the intensification and extension of treatment, as soon as possible[35], since such a strategy may prevent progressive joint damage and irreversible functional disability[36]. Although we did not find evidence that a higher dose of MTX is associated with a better response by 3-6 months, starting with a higher dose may effectively reduce the time to switch to a more effective (combination of) drug(s), while the start of MTX in a lower dose may be associated with a delay in the start of more effective treatments.

In addition, several studies have now shown that a proportion of patients who have achieved rapid suppression of disease activity may taper medication without an ensuing disease flare or damage progression [37-39]. It is possible, though not studied, that the option to taper and stop glucocorticosteroids or bDMARDs is dependent on the dose of MTX co-medication. If true, this would be an argument why the initial MTX dose, either in combination with glucocorticosteroids or with bDMARDs, should be rather high or rapidly escalating.

On the other hand, a higher starting dose may result in more side effects, causing patients

to reduce the dose to ineffective levels or stop MTX. This could not be investigated in the current study since few of the included articles provided information on short-term side effects of the different MTX dosages. Earlier studies have suggested that higher MTX doses are associated with more (subjective) side effects, even though side effects appear to be less common when MTX is combined with glucocorticoids or bDMARDs [40, 41].
Only one study included in this review made a direct comparison between two MTX dosages in combination with a glucocorticoid[42]; therefore indirect comparisons between treatment groups of different studies had to be made, which have a higher risk of bias than direct treatment comparisons[43]. We have tried to reduce possible bias by adjusting for baseline disease activity and time of assessment, but we have insufficient data on -for instance- symptom duration at baseline, and presence or absence of autoantibodies and radiologic damage. We have to make a further reservation to extrapolate results of clinical trials with selected patients to daily practice with unselected patients.
To conclude, the results of this systematic review suggest that for DMARD naive RA patients who start on MTX either as monotherapy or in combination with glucocorticoids or bDMARDs, there is little if any additional benefit to be expected from starting with a high instead of a lower dose of MTX between 3 to 6 months from start of treatment. We therefore suggest that rheumatologists may consider to start MTX at a lower dose, in particular when prescribed in combination with a bDMARD or a glucocorticoid, and increase or change therapy in the setting of a treat-to-target protocol as recommended.

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SUPPLEMENTARY FILE 5: References of included studies

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