

SPECIAL REPORT

Methotrexate Dosing Regimen for Plaque-type Psoriasis: A Systematic Review of the Use of Test-dose, Start-dose, Dosing Scheme, Dose Adjustments, Maximum Dose and Folic Acid Supplementation

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There is a range of methotrexate dosing regimens for psoriasis. This review summarizes the evidence for test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and use of folic acid. A literature search for randomized controlled trials and guidelines was performed. Twenty-three randomized controlled trials (29 treatment groups) and 10 guidelines were included. Two treatment groups used a test-dose, 5 guidelines recommend it. The methotrexate start-dose in randomized controlled trials varied from 5 to 25 mg/week, most commonly being either 7.5 mg or 15 mg. Guidelines vary from 5 to 15 mg/week. Methotrexate was administered as a single dose or in a Weinstein schedule in 15 and 11 treatment groups, respectively; both recommended equally in guidelines. A fixed dose ($n=18$), predefined dose ($n=3$), or dose adjusted on clinical improvement ($n=8$) was used, the last also being recommended in guidelines. Ten treatment groups used folic acid; in 2 it was allowed, in 14 not mentioned, and in 3 no folic acid was used. Most guidelines recommend the use of folic acid. Authors' suggestions for methotrexate dosing are given. *Key words: psoriasis; methotrexate; dosing; systematic review.*

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If topical medication and phototherapy are insufficient in controlling chronic plaque-type psoriasis (termed psoriasis in this article) the next step in the therapeutic strategy is systemic therapy, with methotrexate (MTX) frequently being used (1).

However, MTX has potentially serious side-effects, including myelosuppression, pulmonary fibrosis and gastro-intestinal disorders. The most prominent long-term side-effect is hepatotoxicity (2, 3). Folic acid (FA) is administered to prevent side-effects; however, this may reduce the efficacy of MTX (4, 5).

The US Food and Drug Administration (FDA) approved the use of MTX for the treatment of psoriasis in 1972 (6) before high-quality studies were accepted

as the standard by which to judge efficacy and safety. Guidelines regarding the dosing regimen for MTX are partially based on expert opinions (2) and vary in their recommendations. In daily clinical practice there is a wide variety of dosing regimens (7) and patients with psoriasis are often undertreated (8). Barker et al. (9) have identified a number of key questions about MTX therapy for psoriasis and have emphasized the need for appropriate studies to determine optimal dosing with regard to efficacy and safety. A survey of dermatologists worldwide identified that the clinical use of MTX in psoriasis is not uniform and is not in full agreement with clinical guidelines (7).

The aim of this systematic review is to provide an up-to-date overview of randomized controlled trials (RCTs) using oral MTX monotherapy in adults for the treatment of psoriasis and to summarize evidence from these RCTs for the MTX dosing regimen regarding a test-dose, start-dose, dosing scheme, dose adjustments, maximum dose, and the use of FA. Also, recommendations from aggregated evidence (AgEv; guidelines and expert meetings) were summarized. Based on this review, initial suggestions for MTX dosing are given for future consensus and guidance in daily practice.

METHODS

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (10).

A search for RCTs and AgEv in the following databases was performed by an expert librarian (JL) from inception till 26 September 2013: MEDLINE (OVID), EMBASE (OVID) (both with a methodological filter to identify RCTs adapted from Cochrane (11)), the Cochrane Library complemented with a search of PubMed. TRIP and National Guideline Clearinghouse (NGC) were searched additionally for AgEv, complemented by AgEv known to the authors. The meta-register of controlled trials and clinicaltrials.gov were screened for ongoing trials. The search consisted of Subject Headings (if applicable), keywords and words in title and abstract for psoriasis and MTX. Reference Manager[®] software (version 12.0) was used to manage references.

Selection of articles

Two authors (SM and PD) independently selected all articles for eligibility, based on title, abstract and full-text. In cases of dis-

agreement, a third author (PhS) was consulted. RCTs had to fulfil the following inclusion criteria; reporting on efficacy; oral MTX monotherapy (topical therapy allowed); ≥ 10 adult patients treated with MTX (≥ 18 years of age); only including psoriasis patients (with $\geq 75\%$ of patients having chronic plaque-type psoriasis).

AgEv was included if it contained clear recommendations regarding MTX dosing.

Risk of bias assessment RCTs

The risk of bias was assessed in duplicate by SM and PD independently using the Cochrane RoB tool (Table S1').

Data extraction

Two authors performed data extraction independently (SM and PD). Study characteristics (author, country and year of publication, intervention, the number of patients in the MTX-treated group, duration of treatment and dosage regimen (including use of test-dose, start-dose, dosing scheme (daily, once weekly or in a Weinstein schedule (each weekly dose administered in 3 equally divided portions, given once a week, 12 h apart from each other)), dose adjustments, maximum dose and the use and dose/frequency of FA) and efficacy and safety data from MTX treatment groups were extracted from RCTs. The use of concomitant topical therapy was not further noted in this systematic review.

The number of patients who had a dose adjustment due to inefficacy (defined by individual study protocols) or side-effects was reported. For adverse event (AE) reporting, only the percentage of patients who had to stop MTX treatment due to (serious) side-effects was reported.

If outcomes were reported in a graph, data were extracted from these graphs.

From the AgEv, recommendations on MTX regimens were extracted.

Data reporting

For RCTs, study characteristics were summarized (Table I). Secondly, all efficacy outcome of RCTs making a head to head comparison of 2 or more MTX dosing regimens were reported (Table SII'). Thirdly, the most frequently reported outcome was identified to be used to compare results from RCTs comparing MTX with another active drug or placebo (Table SIII').

In case of clinical homogeneity, a meta-analysis was performed according to the applicable methodology.

Data from AgEv are summarized in Table SIV'.

In the discussion, evidence-based suggestions are made regarding MTX dosing regimen. Suggestions were primarily based on results from the RCTs, with AgEv used to support these.

RESULTS

RCT search result and study characteristics

The search identified 870 hits. A total of 847 hits did not meet the inclusion criteria. In total, 23 eligible studies with 29 treatment groups were included (Fig. S1'). The risk of bias of the included studies is reported in Table SII'.

The included studies randomized 1,352 patients, of whom 1,206 were included in the final analysis. The loss to follow-up was mainly attributable to one study, in which 305 patients were randomized but only 202 patients were analysed (12).

Four studies compared 2 or more different MTX dosing regimens within a single study (12–15) (representing 10 treatment groups), 19 studies compared MTX with another active treatment (representing 19 treatment groups, 2 studies also used an additional placebo arm). The number of patients in each group ranged from 7 to 215. Summarized study characteristics are shown in Table I.

Efficacy outcome of included RCTs

RCTs making a head to head comparison between 2 or more MTX dosing regimens. Of the included RCTs, 4 compared 2 or more (fixed) different MTX dosing regimens within a single study (Table SIII').

In 2002, Chladek et al. (14) found no significant difference between 7.5 mg MTX^{Weinstein}/week ($n=12$) and 15 mg MTX^{Weinstein}/week ($n=12$). In 2005, Chladek (13) compared 4 different MTX dosing regimens and did not report whether there was a significant difference in

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Table I. Summarized study characteristics of included randomized controlled trials (RCTs). In numbers of treatment groups^a

Test-dose	Start-dose	Dosing scheme	Dose adjustments	Folic acid
Yes: 2 (2.5–5 mg) (16, 48)	5 mg: 2 (16, 34)	Single: 15 (13, 15, 30, 31, 33–35, 42–46, 48)	Fixed dose: 18 (12–15, 30, 37, 39, 40, 42–45)	5 mg daily: 1 (48)
Not mentioned: 27	7.5 mg: 9 (13, 14, 17, 35, 38, 39, 41–43) 10 mg: 4 (15, 37, 44, 48) 15 mg: 11 (12–14, 32, 33, 40, 45, 46) (1: 2.5 mg for 6 days/week (12)) 25 mg: 1 (15) Weight-based: 2 (0.3 (30) and 0.5 (31) mg/kg/week)	Two portions: 2 (37, 38) Weinstein: 11 (12–14, 16, 17, 32, 39–41) Six portions: 1 (12)	Pre-defined dosing regimen: 3 (16, 41, 46) Dose based on clinical improvement: 8 (17, 31–35, 38, 48)	5 mg daily except on MTX day: 4 (17, 30, 42, 46) 1 mg/day except on MTX day: 1 (41) 5 mg the day before and after MTX day: 2 (15) 5 mg the day after MTX day: 2 (34, 35) Allowed: 2 (33, 38) Not used: 3 (12, 32) Not mentioned: 14

^aSome studies contain more than 1 treatment group.
MTX: methotrexate.

efficacy between these 4 groups. Both studies included a relatively small number of patients.

Dogra et al (15) found no significant difference ($p > 0.05$) in patients achieving Psoriasis Area and Severity Index 75 (PASI75; meaning 75% improvement of PASI compared with baseline) with 10 mg/week MTX ($n = 30$, 25 analysed) vs. 25 mg/week MTX ($n = 30$, 26 analysed), though the time to reach PASI75 was significantly shorter in the 25 mg/week MTX group.

The fourth study, published by Radmanesh et al. in 2011 (12), found no significant difference in mean Δ PASI comparing 15 mg MTX^{Weinstein}/week (group 1, $n = 147$, 101 analysed) with 2.5 mg MTX 6 days per week (group 2, $n = 158$, 101 analysed) ($p = 0.0001$).

Outcome of RCTs comparing MTX with another active substance. To be able to compare results from RCTs comparing MTX with another active drug or placebo the most frequent reported outcome was identified. The PASI75 was identified as the most frequently reported outcome. In Table SIV¹ the results of different PASI75 obtained with different MTX dosing regimens are shown.

In 13 studies (with 15 MTX treatment groups) the percentage of patients attaining PASI75 ranged from 24% (16, 17) to 92% (15) at week 12 (results shown in Tables SIII and SIV¹).

Meta-analyses

Because of clinical, methodological and statistical heterogeneity, illustrated by the many dosing regimens encountered (differences in start-dose, dosing scheme, dose adjustment, use of and dose of FA) and the diversity in outcome reporting (PASI in many ways and at different time-points), no data was pooled in a meta-analysis.

Aggregated evidence search results

The search included 9 guidelines (2, 18–25), 1 systematic review (3) and 1 consensus conference (6) (previous conferences leading to this conference were not included (26)). One guideline and one consensus conference were known to the authors and did not result from the search (27, 28). Three guidelines did not contain clear recommendations regarding MTX dosing for inclusion in this review (23–25).

Summary of aggregated evidence (AgEv) (Table SI¹)

Test-dose. Five out of 10 AgEv mention the use of a test-dose, and in 5 a test-dose is not mentioned. One recommends the use of a test-dose (29). One states that a test-dose can be considered, though there is no consensus in the guideline committee (27). Three recommend a test-dose in specific cases; for example, for elderly patients or patients with impaired kidney function (6, 19, 20). If a test-dose is recommended, the dose mentioned is 2.5–15 mg.

Start-dose. Eight out of 10 AgEv indicate what the start-dose should be, varying from 5 to 15 mg MTX (3, 6, 18, 20–22, 27, 28).

Dosing scheme. Two AgEv recommend administration in a single dose (18, 29), 5 state that a single dose or a Weinstein schedule can be considered (6, 19, 20, 27, 28) and 1 states a Weinstein schedule (21). Most state that there is no high-quality evidence for either (single or Weinstein schedule).

Dose adjustments and maximum dose. Almost all AgEv advise increasing or decreasing the dose based on efficacy. The maximum dose varies from 22.5 (21) to 30 mg (20, 27) MTX.

Folic acid. Seven out of 10 AgEv recommend the use of FA (3, 6, 18, 21, 27, 29), although its effect on reducing AEs remains unclear (22, 28). The FA dosing advised varies from 1 to 5 mg/day except on the day of MTX administration (2, 6, 21) to 5 mg the day after MTX administration (18).

DISCUSSION

This systematic review further highlights the wide heterogeneity in MTX dosing regimens in several aspects, such as the use of a test-dose, start-dose, dosing scheme, dose adjustment, maximum dose and FA. A great diversity in outcome reporting was found, thus it was not possible to pool the RCT data and no meta-analyses were performed.

Several aspects of MTX dosing regimens are discussed below and initial suggestions regarding the MTX dosing regimen for treating psoriasis are made based on the evidence available.

Test-dose

A test-dose was used in 2 out of 29 treatment groups and recommended (sometimes only in frail patients) in 5 out of 10 included manuscripts presenting aggregated evidence. A test-dose is administered to detect any unusual predisposition to toxic effects, such as myelosuppression, which usually occurs within 7–10 days (26). In AgEv a test-dose and laboratory control after one week is often suggested only for frail patients (for example elderly people or patients with impaired kidney function) (2, 6, 19, 20).

Start-dose

Amongst the included RCTs, start-dose varied from 5 to 25 mg/week MTX (Table I) and the best PASI75 response was obtained in a study using a start-dose of 25 mg/week MTX (15). Two studies based the start-dose on weight (30, 31). In the AgEv it is suggested to start MTX treatment with a dose ranging from 5 to 15 mg/week MTX (3, 18, 20–22, 27, 28). RCTs show that

starting with 15 mg/week MTX (32, 33) or increasing rapidly to 15 mg/week MTX (34) leads to a better PASI75 improvement compared with starting with 5 (16) or 7.5 mg/week MTX (35) and slow increases, or with a fixed dose of 7.5 mg/week MTX (17). The safety of the 15 mg/week MTX start-dose is illustrated by data from Barker et al. (33), where only 4% ($n=8$) of patients stopped due to AEs (Table SIV¹). In AgEv, it is suggested that start-dose may vary depending on severity of disease, age, kidney function and other comorbidities (18, 21). MTX dose ≥ 15 mg/week MTX is suggested to have a more rapid onset of action compared with < 15 mg/week (36). The Psoriasis International Network survey has shown that 7.5 mg/week MTX is the most frequently used start-dose, and 15 mg/week MTX the second most frequently used start-dose (7).

Guideline recommendations on the subject of safety monitoring state that pre-treatment laboratory control is obligatory and advise laboratory control within one week after a test- or start-dose and every 2 weeks during the first 1–2 months. When at a stable dose of MTX or after 2–3 months of treatment, guidelines advise control every 2–3 months.

Dosing scheme

Four different methods of MTX dosing were encountered in the included RCTs (Table I). Daily low dosing (12) (high risk of bias, never suggested in AgEv), weekly dosing with each dose divided in 2 equal dosages (37, 38) (small studies with an intermediate/high risk of bias and never suggested in AgEv), dosing in a Weinstein schedule (12–14, 16, 32, 39–41), or a single weekly dose (13, 15, 17, 30, 31, 33, 34, 42–48), the last 2 most frequently used in clinical practice and suggested in AgEv (1). The Weinstein schedule is thought to decrease AEs (6, 20, 21), although this could not be concluded from included RCTs due to high risk of bias and small numbers of a study comparing single dose with Weinstein dosing (13). AgEv recommend the administration of MTX in a Weinstein schedule and in single dose, though there is little high-quality evidence supporting the use of one regimen over the other (6, 19–21, 27, 28).

Dose adjustments

A fixed dose was used in 18 treatment groups, in 3 a predefined dosing regimen was used and in 8 the dose was adjusted based on clinical improvement (Table I). It is generally accepted that MTX dose should be adjusted to clinical response, individualized per patient (6, 21, 28). Comparing 3 different studies (all low risk of bias, similar inclusion criteria) included in this systematic review (33–35), shows that starting with 15 mg/week MTX and adjusting the dose based on clinical efficacy at week 6 or rapidly increasing the dose to 15 mg/week MTX at week 2 with adjustment based on clinical efficacy at week 10

leads to a greater improvement and similar treatment termination due to AEs compared with slowly increasing the dose from 7.5 mg at week 0 to 15 mg at week 4 (Table SIV¹). Due to the diversity in dose adjustments used in RCTs, no conclusion based on evidence from RCTs can be drawn regarding this topic. In AgEv, adjustment of the dose, based on efficacy or on AEs is advised. It has been suggested that, if an insufficient response is seen at week 8, the dose can be increased to 20 mg/week MTX (28). If with this dosing regimen, patients remain non-responders at weeks 12 (35) to 24 (34), the value of further dose escalation is unclear. Response to dose adjustments may take 4–8 weeks (6).

Maximum dose

The maximum dose of MTX allowed in one included RCT was 30 mg/week (48). In this RCT, it is unclear if 30 mg was actually administered. In another study, it was observed that increasing the dose from 20 to 25 mg/week provided little additional benefit; mean % change in PASI went from 16% to 25% in patients who had not previously obtained 50% improvement in PASI. The effect of increasing MTX to 25 mg/week in patients who have obtained 50% PASI improvement was not investigated (35). In AgEv maximum dose varied from 22.5 (21) to 30 mg/week (19, 20, 27).

Use of folic acid

The use of FA was mentioned explicitly in 10 treatment groups, in 2 it was allowed, in 14 it was not mentioned, and in 3 it was mentioned explicitly that no FA was used (Table I). Most aggregated evidence recommends the use of FA, although in a variety of dosing regimens. Comparing 2 studies with similar MTX dosing, where in the first no FA was used (32) and in the second 5 mg/week of FA was used (34), the use of FA seems to lead to less treatment termination. FA is thought to decrease the risk of AEs (49) and the (negative) influence on efficacy is debatable (5, 50). A meta-analysis performed in rheumatoid arthritis showed that administration of FA reduced the risk of gastro-intestinal side-effects, elevated liver enzymes or withdrawal from MTX for any reason. It did not appear to have a significant effect on efficacy, although only studies in which ≤ 7 mg/

Table II. Authors' suggestions for methotrexate dosing regimen

- Test dose: recommended for elderly or frail patients, for example patients with impaired kidney function.
- Start dose: 5–7.5 mg/week in elderly or frail patients and 15 mg/week in healthy patients.
- Administration as single dose. Use of the Weinstein schedule if gastro-intestinal complaints occur.
- Dose increase at week 8–20 mg/week if an insufficient response is seen.
- Maximum dose of 25 mg/week.
- Folic acid is recommended, though in what dosing and frequency remains unclear.

week FA was used were included in the analyses (51). The use of FA is recommended by an expert meeting to reduce the risk of hepatotoxicity, although there is no consensus on the optimal dosing regimen for FA (9).

Authors' suggestions

We have made suggestions below for several aspects of the MTX dosing regimen, based on this review (Table II).

Test-dose. We suggest a test-dose with laboratory control after one week only for frail patients (for example elderly people or patients with impaired kidney function). This suggestion is based on AgEv (Table S1¹) and could not be based on RCTs.

Start-dose. Based on RCTs (33) we suggest a start-dose of 15 mg/week MTX with laboratory control after one week in healthy patients. It is known that the population included in RCTs is generally more healthy compared with the daily practise population. Therefore we suggest a start-dose of 5–7.5 mg/week MTX in frail patients (e.g. elderly people or patients with impaired kidney function) as suggested in AgEv (18, 21) (Table S1¹).

Dosing scheme. Based on the fact that there is no high-quality evidence supporting increased efficacy or reduction in AEs by administration of MTX in a Weinstein schedule and administration in a single dose will probably increase drug compliance, we suggest administration of MTX in a single dose. If gastrointestinal complaints occur, a Weinstein schedule could be applied, though one should be aware that little high-quality evidence is available to support the schedule.

Dose adjustments. We suggest increasing the dose by 5 mg/week MTX at week 8 if an insufficient response is observed and no substantial AEs are observed. This is based on a recommendation from a consensus report (28). A further increase in the dose by 5 mg/week MTX is possible if 4–8 weeks after the dose increase the response is still insufficient. In good-responders dose reductions should be considered.

Maximum dose. We suggest a maximum dose of 25 mg/week MTX because the effect of a dose increase to 30 mg remains unclear and increase to 25 mg/week MTX has shown at least little benefit in patients who had not obtained 50% improvement in PASI (35). A maximum dose of 25 mg/week MTX is also most often recommended in AgEv (Table S1¹).

Folic acid. We suggest the use of FA, though the dosing and frequency is debatable, varying from 1 to 5 mg/day (except on the day of MTX administration) to 5 or 10 mg/week, 24 or 48 h after MTX. This is based on data from RCTs (32, 34) and AgEv (Table S1¹).

Strengths and weaknesses

By summarizing the dosing regimens and the efficacy obtained in RCTs of the treatment of psoriasis with

oral MTX, and by systematically summarizing the MTX dosage regimens suggested in AgEv, this review creates evidence-based, initial suggestions regarding the MTX dosing regimen, which are more detailed than the existing recommendations in guidelines and consensus conferences. In a future consensus meeting or Delphi procedure, these data could form the basis for further recommendations attained amongst dermatologists worldwide. As mentioned before, more direct high-quality studies comparing the different aspects of MTX dosing regimens are needed.

There are many factors related to MTX dosing, but this review focussed on certain aspects. Due to the exclusion of patients under the age of 18 years and the exclusion of non-oral MTX administration no conclusions can be drawn regarding the treatment of children or the intramuscular/subcutaneous administration of MTX. Also, beyond the scope of this review are combination therapies with MTX (e.g. with etanercept (52)) and whether the optimal dose of MTX depends on factors such as body weight or kidney function. Results from RCTs are extrapolated for use in daily practise; however, it is known that the population included in RCTs is generally different from the population treated in daily practice. The RCT results included are relatively short term (maximum treatment time 52 weeks), but MTX side-effects, such as hepatotoxicity, often develop after years of treatment.

Conflicts of interest: SPM reports carrying out clinical trials for Abbvie, Amgen, Almirall, Novartis, and Pfizer. PMD, JL and LH report no conflicts of interest. PIS has had paid consultancies from LEO Pharma and AbbVie, and currently one from Novartis. She has one unrestricted grant from LEO Pharma. She is involved in the development of clinical trials that are independent of pharmaceutical company funding. She reports carrying out clinical trials for LEO Pharma, Janssen-Cilag, Almirall, Schering-Plough, Merck Serono, Amgen, Pfizer, Biogen Idec, Centocor, Roche, Eli Lilly, AbbVie, Celgene, Novartis and Astellas. She has no pharma- or industry educational grants. She has not personally received any educational grants from pharmaceutical companies to assist attendance at educational meetings.

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