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### Make new friends, but keep the old: Methotrexate treatment in psoriasis patients

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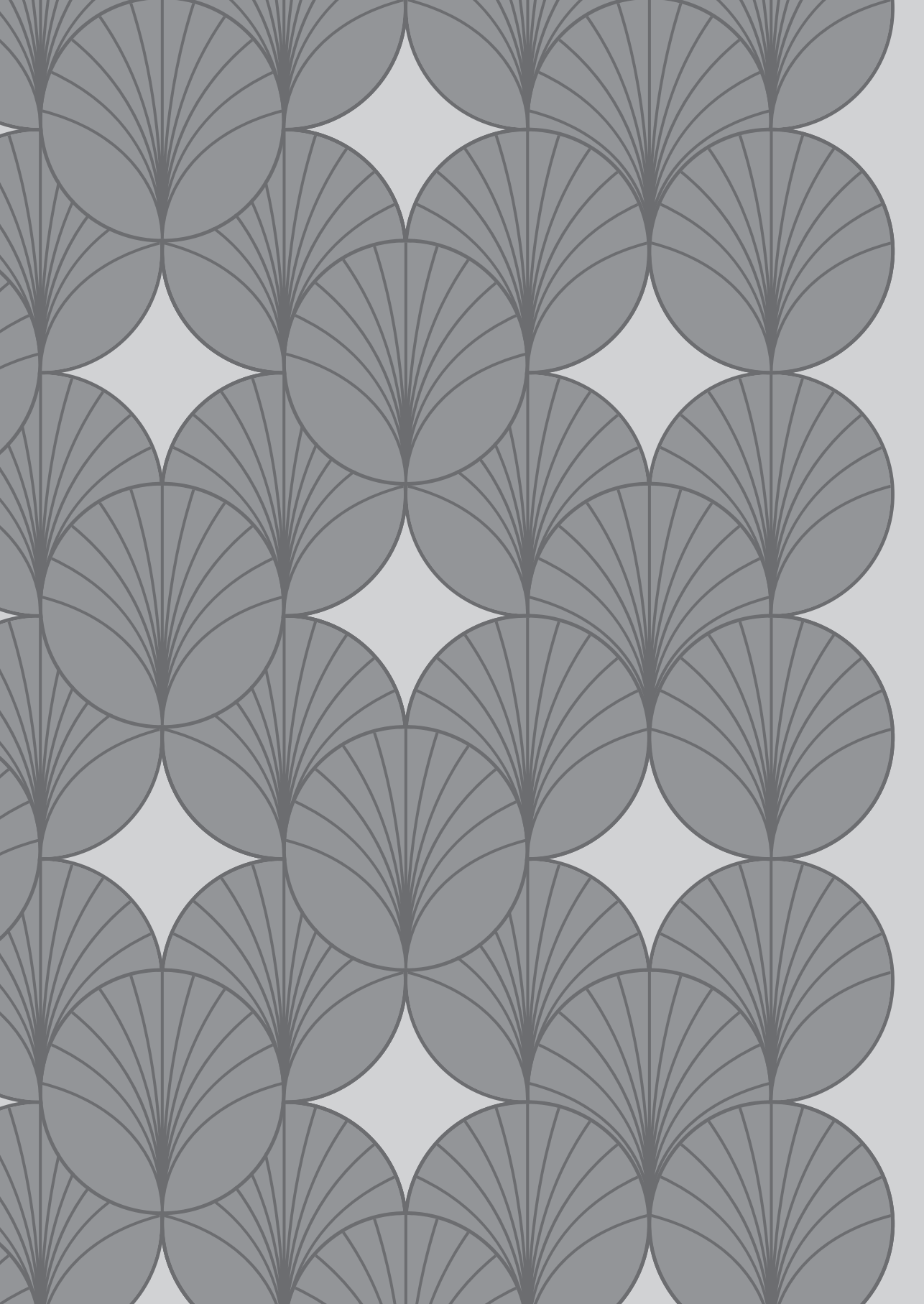
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## CHAPTER 3

# **Methotrexate Dosing Regimen for Plaque-type Psoriasis: An Update of a Systematic Review**

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## **Abstract**

### **Background**

Methotrexate (MTX) is a systemic treatment for plaque-type psoriasis. At the time of approval, no dose-ranging studies were performed. Nowadays, a uniform dosing regimen is lacking. This might contribute to suboptimal treatment with the drug.

### **Objective**

To summarize the literature involving the MTX dosing regimens in psoriasis patients.

### **Methods**

In this SR, RCTs and documents with aggregated evidence (AgEv) on the MTX dosing regimen in psoriasis were summarized. All randomized controlled trials (RCTs) in which oral, subcutaneous or intramuscular MTX was used in patients with psoriasis and AgEv, were included. The MEDLINE, EMBASE and CENTRAL databases were searched up to June 20, 2022. This SR was registered in PROSPERO.

### **Results**

Thirty-nine RCTs had a high risk of bias. Test dosages were given in only 3 RCTs. In the RCTs, MTX was usually prescribed in a start dose of 7.5 mg/week (n = 13). MTX was mostly given in a start dose of 15 mg/week, in the AgEv (n = 5). One guideline recommended a test dose, in other aggregated evidence a test dose was not mentioned or even discouraged.

### **Conclusions**

There is a lack of high-quality evidence and available data for dosing MTX in psoriasis is heterogeneous.

## Introduction

Methotrexate (MTX, a dihydrofolate reductase inhibitor), is a systemic treatment for psoriasis.<sup>1-3</sup> The effectiveness and safety of this drug are acknowledged in guidelines and studies from around the world.<sup>4-6</sup> Even in the era of biological treatments, MTX is an important drug, being globally available and relatively affordable.<sup>7</sup>

Since the drug was approved by the Food and Drug Administration (FDA) before dose ranging studies were performed, a uniform dosing regimen of MTX in psoriasis is lacking. In the first years of use, Rees et al. reported a daily dosage of 1.5 – 2 mg which should be administered for 3 – 12 days in a row.<sup>8</sup> In 1969, a weekly oral dosage of 25 mg MTX was described by Roenigk et al.<sup>9</sup> Three years later, Weinstein and Frost reported a three weekly divided dose in which 2.5 - 5 mg of the drug was administered every 12 hours.<sup>10</sup>

Also in clinical practice there is a wide variety in the different aspects related to MTX dosing, as can be concluded by a global survey from 2015<sup>11</sup> and a systematic review (SR) on the oral use of this drug in psoriasis (23 RCTs, 11 documents with aggregated evidence, search till September 2013)<sup>12</sup>. The variability in dosing regimens might contribute to suboptimal treatment with MTX or can lead to early discontinuation of treatment due to limited efficacy or side effects.

To give a summary of the available literature on this varying dosing and corresponding efficacy, effectiveness and safety, we present an update of our earlier performed SR<sup>12</sup> in which RCTs and documents with aggregated evidence (AgEv, a term which was used for the included expert meetings, SRs with treatment recommendations and guidelines) were included. The inclusion criteria for RCTs from our earlier performed SR, which were limited to oral administration, were extended to oral, subcutaneous and intramuscular administration of MTX. The population selection criteria were extended from adult patients to adult and pediatric patients. This SR was the basis for a consensus process and served to identify future research projects.

## Materials and Methods

### Inclusion and Exclusion Criteria

This systematic review (SR) was registered in PROSPERO<sup>13</sup> with registration number CRD42022303486. The SR was reported according to the Preferred Reporting Items for SRs and Meta-Analysis (PRISMA) statement.<sup>14</sup> We did not publish a protocol.

All randomized controlled trials (RCTs) in which oral, subcutaneous or intramuscular MTX was used in >10 adults or children with psoriasis (>75% chronic plaque psoriasis) were included. These inclusion criteria are extended compared to our earlier performed SR. We excluded RCTs in which no skin effectiveness outcome (e.g. PASI score) was reported, studies that used topical or intralesional MTX, duplicate publications, articles for which the full text was not available, or papers in languages other than Dutch, English, French or German.

For the aggregated evidence, all expert meetings, SRs with treatment recommendations and guidelines starting from 2010 that were found were included. We choose 2010 to include only most up to date expert meeting reports, SRs and guidelines, to prevent inclusion of outdated information.

### **Literature Search**

For RCTs and documents with AgEv, the MEDLINE, EMBASE and CENTRAL databases were searched up to June 20, 2022 by a clinical librarian. As a consequence of the extended inclusion criteria, the literature search was iterated from inception. The complete search strategy can be found in Table 1. We choose to select RCTs during the selection process, instead of adding specific RCT search terms to the search strategy.

**Table 1. Search strategy for MEDLINE, EMBASE, and CENTRAL**

Search no.	Term(s)
1	psoriasis/ or psoriasis vulgaris/
2	psorias*.tw,ot,kw.
3	psoria*.tw,ot,kw. not (Psoriatic Arthritis/ or arthrit*.ti,ot.)
4	OR/1-3 [ psoriasis ]
5	methotrexate/
6	(met?ot?rex* or amet?opterin* or MTX or methopterin* or methylaminopterin* or ledertrexat*).tw,ot,kw.
7	or/5-6 [ MTX ]
8	4 and 7 [ psoriasis + MTX ]
9	(animal/ or animal experiment/ or animal model/ or nonhuman/ or rat/ or mouse/) not human/
10	8 not 9 [ human psoriasis and MTX]
11	remove duplicates from 10 [ human psoriasis and MTX -deduplicated ]
12	exp guideline/ or guideline*.ti,ot. or meta-analysis/ or “systematic review”.pt. or (meta analy* or metaanaly* or meta?analy*).tw,kf. or ((systematic* adj3 (review or literature or evidence or search*)) or ((summari* or review) adj3 evidence)).tw. or systematic.ti. or cochrane.jw. [Filter for secondary evidence]

We searched TRIP<sup>15</sup>, the International Psoriasis Council (IPC) website<sup>16</sup> and Skin Inflammation and Psoriasis International Network (SPIN) website<sup>17</sup> (search date June 21, 2022) for documents with AgEv, complemented with guidelines known to the authors.

### Study Selection

The RCT search results were merged and duplicates were removed. Hereafter, two authors independently selected all articles for eligibility, taking the inclusion and exclusion criteria into account. Articles were screened based on title, abstract and full-text. A third author was consulted in case of disagreements.

As described above, apart from the year of publication, no specific exclusion criteria were used for the documents with AgEv.

### Risk of Bias Assessment

The risk of bias of the RCTs was assessed by two authors using the revised risk of bias tool from Cochrane; ‘RoB 2’<sup>18</sup>. This tool consists of five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. We assessed the risk of bias for the primary efficacy outcomes of all studies.

For the documents with AgEv, no quality assessments were performed.

### **Data Extraction**

For the RCTs and documents with AgEv, data extraction was independently performed by two authors and collected on predefined data-extraction forms. Collected study characteristics for RCTs and -when available- documents with AgEv, included: publication date, number of patients, age, gender, previous treatments, concomitant medication, duration of treatment, duration of follow-up, outcome tool used, efficacy (skin outcome, e.g. PASI score), time to effect, duration of remission, side-effects and serious side-effects. On dosing regimen the data collection for RCTs and -when available- documents with AgEv involved: test dose (a dose was included as test dose, when the authors named this accordingly), start dose, maintenance dose, dose adjustments like increasing and decreasing the dose, maximum weekly dose, whether there is a maximum cumulative dose, whether treatment was stopped in case of efficacy, route of administration, dosing scheme, whether the route of administration was switched because of lack of effect, whether the route of administration was switched because of side-effects and the use and dosing regimen of folic acid. Data on the different aspects of the dosing regimen were collected for adults and children separately.

### **Meta-Analysis**

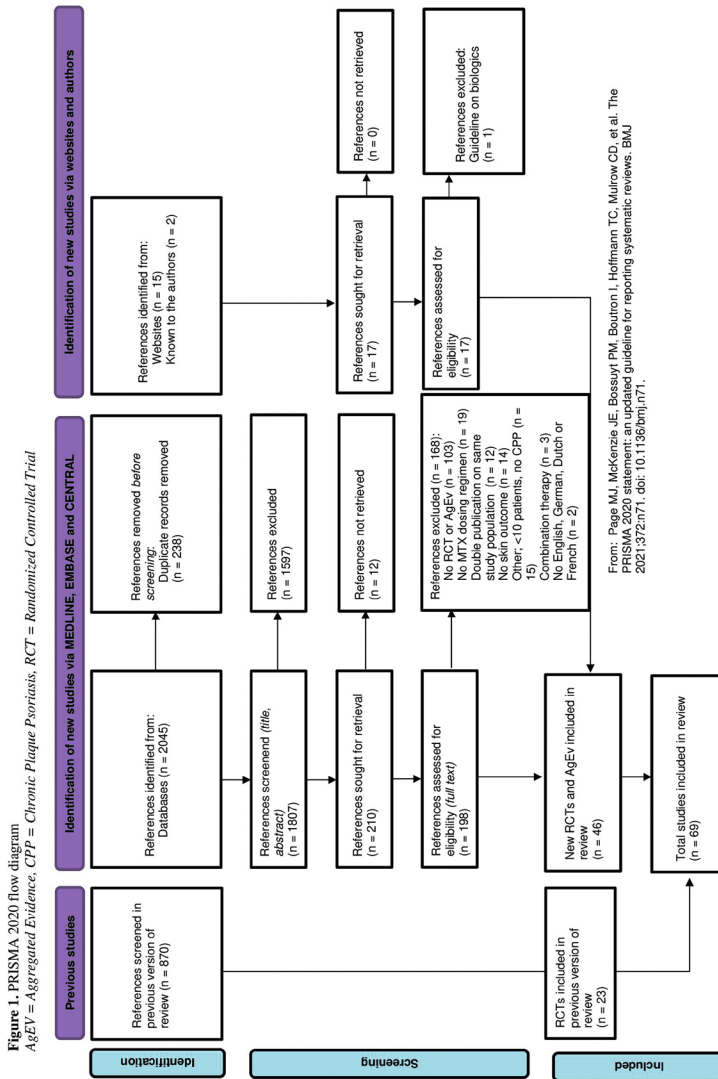
If the included RCTs were clinically (e.g. dosing schemes) and methodologically (e.g. outcome measurements) homogeneous and had a low risk of bias, a meta-analysis of the used MTX dosing (start dose or maintenance dose) in relation to the efficacy outcomes (PASI score or other skin outcome) was performed. If the studies were not homogeneous, data pooling was not possible.

## **Results**

### **Study Selection**

Figure 1 summarizes the selection process. The update from the literature search identified 2045 references of which 46 references (22 RCTs and 24 documents with AgEv; expert meetings, SRs with treatment recommendations and guidelines) were included. In the 45 RCTs in total (earlier performed SR and update), 5350 patients were randomized. Only one RCT involved children. Most RCTs compared MTX to another treatment ( $n = 41$ ), 4 studies compared two different MTX dosing regimens. In these studies, MTX 7.5 mg/week vs. MTX 15 mg/week<sup>19, 20</sup>, MTX 10 mg/week vs. MTX 25 mg/week<sup>21</sup> and MTX 2.5 mg 6 days/week vs. MTX 15 mg/week were investigated<sup>22</sup>.





**Figure 1. PRISMA 2020 flow diagram**  
 AgEV = aggregated evidence, CPP = Chronic Plaque Psoriasis, RCT = Randomized Controlled Trial

### **Data Extraction**

See Table 2 for different aspects on dosing regimens and efficacy of the included RCTs. Since the inclusion criteria for this update SR were extended, we iterated the data-extraction for the RCTs from our earlier performed SR. See Table 3 for details on dosing regimens of the documents with AgEv. In Table S1a *all* details on the characteristics of the included references can be found. See Table S1b for *all* extracted data involving the MTX dosing regimen. All four tables are separated for adults and children. Salient results from the RCTs and documents with AgEv per dosing item can be found below.

**Table 2. Dosing regimens and efficacy from the included RCTs\***

Ref	Author and publication year	MTX dosing						MTX route of administration			Folic acid supplementation			
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
<b>RCTs with adults</b>														
33	Abidi, 2020	RCT MTX vs Pioglitazone vs. MTX+Pioglitazone	Unk	7.5	Unk	7.5	Unk	Unk	% of patients PASI75 after 12 weeks Pioglitazone: 82.75 MTX: 66.66 MTX+pioglitazone: 100	Unk	Wkly	Yes	Unk	Unk
43	Akhyani, 2010	RCT MTX vs. MMF	Unk	7.5	Fixed dosing regimen: in wk 1 15 mg, in wk 4 20 mg	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 58.8 MMF: 73.5	PO	Wein-stein	Yes	1	Daily
34	Ali, 2009	RCT MTX vs. leflunomide	Unk	7.5	Fixed dose	Unk	Unk	Unk	Mean PASI baseline and after 4 and 12 weeks MTX: 14.13 -> 12.24 -> 8.08 Colchicine: 16.29 -> 13.46 -> 7.94	PO	Wein-stein	Unk	Unk	Unk
84	Banerjee, 2021	RCT MTX vs. PUVA	Unk	0.4 mg/kg	Unk	Unk	Unk	15	Number of patients till PASI90 MTX: 30 PUVA: 19	Unk	Wkly	Unk	Unk	Unk

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing					MTX route of administration				Folic acid supplementation			
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
79	Barker, 2011	RCT MTX vs. Infliximab	Unk	15	Fixed dosing regimen: between wk 6 and 16 at least one dose increase	Unk	Unk	Unk	Unk	PO	Wkly	Yes	Unk	Unk
50	Bhuiyan, 2010	RCT MTX vs. Oral Colchicine	Unk	7.5	Fixed dose	Unk	Unk	Unk	Unk	PO	Wkly	Yes	5	Daily
20	Chladek, 2002	RCT MTX 7.5mg Weinstein vs. MTX 15mg Weinstein	Unk	7.5	Fixed dose	Unk	Unk	Unk	Unk	PO	Weinstein	Unk	Unk	Unk



**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing					MTX route of administration					Folic acid supplementation		
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
85	Chladek, 2008	RCT MTX -> MTX + FA vs. MTX+FA ->MTX	Unk	Based on con- tra- tion-time profiles: MTX -> MTX + FA: 10- 22.5 mg MTX+FA ->MTX: 7.5-25 mg	Mean dosing increases: MTX -> MTX + FA: 15.8 (wk 16), 15.3 (wk 32) MTX+FA ->MTX: 13.6 (wk 16), 13.3 (wk 32)	MTX -> MTX + FA: 4 dose re- ductions MTX+FA ->MTX: 9 dose reduc- tions	Based on contra- tion-time profiles, further reduc- tions based on tolerability and PASI response	Unk	Mean PASI reduction after 16 and 32 weeks MTX: -11.3 -> -15.1 MTX+FA: -22.1 -> -20.7	PO	Wkly or divided wkly	Yes	20	Twice wkly: 20 mg divid- ed into 2 single doses of 10 mg
59	Choi, 2017	RCT pilot MTX vs. CsA	Unk	10	Fixed dosing regimen: 2.5 mg/2wks	15	Unk	15	P-value between MTX and CsA after 16 weeks mPASI: 0.44 oPASI: 0.36	Unk	Unk	Yes	1	Daily
63	Choonha- karn, 2022	RCT Or MTX vs. SC MTX	Unk	10	Based on efficacy: 5mg/4wks if no PASI100	Unk	Based on efficacy: 5mg/4wks if no PASI100	25	Percentage of patients PASI75 response after 16 and 32 weeks MTX SC: 47.4 -> 55.3 MTX Or: 30.8 -> 41.0	SC (38), Or (39)	Wkly, SC: single, Or: divided dose	Yes	5	Daily

Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)

Ref	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation				
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wklly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
81	de Jong, 2003	RCT MTX -> calcipotriol vs. MTX -> vehicle	Unk	50% of maintenance dose	Unk	Unk	Based on efficacy: MPSS score, 50% of maintenance dose at the first visit	Unk	Number of patients per MPSS score baseline and end phase II Calcipotriol: 0-19 (49), 20-39 (2) -> 0-19 (49), 20-39 (2) Vehicle: 0-19 (45), 20-39 (1) -> 0-19 (41), 20-39 (5)	PO	Wkly	No	-	-
21	Dogra, 2012	RCT MTX 10 mg vs. MTX 25 mg	Unk	10-25	Fixed dose	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX 10mg: 72 MTX 25mg: 92	PO	Wkly	Yes	5	Daily
68	El-Hanafy, 2021	RCT MTX vs. IM vitD	Unk	0.2-0.4 mg/kg	Unk	Unk	Unk	Unk	Mean PASI after 0 and 3 mo MTX: 29.10 -> 6.64 MTX + vitD: 28.81 -> 6.45	Injections (SC/IM) Un-known	Wkly	Unk	Unk	Unk

Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)

Ref	Author and publication year	MTX dosing							MTX route of administration		Folic acid supplementation			
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
51	Ei-Eishi, 2013 RCT Patients (MTX vs. CsA vs. PUVA) vs. healthy controls	Unk	2 mg/kg/wk	Fixed dose	Unk	Unk	Unk	Unk	Mean PASI scores baseline and after 8 weeks MTX: 11.62 → 2.98 CsA: 11.71 → 2.96 PUVA: 9.89 → 3.24	PO	Wky	Yes	5	Daily
50	Fallah Arani, 2011 RCT MTX vs. FAE	5	7.5	Max 15 mg/wk, when ineffective	Unk	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 24 Fumarates: 19	PO	Wein-stein	Yes	Unk	Unk
35	Flystrom, 2008 RCT MTX vs. CsA	Unk	7.5	Max 15 mg/wk, when ineffective	Unk	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 24 CsA: 58	PO	Wein-stein	Yes	5	Once wky



Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)

Ref	Author and publication year	MTX dosing					MTX route of administration				Folic acid supplementation		
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
36	Gordon, 2017	-	7.5	Mean dosing increases: CHAMPION 10 mg (wk 2-5), 15 mg (4-7), 20 mg (8-11 if PASI50 response was not achieved), 25 mg (12-15 if PASI50 response was not achieved), M10-255 5 mg (wk0), 10 mg (wk 1), 15 mg (wk 2-9), 20 mg (wk 10-15), 25 mg (wk16-24 if PASI75 was not achieved)	-	Unk	25	% of patients PASI75 after 16 weeks Recommended to continue MTX: 65.8 Recommended to discontinue MTX: 21.1	CHAMPION: PO M10-255: Unk	Unk	Unk	Unk	Unk
56	Gumusel, 2011	Unk	15	Fixed dosing regimen: 15 mg for first 3 mo, 10 mg for second 3 mo	Unk	Unk	Unk	Mean NAPSI baseline and after 24 weeks MTX: 39.1 -> 18.0 CsA: 42.1 -> 25.8	PO	Wkly	Yes	5	Daily

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing						MTX route of administration			Folic acid supplementation		
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
52	Gupta & Gupta, 2007	Unk	15	Fixed dose	Unk	Unk	Unk	Number of patients PASI95 and PASI100 after 27.13-33.09 d MTX: 5 and 25 MTX+TCS: 5 and 9	PO	Wkly	Unk	Unk	Unk
44	Gupta, 2005	Unk	15	Fixed dose	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 75 Hydroxyurea: 45	PO	Unk	Unk	Unk	Unk
58	Heydendael, 2003	No	10	Fixed dosing regimen: In wk 4, PASI <50: 22.5 mg, tapering form wk 12	Unk	Unk	Unk	% of patients PASI75 after 16 weeks MTX: 60 CsA: 71	PO	Wein-stein	No	-	-
62	Ho, 2010	Unk	10	Based on efficacy: Until effective, 2.5 mg increasing of dose	Unk	Unk	30	% of patients PASI 75 after 24 weeks MTX: 65 TCM: 0 PB: 18	PO	Wein-stein	No	-	-

Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)

Ref	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation			
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
55	Karapetyan, 2022	Unk	10	Unk	Unk	None	10	Mean PASI change MTX: 11.49 MTX+EPL: 14.3	Or	Wkly	Unk	Unk	Unk
37	Lajevardi, 2015	Unk	7.5	Based on BMI, 2.5 mg/1-2 wks	10-15 (BMI <30: 10, BMI 30-25: 12, 5 and >35: 15mg)	Based on BMI: 2.5mg/1- 2wks	15	% of patients PASI 75 after 16 weeks MTX: 9.1 MTX+pioglitazone: 65.3	PO	Wkly, divided	Yes	1	Daily except MTX days
27	Lajevardi, 2020	Unk	7.5	Based on BMI, 2.5 mg/1-2 wks	10-15	Unk	15	% of patients PASI 75 after 24 wks Group MTX+UCDA: 55 Group MTX: 15	PO	Wkly	Yes	1	Daily except MTX days
53	Malik & Ejaz, 2010	Unk	10	Fixed dose	Unk	Unk	Unk	Number of patients PASI 81 after 8 weeks MTX: 13 AZA: 5	PO	Wkly	Unk	Unk	Unk

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing						MTX route of administration			Folic acid supplementation		
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
22	Radmanesh, 2011	Unk	15	Fixed dose	Unk	Unk	Unk	% of patients PASI75 after 4 mo MTX 15 mg Weinstein: 80 MTX 2.5 mg 6 days/week: 61	PO	Weinstein and 6 days/wk	No	-	-
60	Ranjian, 2007	Unk	15 or 7.5 for 2 days/wk	Based on efficacy. In wk 4, PASI <25: 20 mg	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 66.66 Hydroxyurea: 13.33	PO	Wkly	Allowed	5	Daily
23	Reich, 2011	Unk	5	Based on efficacy: In wk 1, 10, in wk 2-9 15	Unk	Based on efficacy on specific wk: In wk 10 and 16 increment of 5 mg/wk if PASI <75% or 6 point PGA ≠ 0 or 1	Unk	% of patients PASI75 after 12 weeks MTX: 36.2 Briakinumab: 76.6	PO	Wkly	Yes	5	Once wkly

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing					MTX route of administration				Folic acid supplementation		
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
41	Reich, 2014	Unk	Unk	Based on efficacy: In wk 8 no PASI50; 20, In wk 16 no PASI75, dose was increased to 25 mg/wk.	10-25 mg (mean = 14)	Based on the occurrence of AEs	Unk	Median PASI at baseline (Q1, Q3) 15 (12, 20)	Unk	Wkly	Unk	Unk	Unk
38	Reich, 2019	Unk	7.5	Based on efficacy: In wk 4, no PASI 75: 20 mg/wk, in wk 16, no PASI 75: 25 mg/wk	Unk	Unk	30	Mean PASI reduction after 12 and 24 weeks Ixe: 49 MTX: 38 FA: 12	PO	Wkly in single dose or divided into three doses at 12h intervals	Yes	5	Once wklly
80	Revicki, 2008	Unk	7.5-25	Unk	7.5-25	Unk	Unk	DLQI change from baseline after 16 weeks ADA: -9.1 MTX: -5.7 PB: -5.4	PO	Wkly	Unk	Unk	Unk

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing					MTX route of administration			Folic acid supplementation				
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
88	Salim, 2006	RCT MTX+FA vs. MTX+PB	Unk	Unk	Unk	Folic Acid mean: 11 (7.5-17.5) Placebo mean: 12 (2.5-22.5)	Unk	Unk	Mean PASI change after 12 weeks MTX+FA: +4.4 MTX+PB: -0.6	Unk	Unk	Yes	5mg	Daily
42	Sandhu, 2003	RCT MTX vs. CsA	Unk	0.5 mg/kg/wk	Based on efficacy. PASI 75 achieved, tapering	20-30	Unk	Unk	% of mean PASI reduction MTX: 98.5% CsA: 85.6%	PO	Wkly	Unk	Unk	Unk
24/57	Saurat, 2008, & Saurat, subanalysis 2011	RCT MTX vs. ADL vs. PB	Unk	7.5	Fixed dosing regimen: 10 (wk 2-3), 15 (wk 4-7)	Unk	Based on efficacy: 5 mg increase if <PASI50 at wk 8 or wk 12	Unk	% of patients PASI75 after 16 weeks MTX: 35.5 ADL: 79.6 PB: 18.9	PO	Wkly	Yes	5	Once wkly

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation		
		Test dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
54	Shehzaad, 2004	Unk	Fixed dose	Unk	Unk	Unk	% of mean PASI scores baseline and after 8 weeks MTX: 34.6 -> 9 PUVA: 34.25 -> 8.9 PUVA+MTX: 33.75 -> 8.5	PO	Wkly, divided dose	Unk	Unk	Unk
85	Singh, 2021	Unk	None	MTX: 0.3 mg/kg/wk, MTX +CsA: 0.15 mg/kg/wk	None	MTX: 0.5 mg/kg/wk, MTX +CsA: 0.15 mg/kg/wk	Number of patients PASI75 response after 12 weeks (ITT) MTX: 45 MTX+CsA: 55	IM	Wkly	Unk	Unk	Unk
31	Soliman, 2015	Yes, 7.5 mg/wk in three divided doses	Based on efficacy: 5 mg/wk, gradually increase	Individual, max. 50 mg/wk	Individual: dose not further specified	30	Number of patients with PASI90 up to 6 mo MTX: 15 MTX+NBUVB: 17	PO	Wkly	Yes	5	Daily except MTX days

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing						MTX route of administration			Folic acid supplementation				
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily		
40	Tam, 2022	RCT MTX vs. MTX+Metformin	Unk	7.5	Unk	Unk	Unk	Unk	Unk	Wkly, divided dose	Unk	Unk	Unk		
28	Verma, 2021	RCT AZA vs. MTX	Yes, 2.5 mg	15	None	15	None	15	None	15	Or	Wkly	Unk	Unk	



**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation			
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
25	Warren, 2017	Unk	5-15 or 2.5-5 mg/wk (renal impairment)	Unk	Based on efficacy: Lowest dose possible	Based on efficacy: Consider switch to alternative medication or use SC MTX if minimal efficacy within 12-16 wks	Unk	Number of patients with PASI75 response after 16 weeks MTX: 57 PB: 1	PO or SC	Wkly	Yes	Unk	Unk
39	Yan, 2011	Unk	7.5	Fixed dose	Unk	Unk	Unk	% of patients PASI75 after 12 weeks MTX: 22 rhLFA3-IgFB: 29	PO	Wkly	Yes	5	Daily
82	Yousefzadeh, 2017	Unk	7.5-15 mg (0.2-0.3 mg/kg)	Unk	7.5-15 mg (0.2-0.3 mg/kg)	Unk	Unk	Number of patients with PASI75 after 12 weeks MTX: 6 MTX+micronutrients: 11	PO	Wkly	Yes	5	Daily except MTX days

**Table 2. Dosing regimens and efficacy from the included RCTs\* (continued)**

Ref	Author and publication year	MTX dosing				MTX route of administration				Folic acid supplementation			
		Test dose (mg, wk 0)	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Efficacy	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
RCTs with children													
26	Papp, 2017	Unk	0.1 mg/kg (up to 7.5 mg/wk)	Based on efficacy: Titrated upwards according to response and downward according to intolerance	0-1-0.4 mg/kg/wk	Based on efficacy: Titrated upwards according to response and downward according to intolerance	25	Mean PASI reduction after 12 and 24 weeks MTX: 13 ADA high dose: 23 ADA low dose: 30	PO	Wkly	Yes	Unk	Unk

\*Characteristics and safety measurements can be found in supplemental I

--: Not applicable, ADA: Adalimumab, AZA: Azathioprine, CsA: Cyclosporin A, d: days, DLQI: Dermatology Life Quality Index, EPL: Essential Phospholipids, FA: Folic Acid, FAE: Fumaric Acid Esters, Ix: Ixekizumab, MMF: Mycophenolic acid, Mo: Months, mPASI: modified PASI, MPSS: Modified Psoriasis Severity Score, MTX: Methotrexate, NB: Narrowband, oPASI: objective PASI, PASI: Psoriasis Area Severity Index, PB: Placebo, PGA: Patient Global Assessment, PO: Per os, PT: Phototherapy, PUVA: Psoralen Ultra Violet A therapy, RCT: Randomized Controlled Trial, Ref: Reference, SC: Subcutaneous, TCM: Traditional Chinese Medicine, TCS: Topical Corticosteroids, UCDA: Ursodeoxycholic acid, Unk: Unknown, UVB: Ultraviolet B, Vit D: Vitamin D, Wk: Week, Wkly: Weekly

Table 3. Dosing regimens from included aggregated evidence

Ref	MTX dosing						MTX route of administration		Folic acid supplementation				
	Author and publication year	Test dose	Start dose (mg, wk <sup>0</sup> )	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
	<b>Aggregated evidence, adults</b>												
66	Amatore, 2019	Guide-line, France	Not needed	7.5-15	Based on efficacy: Until wk 8, when ineffective	5-25	Based on efficacy: Lowest dose possible	15	PO/SC	Unk	Yes	5	Once wkly 24 h after MTX
46	Armstrong, 2016	Guide-line, USA	Unk	5-15	Based on efficacy and tolerability	7.5-30	Unk	30	PO/IM/SC/IV	Unk	Yes	1-5	Daily
75	Arnone, 2019	Guide-line, Brazil	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk
47	Carretero, 2010	Guide-line, Spain	Yes, 7.5 is recommended in pts with relative contraindications/older patients.	7.5-15	Unk	7.5-25 mg/wk	Based on efficacy: Lowest dose possible	30	PO/SC	Wkly or divided wkly	Depends	> 5 mg	Wkly
77	Daudén, 2016	Guide-line, Spain	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing						MTX route of administration			Folic acid supplementation	
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
86	Echeverría, 2021 Guideline, Argentina	Unk	Unk	Unk	Unk	Unk	Unk	PO/SC	Unk	Yes	5	Once wkly 48 h after MTX
73	Gisoni, 2017 Guideline, Italy	Unk	7.5-15	Unk	7.5-20	Unk	Unk	PO/SC/ IM	Wkly	Yes	Unk	Once wkly 24h after MTX (at least)
74	Kalb, 2009 Consensus report, America	Yes, 5-15 mg	7.5-25	Unk	7.5-15	Based on weight	Unk	PO/IV	Wkly or divided	Yes	1 or 5	Daily or 3x/wk

Table 3. Dosing regimens from included aggregated evidence (continued)

	Author and publication year	MTX dosing					MTX route of administration		Folic acid supplementation			
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wklly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
72	Kolios, 2016	Unk	7.5-15	Unk	<25	Unk	Unk	PO/SC	Unk	Yes	5	Wkly 24-48 h after MTX, twice weekly in case of AEs
64	Menter, 2020	Yes, 2.5-5 is recommended in pts with relative contraindications/older patients.	7.5-25	Based on efficacy: Until wk 8, when ineffective	Unk	Unk	25	PO/SC	Wkly	Yes	5	6 days/wk

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation		
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
12	Menting, 2016	Yes, recommended in pts with relative contra-indications/older patients.	5-7,5 in elderly/frail patients, 15 in healthy patients	Based on efficacy: Until wk 8, when ineffective	Unk	Unk	25 mg (increase 25-50 unclear), most recommended in AgEv.	Unk	Wkly. Wein-stein in GI side effects. No high quality evidence available	Yes	1-5 mg/day, 5-10 mg/wk	Once wkly/daily except on MTX days
65	Mijuskovic, 2016	Yes, 2.5-7.5 mg	5-10 (depends on testdose/age)	Based on efficacy: 2.5mg/wk	15-25	Unk	30	Unk	Wkly	Yes	1-5	Wkly 24h after MTX

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation		
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wklly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
61	Mrowietz 2014 Expert opinion	Unk	5-7.5 (7-13 wks), higher starting doses (15-22.5 mg) lead to more rapid responses	Based on efficacy: Until wk 8, when ineffective	Unk	Unk	Unk	SC (preferably)	Unk	Unk	Unk	Unk
6	Mrowietz, 2021 Guideline, Europe	Unk	15, range 5- 25 mg/wk depending on individual vidual factors.	Unk	15-25	Individual: dosages range 5-25 mg/wk	20, 25 mg in individual cases	SC (preferably)	Wkly	Yes	5	Once wklly 24 h after MTX

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	MTX dosing				MTX route of administration			Folic acid supplementation				
	Author and publication year	Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
70/87	Nast, 2021	Unk	15, range 5-25 mg/wk depending on individual vi- dual factors.	Unk	15-25	Individual: dosages range 5-25 mg/wk	20, 25 mg in individual cases	SC (preferably)	Wkly	Yes	5	Once wkly 24 h after MTX
76	Papp, 2011	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Yes	Unk	Unk
45	Raaby, 2017	Unk	5-15	Based on efficacy: 25-30 mg depending on clinical response	Unk	Based on efficacy on specific wk: Wk 12, evaluation of max dose of MTX	25-30 mg	PO (first choice) /SC	Wkly	Yes	Unk	Unk



Table 3. Dosing regimens from included aggregated evidence (continued)

	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation		
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
48	Raboobee, 2010	Unk	15	Unk	5-25	Unk	Unk	PO/SC/IM	Wkly	Unk	Unk	Unk
32	Rademaker, 2017	No	15-25	Unk	Unk	Unk	Unk	PO/SC/IM	Wkly	Yes	5	Once or twice wky
78	Samarasekera 2012	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk	Unk

**Table 3. Dosing regimens from included aggregated evidence (continued)**

Author and publication year		MTX dosing					MTX route of administration		Folic acid supplementation			
		Test dose	Start dose (mg, wk <sup>0</sup> )	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
4	van der Kraaij, 2017	No	15 (healthy individuals), 7.5-10 mg (elderly, comorbidities), 50% dose adjustments in case of renal dysfunction	Based on efficacy: possible until wk 9-10	15 mg (healthy individuals), 7.5-10 mg (elderly, comorbidities)	Based on comorbidities: to 7.5 mg, renal dysfunction of 20-50ml/min 50% adjustment	30	PO or SC (GI complaints)	Wkly (Weinstein divided in case of GI-complaints)	Yes	5 mg (<15 mg), or 10 mg (>15 mg)	Wkly 24h after MTX

Table 3. Dosing regimens from included aggregated evidence (continued)

	MTX dosing							MTX route of administration		Folic acid supplementation		
	Author and publication year	Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wky dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
67	Warren, 2016	Unk	5-15, 2.5-5mg/week (renal impairment)	None, based on efficacy consider switch to alternative medication or use SC MTX if: Minimal efficacy is achieved within 12-16wks of starting treatment	Unk	Unk	Unk	Unk	Wkly	Yes	Unk (no clear recommendation)	Unk
<b>Aggregated evidence, children</b>												
73	Gisoni, 2017	Unk	Unk	Unk	0.2-0.4 mg/g. wk	Unk	Unk	Unk	Wkly	Unk	Unk	Unk

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing					MTX route of administration			Folic acid supplementation		
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
64	Menter, 2020	Yes, 1.25-5	Test dose: 1.25-5	Based on comorbidities: Dose adjustments in case of renal dysfunction	0.2-0.7 mg/kg/wk 13 years and older: similarly to adults (max dose still 25/wk)	Based on comorbidities: Dose adjustments in case of renal dysfunction	Unk	SC (preferably)	Wkly	Yes	1	Daily or 6 days/wk

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation			
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wklly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily	
45	Raaby, 2017	Expert opinion guideline, children, Denmark	Unk	Unk	Unk	0.2-0.4 mg/kg/wk	Unk	20	PO/SC (SC preferred, fewer side effects and allows administration in higher doses)	Wkly	Yes	5 mg	Wkly
71	Tangtatco, 2017	Guideline, children	No	15mg/m <sup>2</sup> /wk; 0.2-0.4 mg/kg/wk; no test dose	Unk	15 mg/m <sup>2</sup> /wk; 0.2-0.4 mg/kg/wk; no test dose	Unk	Unk	PO/SC	Unk	Yes	Unk	Daily

**Table 3. Dosing regimens from included aggregated evidence (continued)**

	Author and publication year	MTX dosing						MTX route of administration		Folic acid supplementation		
		Test dose	Start dose (mg, wk 0)	Increasing dose	Maintenance dose	Dose adjustments	Maximum wkly dose	Route of administration	Dosing scheme	Yes/No	Dosage (mg/wk)	Wkly/Daily
4	van der Kraaij, 2017	Unk	Unk	Unk	0.2-0.4 mg/kg/wk	Unk	Unk	Unk	Unk	Yes	5-10	Wkly (24h after MTX)

IM: Intramuscular, IV: Intravenous, Ixe: Ixekizumab, MPSS: Modified Psoriasis Severity Score, MTX: Methotrexate, Ref: Reference, SC: Subcutaneous, Unk: Unknown, Wk: Week, Wkly: Weekly

### **Meta-Analysis**

As a consequence of the many dosing regimens included (differences in start-dose, dosing regimen, adjustments in dosing, and folic acid dosing) and the diversity in outcome reporting (PASI in many ways and at different time-points), the studies were clinically and methodologically heterogeneous. Therefore, no data was pooled in a meta-analysis.

### **Risk of Bias in the RCTs**

According to the Cochrane RoB 2 Tool, 39 RCTs had a high risk of bias, indicating a low quality of evidence. Four studies had a low overall risk of bias<sup>25-26</sup>, for two studies there were only some concerns<sup>27, 28</sup>. See Table 4 for details on the RoB.

**Table 4. Risk of Bias assessment of included RCTs**

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Abidi, 2020	+	✗	+	-	-	✗
Akhyani, 2010	-	✗	✗	-	-	✗
Ali, 2009	-	✗	+	-	✗	✗
Banerjee, 2021	+	✗	+	-	+	✗
Barker, 2011	-	✗	+	-	+	✗
Bhuiyan, 2010	+	✗	+	-	✗	✗
Chladek, 2002	-	✗	+	+	✗	✗
Chladek, 2005	-	✗	+	-	✗	✗
Chladek, 2008	-	✗	+	+	✗	✗
Choi, 2017	+	✗	-	✗	-	✗
Choonhakarn, 2022	-	✗	+	+	-	✗
de Jong, 2003	-	+	+	✗	✗	✗
Dogra, 2012	+	+	-	+	✗	✗
El-Eishi, 2013	✗	✗	+	✗	✗	✗
El-Hanafy, 2021	+	✗	+	-	✗	✗
Fallah Arani, 2011	+	✗	+	+	+	✗
Flystrom, 2008	+	✗	-	+	✗	✗
Gordon, 2017	+	+	+	+	✗	✗
Gümüsel, 2011	-	✗	+	✗	✗	✗
Gupta&Gupta, 2007	-	✗	+	-	✗	✗
Gupta, 2005	✗	✗	+	-	-	✗
Heydendael, 2003	+	✗	-	+	+	✗
Ho, 2010	-	+	-	-	-	✗
Karapetyan, 2022	+	✗	+	-	+	✗
Lajevardi, 2015	+	✗	+	+	-	✗
Lajevardi, 2020	+	+	+	+	-	-
Malik & Ejaz, 2010	-	✗	-	✗	-	✗
Papp, 2017	+	+	+	+	+	+
Radmanesh, 2011	-	✗	-	-	✗	✗
Ranjan, 2007	-	+	-	-	-	✗
Reich, 2011	+	+	+	+	+	+
Reich, 2014	✗	✗	+	-	-	✗
Reich, 2019	-	✗	+	+	✗	✗
Revicki, 2008	+	+	+	✗	✗	✗
Salim, 2006	+	+	+	+	✗	✗
Sandhu, 2003	-	✗	+	-	-	✗
Saurat, 2009/Saurat, subanalysis 2011	+	+	+	+	+	+
Shehzad, 2004	-	✗	+	-	✗	✗
Singh, 2021	✗	-	+	✗	+	✗
Soliman, 2015	-	✗	-	-	✗	✗
Tam, 2022	+	✗	+	+	+	✗
Verma, 2021	+	+	+	+	-	-
Warren, 2017	+	+	+	+	+	+
Yan, 2011	✗	✗	-	-	-	✗
Yousefzadeh, 2017	-	✗	+	+	-	✗

Domains:  
 D1: Bias arising from the randomization process.  
 D2: Bias due to deviations from intended intervention.  
 D3: Bias due to missing outcome data.  
 D4: Bias in measurement of the outcome.  
 D5: Bias in selection of the reported result.

Judgement  
 High (Red circle with ✗)  
 Some concerns (Yellow circle with -)  
 Low (Green circle with +)

According to the Cochrane RoB 2.0 tool, designed with robvis McGuinness LA. robvis: An R package and web application for visualising risk-of-bias assessments. <https://mcguinlu.shinyapps.io/robvis/> [cited 2022 13-07]



### Test Dose

A MTX test dose can be given to detect early toxic effects, e.g. idiosyncratic bone marrow failure.<sup>29</sup> Three RCTs used a test dose. In a study from Fallah Arani et al.<sup>30</sup>, the test dose was 5 mg/week. Lab controls were performed three days and one week after start. Hereafter, gradually dose increase was possible. In a RCT from Soliman et al.<sup>31</sup>, a test dose of 7.5 mg in a three divided dose was prescribed, gradually increasing the dose by 5 mg/week in the next weeks until the effective dose was achieved. In a recent RCT from Verma et al.<sup>28</sup> a test dose of 2.5 mg was given, patients were observed 48 hours for any side effects. Hereafter, a start dose of 15 mg/week was given.

One recent guideline from 2020<sup>5</sup>, recommended the use of a test dose in elderly and patients with relative contra-indications. The remaining documents with AgEv do not mention a test dose, or even discourage it.<sup>4, 32</sup>

### Start Dose and Maintenance Dose

In the 45 RCTs, 7.5 mg/week was usually the starting dosage (n = 13<sup>20, 24, 27, 30, 35-40</sup>). A specific maintenance dose was not reported, although some studies did not change the MTX dosing after start, see also Table 2.

The efficacy of the different start doses could not be compared, since the included studies used different outcomes on different time points. Besides, the definition of efficacy was varying: it involved for example the number of patients that achieved PASI50 on week 4<sup>38</sup> and week 8<sup>41</sup> or the achievement of PASI75 without a specific time point<sup>42</sup>.

A few studies used comparable outcomes. After 12 weeks, we found a mean percentage of patients with 7.5 mg/week that achieved a PASI75, of 39.1%.<sup>30, 33, 35, 39, 43</sup> For 15 mg/week, this percentage was 75%.<sup>44</sup> See also Table 5.

**Table 5. Mean percentage of patients that achieved PASI75 from included RCTs\***

MTX start dose	12 weeks, %	16 weeks, %
7.5 mg/week	39.1 (30, 33, 35, 39, 43)	22.3 (24, 37, 57)
10 mg/week	-	60 (55)
15 mg/week	75 (44)	60 (58)

( ) = Reference

\*Only starting doses were comparable in these studies, the dose adjustments were varying.

- Not available

In the documents with AgEv, advised ranges were 5 – 15 mg/week,<sup>45, 46</sup> 7.5 – 15 mg/week<sup>47</sup> or 15 – 25 mg/week<sup>32</sup>. The dosage could be based on individual

factors. The most frequently advised start dose was 15 mg/week (n = 5<sup>4, 6, 32, 48, 49</sup>). A specific maintenance dose was not reported.

### Dose Adjustments

Thirteen studies<sup>19-22, 34, 39, 44, 50-55</sup> prescribed MTX according to a fixed dosing scheme. Pre-defined dosing regimens involved dose adjustments on settled time points in 5 studies<sup>24, 43, 56-58</sup> or a set dose increase of 2.5 mg per 2 weeks in one study<sup>59</sup>. Ten studies based their dose adjustments on clinical efficacy<sup>12, 23, 25, 31, 38, 41, 42, 60-65</sup>. Lajevardi et al.<sup>27, 37</sup> used the BMI from their patients to adjust the MTX dosages. In children, one RCT based their dose adjustments on efficacy<sup>26</sup>, and one guideline on concentration-time profiles<sup>64</sup>.

Five documents with AgEv advised to base the dose adjustments on clinical response<sup>4, 45, 64-66</sup>. In the British Association of Dermatology guideline, no dose adjustments were advised and it was recommended to switch to subcutaneous administration or another treatment, in case of clinical inefficacy of MTX.<sup>67</sup>

### Administration Forms

In the included RCTs, MTX was primarily administered orally (n = 35). MTX was administered orally or subcutaneously in two RCTs<sup>25, 63</sup> or with injections (not reported whether they were subcutaneous) in another study<sup>68</sup>. We found one RCT<sup>63</sup> investigating the difference in efficacy between oral and subcutaneous administration. In this RCT from Choonhakarn et al.<sup>63</sup>, similar effects in PASI score improvements were found. This is in contrast with a controlled clinical trial from 2019, where the subcutaneous administration of MTX showed significant better PASI reduction compared to oral administration.<sup>69</sup> As this study was no RCT, it was not included in our SR.

In 5 documents with AgEv<sup>6, 45, 61, 64, 70</sup>, the authors recommended to start the administration of MTX subcutaneously. In 4 documents with AgEv, MTX could be started subcutaneously or orally.<sup>4, 47, 66, 71, 72</sup> In 5 other documents with AgEv, even IM<sup>32, 46, 48, 73</sup> or IV<sup>46, 74</sup> administration was mentioned as administration option, next to oral or subcutaneous administration. In 9 documents with AgEv, no recommendation for a specific administration form was given.<sup>12, 65, 67, 73, 75-78</sup>

### Dosing Schedule

Twenty-six RCTs<sup>21, 23-25, 27, 28, 31, 33, 39, 41, 42, 50-53, 55-57, 60, 68, 79-84</sup> prescribed MTX in a once weekly dosing schedule. Other schedules used were: Weinstein schedules (n = 7)<sup>20, 30, 34, 35, 43, 58, 62</sup>, weekly divided schedules (n = 3)<sup>37, 40, 54</sup> or combinations of different dosing schedules (n = 5)<sup>19, 22, 38, 63, 85</sup>. In the remaining articles the dosing schedule was not reported.

Three recent documents with AgEv<sup>6, 64, 70</sup>, recommended a once weekly dosing schedule. The other documents with AgEv reported a weekly dose<sup>32, 45, 48, 64, 65, 67, 73</sup> or a combination of weekly and weekly divided dose<sup>4, 47, 74</sup>. The remaining documents with AgEv did not mention the dosing schedule in their recommendations<sup>46, 61, 66, 72, 75-78, 86</sup>.

### Maximum Dose

The maximum dosage of MTX differed among the RCTs: in 7 studies<sup>28, 30, 35, 37, 66, 84</sup> a dose of 15 mg/week was reported, and in 2 studies<sup>6, 70</sup> the maximum dosage was 20 mg/week (25 mg/week in individual cases). Other reported maximum dosages were 25 mg/week<sup>25, 36, 63, 64</sup>, 25 - 30 mg/week<sup>45</sup> or 30 mg/week<sup>4, 31, 38, 46, 47, 62, 65</sup>.

The maximum dose of MTX was 20 mg/week<sup>45, 87</sup>, 25 mg/week<sup>12, 64</sup> or 30 mg/week<sup>4, 47, 65</sup> in the documents with AgEv. In one guideline, the maximum dose of MTX was 15 mg/week<sup>66</sup>. The other 16 documents with aggregated evidence did not report a specific maximum dose.

### Cumulative Dose

Except for three RCTs<sup>51, 84, 88</sup>, in which a cumulative dose was only reported without clinical consequences, the cumulative dosage of MTX was not mentioned in the included RCTs.

In one guideline from 2010<sup>47</sup>, a specific MTX cumulative dose was reported. In this guideline, it is stated that dermatology patients have more issues with hepatotoxicity, probably due to confounding factors as non-alcoholic steatohepatitis. The authors stated that the cumulative dose for patients without these comorbidities can be increased from 1 – 1.5 gram to 3.5 – 4 gram. In the other documents with AgEv the use of a cumulative dose was not described.

### Use of Folic Acid

Thirty-six studies<sup>4, 6, 12, 21, 23-25, 30-33, 35, 37-39, 43, 45, 46, 50, 51, 56, 57, 59, 63-67, 70, 72-74, 76, 79, 82, 85, 86, 88</sup> used folic acid supplementation and in 4 studies<sup>22, 58, 62, 81</sup> no folate was prescribed. The remaining studies did not mention the use of folic acid. Most authors recommended the daily use of 1 mg folic acid<sup>27, 37, 43, 59</sup> or the weekly use of 5 mg folic acid<sup>23, 24, 35, 38, 57, 63</sup>.

In the Dutch guideline<sup>4</sup> it is advised to increase the dosage of folic acid to 10 mg/week when  $\geq$  15 mg/week of MTX is prescribed. This was based on recommendations from rheumatologists in the guideline working group.

### Safety

In the RCTs frequently described side effects were elevated liver enzymes in (18 RCTs)<sup>21, 22, 24, 25, 30, 35, 37, 39, 40, 42, 43, 52, 57, 62, 63, 79, 82, 88</sup>, headache (14 RCTs)<sup>22-25, 34, 35, 37-39, 42, 57, 63, 79, 83, 85, 88</sup> and GI-complaints (30 RCTs)<sup>21-25, 28, 31, 33-35, 37-39, 42, 43, 50, 52, 54, 56-58, 60, 62, 63, 81, 83-85, 88</sup>. Serious side effects that were mentioned were strong elevated liver enzymes<sup>53</sup>, severe nausea<sup>53</sup>, serious infections<sup>79</sup> laboratory adverse effects leading to exclusion (anemia, thrombocytopenia, elevated liver enzymes, increase of creatinine, or hypertension)<sup>83</sup>, and unknown serious side effects<sup>23, 24, 26, 57</sup>. Fourteen RCTs<sup>22, 33, 35, 39, 42, 43, 50, 52, 54, 56, 58, 60, 62, 85</sup> stated there were no serious adverse events, in the 20 remaining studies the occurrence of serious side effects was not reported. Details on safety information can be found in Table S1a.

## Discussion

Since the registration of MTX by the FDA, dermatologists have gained a large quantity of experience with this drug and it has been extensively studied in RCTs and observational studies. Our SR summarizes articles in which different aspects of dosages, dosage schedules and the use of folic acid are studied in psoriasis.

The starting dosage frequently advised in the RCTs and documents with AgEv was 7.5 mg/week and 15 mg/week, respectively. Most included studies reported a weekly dosing schedule in which MTX was administered orally. No papers were found supporting the use of a Weinstein schedule or a weekly divided schedule over a weekly administration schedule. The majority prescribed a maximum MTX dose of 15 mg/week or 30 mg/week. The use of folic acid might be beneficial, although this has not been studied in a randomized controlled study. The dosage however, is controversial<sup>188-90</sup>, and is mostly 1 mg/day or 5 mg/week. Safety data found in the included RCTs is in line with the AEs described in AgEv.

It is not possible to give recommendations on the most efficient and safe dosing regimen of MTX in psoriasis, since the quality of the literature is low, with only four studies with a low risk of bias<sup>23-26</sup>. One of those studies was the RCT from Reich<sup>25</sup> et al. in which 36.2% of the patients achieved a PASI75 score after 12 weeks. Patients were treated with a dosage of 5 mg in week 0, 10 mg in week 1 and 15 mg from week 2, with further increase of the dose based on clinical response. Another high quality study, namely from Saurat<sup>57</sup> et al., reported that 35.5% of the patients achieved PASI75 after 12 weeks. Patients started with 7.5 mg, received 10 mg in week 2 - 3 and 15 mg in week 4 - 7. Based on the efficacy of the drug, MTX dosages could be increased with 5 mg if <PASI50 at week 8 or week 12. Warren<sup>25</sup> et al. presented a PASI75 response in 37 patients after 16 weeks. Patients were treated with 5 - 15 mg/week or 2.5 - 5 mg/week in case of renal impairment. The last high quality study was from Papp<sup>26</sup> et al. They presented a mean PASI reduction of 13 in pediatric and adolescent patients treated with 0.1 mg/kg/week (up to 7.5 mg/kg/week) MTX. The dosage could be titrated upwards according to response or downwards in case of intolerance.

### Strengths and Limitations

To the best of our knowledge, this update is the first study summarizing the literature on the MTX dosing regimens in psoriasis patients including studies with oral, subcutaneous and intramuscular administration of the drug.

The extended inclusion criteria for the administration forms of MTX make this study of interest for daily practice. The addition of the subcutaneous adminis-

tration form to the inclusion criteria, is of special importance for the prescription of MTX in Europe, since the recent European Dermatology Forum (EDF) guideline<sup>6</sup> advised to start with subcutaneous administered MTX. In the EDF guideline, the primary administration of the subcutaneous form of MTX was advised due to safety risks, since the use of oral tablets had a higher risks for overdosing. In this SR, we did not find any RCTs in which the subcutaneous administration of MTX is compared to orally prescribed tablets.

Another strength of this study is the complete and recent overview of the risk of bias of the included studies, which is a consequence of the use of the most recent Cochrane Risk of Bias tool.

A limitation is the narrowing of our SR in the selection of RCTs and documents with AgEv. We excluded case reports and case series to prevent the development of an overly extensive SR. The inclusion criterion of 75% of the patients with CPP is a limitation as well. Based on a preparatory literature search we expected to oversight studies if we would narrow our SR to studies with a 100% of patients with CPP. The inclusion criterion of a minimum of 10 patients was chosen arbitrarily to reduce the chance of missing small RCTs.

Another limitation is the selection of languages that were considered; only studies in Dutch, English, French and German were included. This decision was made, since the authors were not able to extract data from studies written in other languages.

### **Clinical Implications and Future Perspective**

Our consensus study<sup>91</sup> and this SR are a first step to optimize the treatment of psoriasis patients with MTX. However, our consensus should be supported with more evidence. High-quality RCTs or observational studies (e.g. cohort studies) comparing different dosing regimens of MTX are needed, especially for subpopulations as children.

Based on the literature included in this SR we performed a previously published consensus project<sup>91</sup>, resulting in the following recommendations for daily practice: a test dose may not be needed in adults, children and vulnerable patients (elderly, patients with renal insufficiency). The start dose of MTX could be 15 mg/week, 10 mg/m<sup>2</sup>/week in children and 7.5 – 15 mg/week in vulnerable patients. MTX can be administered once a week. The maximum weekly dose of MTX is 25 mg/week in adults and vulnerable patients and 15 mg/m<sup>2</sup>/week in children. Start with the administration of MTX in oral tablets, switch to the subcutaneous form can be made in case of inefficacy or gastro-intestinal adverse events. Folic acid should be supplemented in all patients once a week and at least 24 hours after MTX intake. Since the dosage of folic acid depends on prescrip-

tion habits and the available evidence is controversial, no recommendations on dosage of folic acid can be made.<sup>91</sup>

In future research, focus could lay on the use of folic acid for which the evidence is still quite controversial and depends on habits and local availability.<sup>91</sup>

Other knowledge gaps involve the administration forms of MTX: in a low-quality study<sup>69</sup> not included in this SR, we found indications that the subcutaneous administration form of the drug might be more effective.<sup>69</sup>

Although there is no financial incentive for pharmaceutical companies to perform studies with MTX, the drug is used for many diseases in dermatology. It is, for example, prescribed off-label in alopecia areata, atopic dermatitis and morphea.<sup>92</sup> Unfortunately, experience from the past has taught that dosing mistakes can result in fatal outcomes.<sup>93</sup> Since MTX remains a significant and relatively affordable drug in the treatment of psoriasis patients in western and non-western countries, we should keep a future research focus on MTX.

## Appendix

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### Conflicts of interest

A.H. is involved as sub-investigator in clinical trials and observational studies from Abbvie, Janssen, LeoPharma, Lilly, Sanofi and UCB. R.S., A.C. and S.M. report no conflict of interest.

P.S. has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), receives departmental independent research grants for TREAT NL registry, for which she is Chief Investigator (CI), from pharma companies since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital.

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## Supplementary material

Table S1a. Characteristics and efficacy of the included RCTs and aggregated evidence for adults and children and adults

Table S1b. Dosing regimens in the included RCTs and aggregated evidence

This supplementary material can be found at:

<https://data.mendeley.com/datasets/ctvvsbn3kx/1>

