

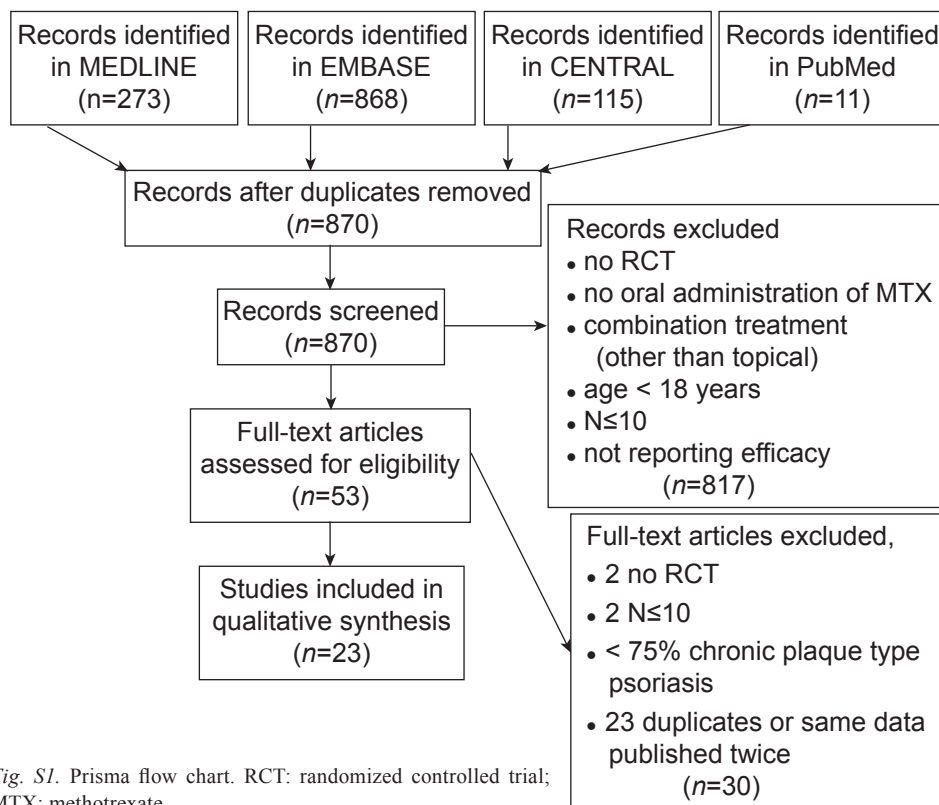


Fig. S1. Prisma flow chart. RCT: randomized controlled trial; MTX: methotrexate.

Table SIII. Randomized controlled trials (RCTs) comparing methotrexate (MTX) with another active substance

Author (year), country	Therapy	MTX-dose and use of FA	Dose adjustment	PASI75
Gupta et al. (40) (2005), India	I: MTX ^{Weinstein} vs hydroxyurea N: 20 D: 12 weeks	TD: not mentioned FA: not mentioned SD: MTX ^{Weinstein} 15 mg/week (fixed dose)	No DA: fixed dose No stopped patients mentioned	75% at week 12
Akhyani et al. (41) (2010), Iran	I: MTX ^{Weinstein} vs mycophenolate mofetil N: 18 (15 analysed) D: 12 weeks	TD: not mentioned FA: 1 mg/day except on the day of MTX administration SD: 7.5 mg/week ^{Weinstein} , then week 1: 15 mg/week, week 4: 20 mg/week	86.7% (13/15 pt) failed to increase/needed to lower the dose due to AE. 13.3% (2/15) reached 20 mg/week No stopped patients due to AE DA: 40% (6/15) had a dose increase from 15 to 20 mg/week. No stopped patients due to AE	73.3% at week 12
Ranjian et al. (38) (2007), India	I: MTX vs hydroxycarbamide N: 17 (15 analysed) D: 12 weeks	TD: not mentioned FA: 5 mg/day allowed SD: week 0–4: 7.5 mg 2days/week (15 mg/week) ↑↓: week 4 < PASI25: 20 mg (in "divided dosage")	DA: 40% (6/15) had a dose increase from 15 to 20 mg/week. No stopped patients due to AE	66.7% at week 12
Ho (48) et al. (2009), China	I: MTX vs traditional Chinese medicine vs placebo N: 20 (19 analysed) D: 24 weeks	TD: 2.5–5 mg/week FA: 5 mg/day SD: 10 mg/week ↑↓: 2.5 mg until "good clinical response" Max: 30mg/week	DA unclear 5% (n = 1) stopped due to AE	63% at week 24
Heydendaal et al. (32) (2003), The Netherlands	I: MTX ^{Weinstein} vs cyclosporine N: 43 D: 16 weeks	TD: not mentioned FA: not used SD: week 0–4: 15 mg/week ^{Weinstein} ↑↓: if <PASI25 at week 4: 22.5 mg/week ^{Weinstein} , tapering from week 12	DA: 9.3% (n = 4) dose increase at week 4 27.9% (n = 12) stopped due to AE	60% at week 16
Barker et al. (33) (2011), Europe and Canada	I: MTX vs infliximab N: 215 D: 16 weeks	TD: not mentioned FA: recommended, dose not mentioned SD: 15 mg/week ↑↓: 5 mg if <PASI–25 at week 6	DA: 25% (n = 54) had at least one dose increase between week 6 and 16. 4% (n = 8) stopped due to AE	27.0% at week 10 39.5% at week 14 41.9% at week 16
Reich et al. (34) (2011), Europe and Canada	I: MTX vs briakinumab N: 163 D: 52 weeks	TD: not mentioned FA: 5 mg/week SD: 5 mg/week at week 0, 10 mg/week at week 1, 15 mg/week from week 2–9 ↑↓: increment of 5 mg/week at week 10 and 16 if PASI < 75% or 6 point PGA# 0 or 1	DA: 10.4% (n = 17) dose increase at week 10 to 20 mg/week. 61.3% (n = 100) dose increase at week 16 to 25 mg/week. 6.1% (n = 10) stopped due to AE (5 out of 10 were an SAE) DA: 36.4% (n = 40) no dose increase. 20% (n = 22) Dose increase at week 8. 29.3% (n = 41) Dose increase at week 8 and week 12 5.5% (n = 6) stopped due to AE DA: No dose increase: fixed dose 2.9% (3/105) stopped due to AE	36.2% at week 12 39.9% at week 24
Saurat et al. (CHAMPION) (2011) (35), Europe and Canada	I: MTX vs adalimumab vs placebo N: 110 D: 16 weeks	TD: not mentioned FA: 5 mg/week SD: Week 0–1: 7.5 mg/week, week 2–3: 10 mg/week, week 4–7: 15 mg/week ↑↓: 5mg if <PASI50 at week 8 or week 12	DA: 36.4% (n = 40) no dose increase. 20% (n = 22) Dose increase at week 8. 29.3% (n = 41) Dose increase at week 8 and week 12 5.5% (n = 6) stopped due to AE DA: No dose increase: fixed dose 2.9% (3/105) stopped due to AE	9.1% at week 8 24.5% at week 12 35.5% at week 16
Yan et al. (43) (2011), China	I: MTX vs rhLFA3-IgFP N: 105 (92 analysed) D: 12 weeks	TD: not mentioned FA: not mentioned SD: 7.5 mg/week (fixed dose)	DA: 36.4% (n = 40) no dose increase. 20% (n = 22) Dose increase at week 8. 29.3% (n = 41) Dose increase at week 8 and week 12 5.5% (n = 6) stopped due to AE DA: No dose increase: fixed dose 2.9% (3/105) stopped due to AE	9.1% at week 8 24.5% at week 12 35.5% at week 16
Flyström et al. (17) (2008), Sweden	I: MTX ^{Weinstein} vs cyclosporine N: 41 (37 analysed) D: 12 weeks	TD: not mentioned FA: 5 mg/day except on the day of MTX administration SD: 7.5 mg/week ↑↓: if <PASI50 → increment, max: 15 mg/week	DA: 36.4% (n = 40) no dose increase. 20% (n = 22) Dose increase at week 8. 29.3% (n = 41) Dose increase at week 8 and week 12 5.5% (n = 6) stopped due to AE DA: No dose increase: fixed dose 2.9% (3/105) stopped due to AE	31.5% at week 12
Fallah Arani et al. (16) (2011), The Netherlands	I: MTX ^{Weinstein} vs fumarates N: 30 (25 analysed) D: 12 weeks	TD: 5 mg/week FA: not mentioned SD: from TD 5 mg/week gradually to 15 mg/week ^{Weinstein} at week 12, then ↓ to 12.5 to 10 to 5 to 2.5 mg/week at week 13, 14, 15 and 16, respectively.	DA unclear No stopped patients due to AE	24% at week 12

I: intervention; N: number of patients in MTX-treated group; D: duration of therapy; TD: MTX test-dose; FA: use of folic acid; SD: MTX start-dose; ↑↓: increments; DA: dose adjustment; AE: adverse event; PASI75: Psoriasis Area and Severity Index 75; SAE: serious adverse event.

Table SII. Randomized controlled trials (RCTs) making a head to head comparison between 2 or more methotrexate (MTX) dosing regimens

Author, year Country	MTX groups	Patients <i>n</i>	MTX test-dose, use of folic acid and duration of therapy	Dose adjustment and number of patients stopped	Results		
					Week 12 or 13	Week 16	Other time-point
Chladek et al. 2002 (14) Czech Republic	Group 1: MTX ^{Weinstein} 7.5 mg/week	12	TD: not mentioned FA: not mentioned D: 13 weeks	No DA: fixed dose No stopped patients mentioned	PASI50: 66.7% Mean ΔPASI: 33.26% PASI50: 75%		
	Group 2: MTX ^{Weinstein} 15 mg/week	12			Mean ΔPASI 27.46% Mean ΔPASI: 55% Mean ΔPASI: 62% Mean ΔPASI: 42% Mean ΔPASI: 58%		
Chladek et al. 2005 (13) Czech republic	Group 1: MTX ^{Weinstein} 7.5 mg/week	12	TD: not mentioned FA: not mentioned D: 13 weeks	No DA: fixed dose No stopped patients mentioned			
	Group 2: MTX ^{Weinstein} 15 mg/week Group 3: MTX 7.5 mg/week Group 4: MTX 15 mg/week Group 1: MTX 10 mg	12 7 10 30 (25 analysed)			PASI75: 72% PASI100: 30%		Median time to achieve PASI75 (mean ± SD): 66.29 ± 16.03
Dogra et al. 2012 (15) India	Group 2: MTX 25 mg	30 (26 analysed)	TD: not mentioned FA: 5 mg the day before and after MTX administration D: 12 weeks	No DA: fixed dose 3% (n=1) stopped due to AE			Median time to achieve PASI75 (mean ± SD): 55.44 days ± 13.37
				10% (n=3) stopped due to AE	PASI75: 92% PASI100: 69%		
Radmanesh et al. 2011 (12) Bangladesh	Group 1: MTX ^{Weinstein} 15 mg/week	147 (101 analysed)	TD: not mentioned FA: no folic acid allowed D: 4 months	No DA: fixed dose 6% (9/147) stopped due to AE No DA: fixed dose 3.5% (4/158) stopped due to AE	PASI25: 94% PASI75: 80% PASI25: 78% PASI75: 61%		
	Group 2: MTX 2.5 mg 6 days/week	158 (101 analysed)					

I: intervention; N: number of patients in MTX-treated group; D: duration of therapy; TD: MTX test-dose; FA: use of folic acid; SD: standard deviation; ↑↓: increments; DA: dose adjustment.

Table SI. Risk of bias of included randomized controlled trials (RCTs). The quality varied strongly amongst included studies from low risk of bias (RoB), to high RoB. Half of the studies reported an adequate randomization process; the rest did not report the randomization process or reported it inadequately. In general, most of the studies did not report on concealment of allocation and blinding of patients or outcome assessor. Reporting of incomplete outcome data was variable. Selective outcome reporting and other sources of bias were not thought to create a substantial risk of bias for most studies. Not having Psoriasis Area and Severity Index (PASI) as a primary outcome was seen as a potential additional source of bias

Study	Risk of bias						
	Sequence generation	Allocation concealment	Blinding		Incomplete outcome data	Selective outcome reporting	Other sources of bias
			Patient	Outcome assessor			
Chladek et al. 2002 (14)	?	?	—	—	?	+	—
Chladek et al. 2005 (13)	?	?	—	—	?	?	—
Dogra et al. 2012 (15)	+	+	+	+	—	+	+
Radmanesh et al. 2011 (12)	?	?	—	—	—	—	?
Bhuiyan et al. 2011 (42)	?	?	—	—	?	—	+
Yan et al. 2011 (43)	?	?	+	+	—	+	+
Ali et al. 2009 (39)	?	?	—	—	?	—	+
Malik & Ejaz 2010 (44)	?	?	—	—	—	—	+
Shehzad et al. 2004 (37)	?	?	—	—	?	+	+
Gupta et al. 2005 (40)	—	?	—	—	?	?	+
Gupta & Gupta 2007 (45)	—	—	—	—	?	+	+
El-Eishi et al. 2012 (30)	?	?	—	—	?	?	—
Fallah Arani et al. 2011 (16)	+	+	—	—	—	+	+
Gümüşel et al. 2011 (46)	+	?	—	+	—	+	—
Akhyani et al. 2010 (41)	+	?	—	—	—	+	+
Saurat et al. 2011 (35)	+	+	+	+	+	+	+
Reich et al. 2011 (34)	+	+	+	+	+	+	+
Flytström et al. 2008 (17)	+	+	—	+	+	+	+
Ho et al. 2009 (48)	+	?	—	+	—	+	+
Barker et al. 2011 (33)	+	+	—	—	+	+	+
Ranjan et al. 2007 (38)	—	—	—	—	—	+	+
Heydendael et al. 2003 (32)	+	+	—	+	+	+	+
Sandhu et al. 2003 (31)	?	?	—	—	?	+	+

Table SIV. Aggregated evidence

	BSR/BHPR (18) (UK, 2008)	NICE (22) (UK, 2012)	Update S3 guideline (21) (Germany, 2012)	European S3 guideline (20) (EU, 2009)	Guideline psoriasis (27) (The Netherlands, 2011)	AAD guideline (2) (US, 2009)	Guideline MTX in psoriasis (19) (Spain, 2010)	SR Treatment modalities (3)	Consensus conference NPF 2009 (6)	Consensus report TTP 2013 (28)
Test-dose	Not mentioned	Not mentioned	Not mentioned	2.5 mg in elderly patients	2.5–5 mg can be considered (no consensus)	2.5–5 mg recommended	Recommended in patients with a relative contraindication and elderly patients	Not mentioned	5–15 mg mandatory in patients with decreased glomerular filtration rate or risks for haematological toxicity	Not mentioned
Start-dose Single/ Weinstein	5–10 mg/week Single	5–10 mg/week Not mentioned	7.5–15 mg/week Weinstein (no clear evidence)	5–10 mg/week Single or Weinstein (no evidence)	5–10 mg/week Single or Weinstein (no evidence)	Not mentioned Single	Not mentioned Single or Weinstein (no evidence)	5–10 mg/week Not mentioned	7.5–15 mg/week Single or Weinstein	5–15 mg/week Single or Weinstein (no evidence)
Dose increments	2.5–5 mg increments every 2–6 weeks until stable disease	Gradually increase up to an effective dose. Assessment after 3 months on target dose.	Increase up to 22.5 mg/week depending on treatment response	Not mentioned	Depending on response increment up to 15 mg/week, perhaps to 22.5 mg/week	Dose increase until optimal response. Effect of dose increase noticeable after 4 weeks.	Lower the dose when treatment goal is reached	Rapid dose increase over 4 weeks to reach a target therapeutic dose between 15–25 mg/week	Dose ↑↓ to obtain adequate control. It can take 4–8 weeks to determine the result of a dose change	In case of low MTX start dose, rapid ↑ to 15 mg/ week at week 3 and if necessary and possible to 20 mg/week at week 8
Max dose FA	25 mg/week 5 mg the day after MTX	25 mg/week Effect of FA on efficacy and AEs is unclear.	22.5 mg/week 1–5 mg on non- MTX days with maximum of 20 mg/week. Perhaps no FA during induction phase	30 mg/week There is evidence that FA might reduce AEs without affecting efficacy	30 mg/week 1 mg/day except on MTX days till 5–10 mg/week 24 h after MTX administration. (In RA: MTX < 15 mg; 5 mg FA, MTX ≥ 15 mg; 10 mg FA)	25 mg/week 1–5 mg/day except on the day of MTX administration	30 mg/week FA only in patient with FA deficiency or high need patients (infectious disease, use of certain antibiotics)	25 mg/week 5 mg/day for 1–3 days to be taken 48 h after MTX dose	25 mg/week Adding FA to MTX treatment is beneficial. An options is 1 mg daily	Not mentioned Often recommended though there is little evidence about its effect on tolerability of MTX

MTX: methotrexate; FA: folic acid; AE: adverse event; AAD: American Association of Dermatologists; SR: systematic review; NPF: National Psoriasis Foundation; TTP: Transitioning Therapies Program; BSR/BHPR: British Society for Rheumatology/British Health Professionals in Rheumatology; NICE: National Institute for Health and Care Excellence; RA: rheumatoid arthritis.