GRADE tabellen bij richtlijn Off-label geneesmiddelen 5-6-2023

Table 3 - 14 GRADE evidence profiles

Atopic Dermatitis

Table 1 GRADE evidence profile: MTX compared to CSA for atopic dermatitis

Bibliography: El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. European Journal of Pediatrics. 2013;172(3):351-6.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	CSA	Relative (95% CI)	Absolute (95% CI)	
SCORAD after the end of treatment period (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	mean 2 lower (6.78 lower to 2.78 higher)	⨁◯◯◯ VERY LOW

Absolute reduction in SCORAD at the end of treatment period from baseline (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomized trials	serious [a]	not serious	not serious	very serious[b]	none	20	20	-	mean 1.24 points lower (3.5 lower to 5.98 higher)	⨁◯◯◯ VERY LOW
SCORAD after the end of follow-up period (follow up: 24 weeks; Scale from: 0 to 108)											
1	randomized trials	serious [a]	not serious	not serious	very serious[b]	none	20	20	-	mean 3.89 higher (2.86 lower to 10.64 higher)	⨁◯◯◯ VERY LOW
Absolute reduction in SCORAD at the end of follow-up period from baseline (follow up: 24 weeks; Scale from: 0 to 108)											

1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	20	-	3.89 higher (2.86 lower to 10.64 higher)	⊕◯◯◯ VERY LOW
Adverse events (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 43 AEs occurred in total. Reported AEs were GI discomfort (9), anemia (6), fatigue (6), elevated liver enzymes (5), nausea and vomiting (4), oral ulceration (4), headache (3), leukopenia (2), pancytopenia (1), abnormal renal function test (1), fever (1) and flu-like symptoms (1). No SAEs were mentioned.					⊕◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CSA**: Cyclosporine-A; **MTX**: Methotrexate; **SAE**: Serious adverse event; **SCORAD**: Scoring atopic dermatitis

Explanations

a. Downgraded one level for risk of bias due to unclear allocation concealment and blinding of participants, personnel and outcome assessors. There was no data on patients lost to follow-up.

b. Downgraded two levels for imprecision due to a small sample size and a wide confidence interval that included both no effect and beneficial or harmful effect.

Table 2 GRADE evidence profile: MTX compared to CSA for atopic dermatitis

Bibliography: Goujon C, Viguier M, Staumont-Salle D, Bernier C, Guillet G, Lahfa M, et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. Journal of Allergy and Clinical Immunology: In Practice. 2017.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	CSA	Relative (95% CI)	Absolute (95% CI)	
SCORAD 50 (≥50% reduction) (follow up: 12 weeks)											
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	7/36 (19.4 %)	21/41 (51.2 %)	**RR 0.38** (0.18 to 0.79)	**32 fewer per 100** (from 52 fewer to 12 fewer)[d]	⨁◯◯◯ VERY LOW
SCORAD 50 (≥50% reduction) (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	9/23 (39.1 %)	22/31 (71.0 %)	**RR 0.55** (0.32 to 0.96)	**32 fewer per 100** (from 57 fewer to 6 fewer)[d]	⨁◯◯◯ VERY LOW
EASI 50 (≥50% reduction) (follow up: 12 weeks)											

1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	16/37 (43.2 %)	31/41 (75.6 %)	**RR 0.57** (0.38 to 0.86)	**32 fewer per 100** (from 53 fewer to 12 fewer)[d]	⊕◯◯◯ VERY LOW
EASI 50 (≥50% reduction) (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	20/23 (87.0 %)	25/31 (80.6 %)	**RR 1.08** (0.85 to 1.36)	**6 more per 100** (from 13 fewer to 26 more)[d]	⊕◯◯◯ VERY LOW
DLQI (≤5) (follow up: 12 weeks)											
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	15/37 (40.5 %)	28/41 (68.3 %)	**RR 0.59** (0.38 to 0.92)	**28 fewer per 100** (from 49 fewer to 6 fewer)[d]	⊕◯◯◯ VERY LOW
DLQI (≤5) (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	15/23 (65.2 %)	25/31 (80.6 %)	**RR 0.81** (0.57 to 1.14)	**15 fewer per 100** (from 39 fewer to 8 more)[d]	⊕◯◯◯ VERY LOW
Adverse events (follow up: 24 weeks)											

1	randomized trials	serious[a]	not serious	serious[b]	serious[c]	none	In the MTX group 31 AEs occurred in total. Reported AEs were infections (12), gastro-intestinal disorders (9), fatigue (6), acne/virus papilloma (1), elevated liver enzymes (1), headache (1), lymphocytopenia (1). There were no SAEs.	⊕◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CSA**: Cyclosporine-A; **DLQI:** Dermatology life quality index; **EASI:** Eczema area severity index; **MTX:** Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event; **SCORAD**: Scoring atopic dermatitis

Explanations

a. Downgraded one level for risk of bias due to a lack of blinding of patients and physicians. Randomization, concealment of allocation and blinding of outcome assessors were adequate.

b. Downgraded one level for indirectness, since MTX treatment was evaluated too early to assess effect (after 8 weeks)

c. Downgraded one level for imprecision due to a small sample size and because the 90% CI includes both neglectable and appreciable benefit or appreciable harm (the non-inferiority limit was -20%).

d. Calculated with Review Manager.

Table 3 GRADE evidence profile: MTX compared to AZA for atopic dermatitis

Bibliography: Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. J Allergy Clin Immunol. 2011;128(2):353-9.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MTX**	**AZA**	**Relative (95% CI)**	**Absolute (95% CI)**	
Mean change in SCORAD (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean 0.5 points lower (8.22 lower to 7.22 higher)	⨁◯◯◯ VERY LOW
SCORAD reduction of 50% (follow up: 12 weeks; Scale from: 0 to 108)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	8/20 (40.0 %)	10/22 (45.5 %)	**RR 0.88** (0.43 to 1.78)	**5 fewer per 100** (from 35 fewer to 24 more)[c]	⨁◯◯◯ VERY LOW
Change in mean IGA (follow up: 12 weeks; Scale from: 0 to 6)											

1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean 0.4 lower (0.89 lower to 0.09 higher)	⊕◯◯◯ VERY LOW
Achieving mild disease (follow up: 12 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	15/20 (75.0 %)	15/22 (68.2 %)	**RR 1.10** (0.75 to 1.61)	**7 more per 100** (from 20 fewer to 34 more)[c]	⊕◯◯◯ VERY LOW
Mean change in EASI (follow up: 12 weeks; Scale from: 0 to 72)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean 0.2 lower (6.36 lower to 6.76 higher)	⊕◯◯◯ VERY LOW
Mean change in POEM (follow up: 12 weeks; Scale from: 0 to 28)											

1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	20	22	-	mean 1 lower (5.07 lower to 3.07 higher)	⊕◯◯◯ VERY LOW
Adverse Events (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 112 AEs occurred in total. Frequently reported AEs were infections (14), gastro-intestinal complaints (11), elevated liver enzymes (7), abnormalities in blood count (6) and exacerbation of eczema (3). There were no SAEs.				⊕◯◯◯ VERY LOW

AE: Adverse event; **AZA**: Azathioprine; **CI:** Confidence interval; **EASI**: Eczema area severity index; **IGA:** Investigator global assessment; **MTX:** Methotrexate; **POEM**: Patient oriented eczema measure; **RR:** Risk ratio; **SAE**: Serious adverse event; **SCORAD**: Scoring atopic dermatitis

Explanations

a. Downgraded one level for risk of bias; no allocation concealment since patients were not blinded. Randomization, concealment of allocation and blinding of researchers was adequate. Concomitant topical corticosteroids and oral antihistamines were allowed. Rescue medication of maximal 2 courses of oral prednisolone was allowed, but this was not considered serious enough to downgrade for risk of bias.

b. Downgraded two levels for imprecision due to small sample size and a wide confidence interval that includes both no effect and (beneficial or harmful) effect.

c. Calculated with Review Manager.

Dermatomyositis

Table 4 GRADE evidence profile: Pred compared to pred+MTX for dermatomyositis

Bibliography: Ruperto N, Pistorio A, Oliveira S, Zulian F, Cuttica R, Ravelli A, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomized trial. Lancet. 2016;387(10019):671-8.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pred	pred+MTX	Relative (95% CI)	Absolute (95% CI)	
Achieving PRINTO 20 (follow up: 6 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	24/47 (51.1 %)	33/46 (71.7%)	**RR 0.71** (0.51 to 0.99)	**21 fewer per 100** (from 40 fewer to 1 fewer)[c]	⨁⨁◯◯ LOW
Achieving PRINTO 50, 70 or 90 (follow up: 24 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	No exact data was provided. For achieving PRINTO 50 or 70, there was a significant difference between the combination of prednisone plus MTX versus prednisone alone.				⨁⨁◯◯ LOW

Achieving clinical remission proportion of patients (follow up: 60 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[d]	none	8/47 (17.0 %)	15/46 (32.6%)	**RR 0.52** (0.25 to 1.11)	**16 fewer per 100** (from 33 fewer to 33 more)[c]	⊕◯◯◯ VERY LOW
Treatment failures proportion of patients (follow up: 60 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	30/47 (63.8 %)	17/46 (37.0%)	**RR 1.73** (1.12 to 2.67)	**27 more per 100** (from 7 more to 46 more)[c]	⊕⊕◯◯ LOW
Achieving discontinuation of prednisone (follow up: 60 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[d]	none	19/47 (40.4 %)	25/46 (54.3%)	**RR 0.74** (0.48 to 1.15)	**14 fewer per 100** (from 34 fewer to 6 more)[c]	⊕◯◯◯ VERY LOW

Adverse events (follow up: 60 months)								
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	A total of 52 AEs were reported in the prednisone group compared to 74 in the prednisone + MTX group. The most frequently reported AEs in the MTX group were infections (30%). Reported SAEs were dermohypodermitis (1) and paronychia (1).	⊕⊕◯◯ LOW

AE: Adverse event; **CI:** Confidence interval; **MTX**: Methotrexate; **pred**: Prednisone; **PRINTO**: Pediatric rheumatology international trials organisation; **RR:** Risk ratio; **SAE**: Serious adverse event

Explanations

a. Downgraded one level for risk of bias due to lack of blinding of participants, clinicians (treating and assessing) and statisticians, which accounts for a high risk of performance and detection bias.

b. Downgraded one level for imprecision due to a small sample size and wide confidence intervals.

c. Calculated with Review Manager.

d. Downgraded two levels for imprecision due to a small sample size and wide confidence interval that includes both no effect and (beneficial or harmful) effect.

Lupus erythematosus

Table 5 GRADE evidence profile: MTX compared to placebo for cutaneous SLE

Bibliography: Carneiro JR, double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus, 1999;26:1275-9

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MTX**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Presence of cutaneous lesions (follow up: 6 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	3/20 (15.0 %)	16/21 (76.2%)	**RR 0.20** (0.07 to 0.57)	**61 fewer per 100** (from 85 fewer to 37 fewer)[c]	⨁◯◯◯ VERY LOW
Mean change in SLEDAI (follow up: 6 months; Score from: 0 to 108)											

1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	Data was insufficient to calculate a mean, SD, MD or CI. After 6 months the SLEDAI significantly decreased in the MTX group compared to baseline scores. In the placebo group the mean SLEDAI was significantly higher after 6 months compared to baseline scores. The difference in SLEDAI between placebo and MTX groups was significant.				⊕◯◯◯ VERY LOW
Achieving 50% decrease in prednisone dose (follow up: 6 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	13/20 (65.0 %)	1/21 (4.8%)	**RR 13.65** (1.96 to 94.95)	**60 more per 100** (from 37 more to 83 more)[c]	⊕◯◯◯ VERY LOW
Adverse events (follow up: 6 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 67 AEs occurred in total. Reported AEs were elevated liver enzymes (31), dyspepsia (9), nausea (6), oral ulceration (6), weakness (5) diarrhea (5), infection (4) and urticaria (1). No SAEs were mentioned.				⊕◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **MTX:** Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event; **SLE:** Systemic lupus erythematosus; **SLEDAI:** Systemic lupus erythematosus disease activity index

Explanations

a. Downgraded one level for risk of bias due to allocation concealment.

b. Downgraded two levels for imprecision due to very small sample size.

c. Calculated with Review Manager.

Table 6 GRADE evidence profile: MTX compared to CQ for cutaneous SLE

Bibliography: Islam MN, Hossain M, Haq SA, Alam MN, Ten Klooster PM, Rasker JJ. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus. International Journal of Rheumatic Diseases. 2012;15(1):62-8.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MTX**	**CQ**	**Relative (95% CI)**	**Absolute (95% CI)**	
Number of subjects with skin rash (follow up: mean 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	0/13 (0.0%)	3/24 (12.5%)	**RR 0.41** (0.02 to 6.95)	**13 fewer per 100** (from 29 fewer to 4 more)[c]	⨁◯◯◯ VERY LOW
Adverse events (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 9 AEs occurred in total. Reported AEs were anorexia and nausea (7) and elevated liver enzymes (2). There were no SAEs.				⨁◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **CQ**: Chloroquine; **MTX:** Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event; **SLE:** Systemic lupus erythematosus

Explanations

a. Downgraded one level for risk of bias due to no allocation concealment.

b. Downgraded two levels for very small sample size.

c. Calculated with Review Manager.

Table 7 GRADE evidence profile: MTX compared to Or CST for Lichen Planopilaris

Bibliography: Bakhtiar R, Noor SM, Paracha MM. Effectiveness of oral methotrexate therapy versus systemic corticosteroid therapy in treatment of generalized lichen planus. Journal of the College of Physicians and Surgeons Pakistan. 2018;28(7):505-508.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Or CST	Relative (95% CI)	Absolute (95% CI)	
Effectiveness (follow up: 8 weeks)											
1	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	63/97 (64.9 %)	47/79 (59.5 %)	**RR 1.09** (0.86 to 1.38)	**5 more per 100** (from 9 fewer to 20 more)[c]	⨁◯◯◯ VERY LOW
Adverse events (follow up: 8 weeks)											
1	randomized trials	very serious[a]	not serious	not serious	serious[b]	none	In the MTX group no AEs occurred. No SAEs were mentioned.				⨁◯◯◯ VERY LOW

AE: Adverse event, **CI:** Confidence interval; **Or CST**: Oral corticosteroids; **MTX**: Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event

Explanations

a. Downgraded two levels for risk of bias, poor clarification of randomization, unclear outcome and lack of blinding of participants.

b. Downgraded one level for imprecision due to a small sample size.

c. Calculated with Review Manager.

Table 8 GRADE evidence profile: MTX compared to HCQ for refractory lichen planopilaris

Bibliography: Naeini FF, Saber M, Asilian A, Hosseini SM. Clinical efficacy and safety of methotrexate versus hydroxychloroquine in preventing lichen planopilaris progress: A randomized clinical trial. International Journal of Preventive Medicine. 2017;8 (37).

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	HCQ	Relative (95% CI)	Absolute (95% CI)	
Change in LPPAI - month 6 (follow up: 6 months; Score from 0 to 10)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	15	14	-	mean 1.95 higher (0.79 higher to 3.11 higher)	⨁◯◯◯ VERY LOW
Global photographic assessment 1 - slightly decreased (follow up: 6 months)											
1	randomized trials	serious[c]	not serious	not serious	very serious[b]	none	2/15 (13.3 %)	1/14 (7.1%)	**RR 1.87** (0.19 to 18.38)	**6 more per 100** (from 16 fewer to 28 more)[d]	⨁◯◯◯ VERY LOW
Global photographic assessment 2 - slightly decreased (follow up: 6 months)											

1	randomized trials	serious[c]	not serious	not serious	very serious[b]	none	1/15 (6.7%)	0/14 (0.0%)	**RR 2.81** (0.12 to 63.38)	**7 more per 100** (from 10 fewer to 24 more)[d]	⨁◯◯◯ VERY LOW
Adverse events (follow up: 6 months)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 1 AE occurred in total. The reported AE was elevated liver enzymes (1). There were no SAEs.				⨁◯◯◯ VERY LOW

AE: Adverse event; **CI:** Confidence interval; **HCQ**: Hydroxychloroquine; **LPPAI**: Lichen planopilaris activity index**; MTX:** Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event

Explanations

a. Downgraded one level for risk of bias due to unclear sequence generation and no blinding of participants.

b. Downgraded two levels for imprecision due to a very small sample size.

c. Downgraded one level for risk of bias due to an unclear sequence generation.

d. Calculated with Review Manager.

Morphea

Table 9 GRADE evidence profile: MTX compared to placebo for morphea

Bibliography: Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A, et al. Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2011;63(7):1998-2006.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	
Target skin lesion activity (follow up: 12 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	46	24	-	MD 32.3 percent lower (37.92 lower to 26.68 lower)	⨁⨁◯◯ LOW
Change in SSR (follow up: 12 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	46	24	-	mean 0.31 lower (0.35 lower to 0.27 lower)	⨁⨁◯◯ LOW
Development of new lesions (follow up: 12 months)											

1	randomized trials	serious[a]	not serious	not serious	very serious[c]	none	3/46 (6.5%)	4/24 (16.7%)	**RR 0.39** (0.10 to 1.61)	**10 fewer per 100** (from 27 fewer to 6 more)[d]	⊕◯◯◯ VERY LOW
Achieving individual response (follow up: 12 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	31/46 (67.4%)	7/24 (29.2%)	**RR 2.31** (1.20 to 4.45)	**38 more per 100** (from 16 more to 61 more)[d]	⊕⊕◯◯ LOW
Adverse events (follow up: 12 months)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	In the MTX group 26 AEs occurred in total, of which 20 were MTX treatment related. Reported AEs related to MTX treatment were nausea (8), headache (5), hepatotoxicity (3), alopecia (2) and fatigue (2). There were no SAEs.				⊕⊕◯◯ LOW

AE: Adverse event; **CI:** Confidence interval; **MD:** Mean difference; **MTX**: Methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event; **SSR**: Skin score rate

Explanations

a. Downgraded one level for risk of bias due to lack of allocation concealment.

b. Downgraded one level for imprecision due to a small sample size.

c. Downgraded two levels for imprecision due to a small sample size and wide confidence interval that includes both no effect and (beneficial or harmful) effect.

d. Calculated with Review Manager.

Systemic sclerosis

Table 10 GRADE evidence profile: MTX compared to placebo for systemic sclerosis

Bibliography:

Pope JE, Bellamy N, Seibold JR, Baron M, Ellman M, Carette S, et al. A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. Arthritis Rheum. 2001;4(6):1351–8.

van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24 week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol. 1996;35(4):364-72.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	
Mean change in UCLA skin score (follow up: 12 months; Scale from 0 - 30)											
1	randomized trials	not serious[a]	not serious	not serious	very serious[b]	none	27	24	-	MD 2.45 lower (2.74 lower to 2.16 lower)	⨁⨁◯◯ LOW
Mean change in modified RSS (follow up: 12 months; Scale from 0 - 78)											
1	randomized trials	not serious[a]	not serious	not serious	very serious[b]	none	27	24	-	MD 5.9 lower (6.56 lower to 5.25 lower)	⨁⨁◯◯ LOW
Change in MD global assessment (follow up: 12 months)											

1	randomized trials	not serious[a]	not serious	not serious	very serious[b]	none	At 12 months the difference was statistically significant (4.2 ± 0.5 and 5.5 ± 0.4 in the MTX and placebo groups, respectively; P 0.035).					⨁⨁◯◯ LOW
Response to treatment (follow up: 24 weeks)												
1	randomized trials	serious[c]	not serious	not serious	very serious[d]	none	8/15 (53.3 %)	1/10 (10.0%)	**RR 5.33** (0.78 to 36.33)	**43 more per 100** (from 12 more to 75 more)		⨁◯◯◯ VERY LOW
Mean change in TSS (follow up: 24 weeks; Scale from: 0 to 5)												
1	randomized trials	serious[c]	not serious	not serious	very serious[d]	none	15	10	-	mean 1.9 lower (5.19 lower to 1.39 higher)		⨁◯◯◯ VERY LOW
Mean change in VAS general well-being (follow up: 24 weeks; Scale from: 0 to 10)												
1	randomized trials	serious[c]	not serious	not serious	very serious[d]	none	15	10	-	mean 5.5 higher (6.86 lower to 17.86 higher)		⨁◯◯◯ VERY LOW
Adverse events (follow up: 5.5-12 months)												

2	randomized trials	serious[e]	not serious	not serious	serious[f]	none	In the MTX group 11 AEs occurred in total. Reported AEs were elevated liver enzymes (6), oral ulceration (1), pancytopenia (1) and headache (1). Two SAEs were reported: sudden death presumably due to acute myocardial infarction (1) and renal crisis (1).	⊕⊕◯◯ LOW

AE: Adverse event**; CI:** Confidence interval; **Dlco**: Lung diffusion capacity; **MD:** Mean difference; **MTX**: Methorexate; **RR:** Risk ratio; **RSS**: Rodnan skin score; **SAE**: Serious adverse event; **TSS**; Total skin score; **UCLA**: University of California Los Angeles **VAS**; Visual analogue scale

Explanations

a. No downgrading for risk of bias. Randomization, concealment of allocation and blinding of patients was adequate. Data was anlayzed per protocol and intention to treat. Results were adjusted for differences in baseline characteristics (differences in sex distribution and prednisone use).

b. Downgraded two levels for imprecision due to very small sample size.

c. Downgraded one level for risk of bias due to possible inadequate allocation concealment since groups were balanced for disease duration and extent of skin involvement.

d. Downgraded two levels for imprecision due to very small sample size and wide confidence intervals that includes both (beneficial and harmful) effects.

e. Downgraded one level for risk of bias due to possible inadequate allocation concealment since in 1 study groups were balanced for disease duration and extent of skin involvement.

f. Downgraded one level for imprecision due to small sample size.

Urticaria

Table 11 GRADE evidence profile: MTX compared to placebo for chronic urticaria

Bibliography:

Leducq S, Samimi M, Bernier C, Soria A, Amsler E, Staumont-Salle D, et al. Efficacy and safety of methotrexate add-on therapy versus placebo for patients with chronic spontaneous urticaria resistant to H1-antihistamines: a randomized, controlled trial. J Am Acad Dermatol. 2019.
Sharma V, Singh S, Ramam M, Kumawat M, Kumar R. A randomized placebo-controlled double-blind pilot study of methotrexate in the treatment of H1 antihistamine-resistant chronic spontaneous urticaria. Indian Journal of Dermatology, Venereology and Leprology. 2014;80(2):122-8.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	placebo	Relative (95% CI)	Absolute (95% CI)	
Primary outcome (follow up: 12 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	The sentence 'Out of 17 patients who completed therapy, the primary outcome was achieved by 3.5 ± 1.9 (out of 10) patients in the methotrexate group and by 3.67 ± 1.03 (out of 7) patients in the placebo group (*P* > 0.05).' is unclear to interpret.				⨁◯◯◯ VERY LOW
Wheal score (follow up: 12 weeks; Scale from: 0 to 3)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	14	15	-	mean 3.36 lower (3.52 lower to 3.2 lower)	⨁◯◯◯ VERY LOW

Pruritus score (follow up: 12 weeks; Scale from 0 to 3)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	14	15	-	mean 0.24 higher (0.09 higher to 0.39 higher)	⨁◯◯◯ VERY LOW
Complete remission (follow up: mean 18 weeks)											
1	randomized trials	serious[c]	not serious	not serious[d]	very serious[e]	none	3/38 (7.9%)	0/32 (0.0%)	**RR 5.92** (0.32 to 110.56)	**0.8 more per 100** (from 0.2 fewer to 0.2 more)[f]	⨁◯◯◯ VERY LOW
Self-assessment of pruritus (follow up: 18 weeks)											
1	randomized trials	serious[c]	not serious	not serious	very serious[e]	none	The MD in the MTX group was 15.0 with an Q1-Q3 range [3.5-32.7] and in the placebo group 15.6 with an Q1-Q3 range range[6.4-51.1]. The difference was 0.6 points.				⨁◯◯◯ VERY LOW
Self-assessment of quality of sleep (follow up: 18 weeks; Scale from 0 to 100)											
1	randomized trials	serious[c]	not serious	not serious	very serious[e]	none	The MD in the MTX group was 84.5 with an Q1-Q3 range [67.5-95.3] and in the placebo group 77.7 with an Q1-Q3 range [68.4-89.6]. The difference was 6.8 points.				⨁◯◯◯ VERY LOW

Adverse events (follow up: 12-18 weeks)								
2	randomized trials	serious[g]	not serious	not serious	very serious[e]	none	A total of 74 AEs were reported in the MTX group. Reported AEs were elevated liver enzymes (19), gastrointestinal discomfort (17), cholestasis (5), nasopharyngitis (5), anemia (4), asthenia (4), leukopenia (4), respiratory tract infection (4), lymphopenia (3), headache (3), insomnia (1), nausea/vomiting (1), neutropenia (1) and urinary tract infection (1). Reported SAEs were cerebrovascular stroke (1) and unstable angina (1).	⨁◯◯◯ VERY LOW

AE: Adverse event**; CI:** Confidence interval; **MD:** Mean difference; **MTX:** Methotrexate**; RR:** Risk ratio; **SAE**: Serious adverse event

Explanations

a. Downgraded one level for risk of bias since no assessments were made for incomplete data.

b. Downgraded two levels for imprecision due to a very small sample size.

c. Downgraded one level for risk of bias due to selective outcome reporting, because not all secondary outcomes are reported (including the baseline), and many patients were lost to follow-up.

d. No downgrading for indirectness; possible differences in baseline characteristics in the intervention and control group are not reported. However we did not find reasons to assume these differences exist.

e. Downgraded two levels for imprecision due to a very small sample size and a small number of events.

f. Calculated with Review Manager.

g. Downgraded one level for risk of bias due to the facts that no assessments were made for incomplete data, there was selective outcome reporting, not all secondary outcomes were reported (including the baseline) and many patients were lost to follow-up.

Table 12 GRADE evidence profile: OMP compared to MTX for vitiligo

Bibliography:
Singh H, Kumaran MS, Bains A, Parsad D. A randomized comparative study of oral corticosteroid minipulse and low-dose oral methotrexate in the treatment of unstable vitiligo, Dermatology 2015;231:286–290

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	OMP	MTX	Relative (95% CI)	Absolute (95% CI)	
Development of new lesions (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	7/25 (28.0 %)	6/25 (24.0 %)	**RR 1.17** (0.46 to 2.98)	**4 more per 100** (from 20 fewer to 28 more)[c]	⨁◯◯◯ VERY LOW
Reduction in mean VIDA (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	No exact data was provided. Both groups showed a similar reduction in the VIDA score.				⨁◯◯◯ VERY LOW
Reduction in mean VASI (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	No exact data was provided. Both groups demonstrated reduction in the VASI score.				⨁◯◯◯ VERY LOW
Achieving >50% repigmentation (follow up: 24 weeks)											

1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	9/25 (36.0 %)	14/25 (56.0 %)	**RR 0.64** (0.34 to 1.20)	**20 fewer per 100** (from 47 fewer to 7 more)[c]	⊕◯◯◯ VERY LOW
Achieving no repigmentation (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	10/25 (40.0 %)	16/25 (64.0 %)	**RR 0.63** (0.36 to 1.10)	**24 fewer per 100** (from 51 fewer to 3 more)[c]	⊕◯◯◯ VERY LOW
Adverse events (follow up: 24 weeks)											
1	randomized trials	serious[a]	not serious	not serious	very serious[b]	none	In the MTX group 5 AEs occurred in total. Reported AEs were not severe nausea (4) and severe nausea (1). There were no SAEs.				⊕◯◯◯ VERY LOW

AE: Adverse event**; CI:** Confidence interval; **OMP:** Oral corticosteroid minipulse, **MTX**: methotrexate; **RR:** Risk ratio; **SAE**: Serious adverse event; **VIDA**: Vitiligo disease activity; **VASI:** Vitiligo area scoring index

Explanations

a. Downgraded one level for risk of bias due to a lack of blinding of participants and investigators. Analysis was done according to the worst-case-scenario.

b. Downgraded two levels for imprecision due to small sample size and a wide confidence interval that includes both no effect and (beneficial or harmful) effect.

c. Calculated with Review Manager.