Chapter 6

Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide

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Abstract

Background
Although glucocorticosteroids are considered the first-line treatment in sarcoidosis, refractory cases require alternatives, such as methotrexate (MTX). The aim of this study was to develop, on behalf of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), multinational evidence-based recommendations for the use of MTX in sarcoidosis for routine clinical practice.

Methods
A systematic literature search was conducted and combined with the opinions of sarcoidosis experts worldwide to formulate the recommendations. An online survey concerning 10 clinical questions was sent through the WASOG newsletter to sarcoidosis experts. Agreement about the recommendations among the world's leading sarcoidologists was evaluated.

Results
A total of 237 articles were identified, 43 of which were included. Randomized controlled trial evidence supporting the use of MTX in sarcoidosis was limited. Forty-five per cent (113 of 250) of the sarcoidosis experts contacted completed the survey (Europe 55%, North America 26%, and Asia 12%). Ten recommendations were formulated concerning the indications for use, starting dose, folic acid, work-up, contraindications, monitoring, administration options in case of adverse gastrointestinal effects, hepatotoxicity, long-term safety and use during pregnancy and breast feeding.

Conclusion
Ten multinational evidence-based recommendations for the use of MTX in sarcoidosis were developed, which are supported by the world's foremost sarcoidosis experts.

Introduction

Sarcoidosis is a multisystemic disease of unknown cause, characterized by inflammatory activity with noncaseating granulomas commonly developing in the lungs, but in other organ systems as well.[1-3] In severe sarcoidosis, the release of inflammatory mediators causes derangement of organ physiology and ultimately functional impairment and related symptoms. The disease stabilizes or improves in many cases over the first 2 years, but may worsen and become chronic in others.[1] As virtually any organ can be involved, patients may present with a wide variety of clinical signs and symptoms,[1,2] and may first present to any one of a variety of organ specialists. As high-quality care and patients' expectations may not be covered by an individual specialist's expertise, recommendations for practical use can be expected to provide added value to optimize expertise in the field of sarcoidosis treatment.

Traditionally, glucocorticosteroids are considered the first-line treatment option in serious systemic sarcoidosis, but alternative treatment options have expanded tremendously.[4,5] Refractory cases, with steroid resistance or steroid-induced adverse effects, require alternatives to glucocorticosteroids,[6,7] for which we propose to introduce the term disease-modifying antisarcoid drugs (DMASDs). One option to be considered is that of potentiators of glucocorticosteroids, such as methotrexate (MTX) and azathioprine (AZA). Other DMASDs that may also play a role in controlling chronic granulomatous inflammation include leflunomide, mycophenolate mofetil, (hydroxy) chloroquine, cyclosporine, cyclophosphamide and pentoxifylline.[6-9] If traditional cytotoxic DMASDs fail, new immunomodulating biological treatment modalities, such as tumor necrosis factor-alpha (TNF-α) inhibitors, are available, providing elegant therapeutic options for refractory sarcoidosis patients.[10,11] In view of these promising results, a trend seems to be emerging amongst the healthcare providers towards a low threshold for switching from other second-line treatment options to biologicals. However, one of the drawbacks of using biologicals is their considerable costs.[12] It is important to optimize the utilization of less expensive, but effective disease-modifying therapeutics for granulomatous inflammation, in order to keep the healthcare system affordable and accessible to all.

MTX is often considered the first-choice DMASD used for patients with sarcoidosis, with 80% of physicians reporting MTX as their preferred second-line option.[13,14] MTX has proved to be a cornerstone therapeutic agent in a large group of immune-mediated diseases, such as rheumatoid arthritis (RA) and polymyositis.[15,16] The anti-inflammatory action of MTX can be attributed to the release of adenosine which elicits its effect via adenosine A_{2A} receptors.[17] This action differs from the mode of action of steroids in inflammation.[18] Unfortunately, evidence for the use of MTX in sarcoidosis is limited, and evidence-based recommendations for its use in clinical practice are lacking.

On behalf of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), we aimed to develop practical recommendations for the use of

MTX in sarcoidosis by integrating the evidence obtained through a systematic literature review and the opinions of sarcoidosis experts worldwide.

Methods

The new recommendations for the use of MTX in sarcoidosis on behalf of the WASOG were developed in four phases. First, we conducted a review of scientific evidence to create an evidence report on the use of MTX in sarcoidosis. The second phase comprised an evaluation of the experience with MTX amongst sarcoidosis experts around the world by means of an online web-based questionnaire. In the third phase, evidence obtained during phases 1 and 2 was combined to design 10 multinational recommendations. Finally, the recommendations were submitted to the world's leading sarcoidosis experts to assess whether they agreed with them and to evaluate how the recommendations would influence clinical practice.

Systematic review of the literature

The literature search was carried out by five experienced sarcoidologists (M.D., H.S., R.B., D.V. and N.S.) from three countries, one rheumatologist (T.J.), and one internal medicine resident and PhD student (J.C.). The computerized literature search for MTX relied predominantly on PubMed (articles from December 1968 to 28 March 2013). Reference lists of relevant review studies were checked to identify additional studies not found by the database search.

The terms 'sarcoidosis' and 'methotrexate' were entered as MeSH terms and free text. The search was limited to original research involving humans and published in English. Review articles were excluded from the systematic search, but were examined later to find other references. Data specifically relating to sarcoidosis were supplemented with data obtained from important studies on other inflammatory diseases, with specific emphasis on rheumatic disorders, in view of the wide availability of evidence in this field.

Establishing expert opinion of sarcoidologists worldwide

In view of the lack of sufficient high-quality studies on the use of MTX in sarcoidosis, the available evidence was supplemented with the expert opinion obtained from sarcoidologists worldwide. An online questionnaire was sent by e-mail through the WASOG newsletter to 250 experts around the world. The questionnaire addressed the following aspects: indications for use, starting dose, prescription of folic acid to reduce MTX toxicity, work-up prior to the start of MTX, contraindications, monitoring during use, administration options in case of adverse effects, hepatotoxicity, long-term safety, and use during pregnancy and breast feeding. Questions concerning the experts' clinical

experience, specialty, the continent where they worked and the type of hospital were added as well. Experience with MTX in the treatment of sarcoidosis was assessed by the frequency of prescription: respondents prescribing MTX to more than five patients a year were defined as experienced and experts treating less than five patients a year with MTX as less experienced. Differences in response between experienced and less experienced specialists were examined using the Pearson's chi-squared test. When recapitulating the expert opinion based on the answers, the opinions of experienced sarcoidologists were given greater weight than those of less experienced respondents.

Establishing World Association of Sarcoidosis and Other Granulomatous Disorders recommendations

The above-mentioned investigators (J.C., M.D., T.J., R.B., H.S., D.V. and N.S.) combined the information gathered during phases 1 and 2 to formulate the 10 WASOG recommendations. Proposals were discussed via e-mail, phone and videoconference to finalize each of the recommendations.

The level of evidence for each recommendation was determined from the methodological quality of available studies in sarcoidosis, according to the levels of evidence of the Oxford Centre for Evidence-Based Medicine.[19] The grade of recommendation for each item was defined according to the Oxford Level of Evidence.[19] The authors focussed on formulating the recommendations in such a way so as to ensure their practical value to clinicians with less MTX prescription experience in sarcoidosis.

Evaluation of experts' agreement

During the last phase of this study, the proposed set of recommendations was evaluated by 17 of the world's leading sarcoidologists, who answered three questions for every recommendation. Experts were asked to indicate whether they agreed with the recommendation; their level of agreement was measured on a 10-point visual analogue scale (1, no agreement to 10, full agreement);[20] and the potential impact amongst the participants was assessed using three statements: 'This recommendation will change my practice'; 'I'm already working in accordance with this recommendation' and 'I will not change my practice with regard to this aspect'.

The total set of recommendations was also evaluated using these three questions, plus two additional queries: 'Do you think that these recommendations should be implemented in general clinical practice?' and 'Would you encourage your fellow physicians to implement these recommendations?'.

Results

The results of every phase were combined to develop the recommendations, which will be discussed subsequently.

Findings of the literature review

The literature search identified 237 citations of potential interest. We screened each title and abstract for relevance resulting in the exclusion of 194 articles, as MTX had been used for non-sarcoidosis conditions (40 articles) or MTX had not been used as a pharmacological treatment option but in a different context (78 articles). Review articles were excluded as well (76 articles). After this exclusion process, 43 articles were retrieved and considered further for full review. Checking the references in review articles yielded no additional original studies. Included were one randomized controlled trial (RCT), 10 case series involving more than 10 patients and 32 case reports involving fewer than 10 patients, examining the effectiveness of MTX in sarcoidosis. Study characteristics and results for each included article are summarized in Appendix 1. Summarizing the available studies, it can be said that RCT evidence supporting the use of MTX in sarcoidosis was very limited, as only one RCT was available[21] and most of the published data were observational case series.[22-63] A Cochrane review for DMASDs in pulmonary sarcoidosis found no data on MTX available for meta-analysis.[7]

Findings regarding expert opinion

A total of 113 of 250 (45%) experts completed the questionnaire. Characteristics of the respondents are presented in Table 6.1. The questionnaire was completed mainly by pulmonologists, rheumatologists and neurologists, working in countries all over the world (55% Europe, 26% North America, and 12% Asia). Almost 60% of respondents could be classified as experienced with regard to MTX prescription for sarcoidosis. Eleven per cent of the respondents did not prescribe MTX at all in sarcoidosis patients, 70% of them quoting fear of toxicity as their reason for not doing so. Other reasons were ‘too little experience’ (42%) and ‘no indication for MTX as sarcoidosis cases were not severe enough’ (25%) (multiple options could be selected). The number of respondents experienced in MTX prescription for sarcoidosis was significantly higher in specialized sarcoidosis clinics and university hospitals than in general hospitals (p=0.001) (data not shown).

Table 6.1 Summary of characteristics of sarcoidosis experts who participated in this study.

Number of respondents	113/250 (45.2%)
Pulmonologist/rheumatologist/neurologist/other	87.6/5.3/4.4/2.7%
Type of hospital: general/university/sarcoidosis clinic	21.2/56.6/22.1%
Continent: Europe/North America/Asia/other	54.9/25.7/12.4/7.1%
Working experience: 0–10/10–20/>20 years	24.8/31.0/44.2%
Average number of sarcoidosis patients treated with methotrexate: none/1–5/5–25/>25 a year	10.6/31.0/37.2/21.2%

Table 6.2 summarizes the results of the online questionnaire for each recommendation. Glucocorticosteroid monotherapy was by far the most commonly prescribed first-line treatment option, although MTX monotherapy was sometimes used as first-line therapy. Experienced respondents were significantly more likely to prescribe steroid/MTX combination therapy as the first-choice treatment option than the less experienced respondents (p=0.003). Furthermore, experienced respondents were significantly more likely to use the parenteral administration mode of MTX in cases complicated by gastrointestinal side-effects (including mucositis), whereas less experienced specialists were more likely to split the oral MTX dose as an alternative option (p=0.005). Hepatic disease was significantly more often quoted as a contraindication for starting MTX by experienced participants (p=0.013). No other significant differences between experienced and less experienced respondents were found. A small subgroup of sarcoidosis experts (n=14) reported a 10% discontinuation rate of MTX, with the most important reported reasons for discontinuation including gastrointestinal (30% of cases), liver (27%) and haematological (17%) toxicity (data not shown). The results of the questionnaire were processed to formulate the recommendations.

Table 6.2 Expert opinion amongst sarcoidologists, based on questionnaire answers, for each recommendation and level of methotrexate experience.[a]

	MTX prescription to 1–5 patients a year	MTX prescription to >5 patients a year	Total	p value
Number of respondents	35 (34.7%)	66 (65.3%)	101 (100%)	-
Recommendation 1				
First-choice treatment option (often/sometimes/never in %)				
- Steroid monotherapy	97.1/2.9/0%	81.8/16.7/1.5%	87.0/12.0/1.0%	0.098
- MTX monotherapy	0/38.2/61.8%	1.5/57.6/40.9%	1.0/51.0/48.0%	0.123
- Steroid/MTX combination therapy	0/61.8/38.2%	18.2/66.7/15.2%	12.0/65.0/23.0%	0.003*
Recommendation 2				
Starting dosage of MTX				
- 0–5 mg weekly	4 (12.1%)	10 (15.4%)	14 (14.3%)	0.409
- 5–10 mg weekly	20 (60.6%)	34 (52.3%)	54 (55.1%)	
- 10–15 mg weekly	8 (24.2%)	21 (32.3%)	29 (29.6%)	
- >15 mg weekly	1 (3.0%)	0 (0%)	1 (1.0%)	

	MTX prescription to 1–5 patients a year	MTX prescription to >5 patients a year	Total	p value
Maintenance dosage of MTX				
- 0–5 mg weekly	2 (6.1%)	0 (0%)	2 (2.0%)	0.068
- 5–10 mg weekly	12 (36.4%)	14 (21.5%)	26 (26.5%)	
- 10–15 mg weekly	16 (48.5%)	42 (64.6%)	58 (59.2%)	
- >15 mg weekly	3 (9.1%)	9 (13.8%)	12 (12.2%)	
Recommendation 3				
Mean folic acid dosage				
- 1 mg daily	7 (21.9%)	22 (33.8%)	29 (29.9%)	0.052
- 5 mg once weekly	19 (59.4%)	18 (27.7%)	27 (38.1%)	
- 5 mg twice weekly	2 (6.3%)	7 (10.8%)	9 (9.3%)	
- 5 mg thrice weekly	1 (3.1%)	6 (9.2%)	7 (7.2%)	
- Depending on MTX dosage	3 (9.4%)	12 (18.5%)	15 (15.5%)	
Recommendation 4				
Work-up before start of MTX				
- AST	30 (85.7%)	62 (93.9%)	92 (91.1%)	0.167
- ALT	31 (88.6%)	63 (95.5%)	94 (93.1%)	0.195
- ALP and bilirubin	25 (71.4%)	59 (89.4%)	84 (83.2%)	0.022*
- CBC	33 (94.3%)	65 (98.5%)	98 (97.0%)	0.237
- Creatinine	27 (77.1%)	55 (83.3%)	82 (81.2%)	0.449
Recommendation 5				
Contraindications				
- Renal disease	23 (65.7%)	48 (72.7%)	71 (70.3%)	0.463
- Hepatic disease	28 (80.0%)	63 (95.5%)	91 (90.1%)	0.013*
- Pulmonary disease	13 (37.1%)	13 (19.7%)	26 (25.7%)	0.056
- Leucocytopenia	28 (80.0%)	52 (78.8%)	80 (79.2%)	0.886
- Thrombocytopenia	27 (77.1%)	45 (68.2%)	72 (71.3%)	0.344
- Anaemia	16 (45.7%)	33 (50.0%)	49 (48.5%)	0.682
- Infection acute/chronic	28 (80.0%)	53 (80.3%)	81 (80.2%)	0.971
- Alcohol/drugs use (current or past)	19 (54.3%)	34 (51.5%)	53 (52.5%)	0.791
Contraindicating creatinine clearance				
- Stage 2 (GFR 60–89)	2 (8.7%)	3 (6.3%)	5 (7.0%)	0.427
- Stage 3 (GFR 30–59)	11 (47.8%)	19 (39.6%)	30 (42.3%)	
- Stage 4–5 (GFR <29)	10 (43.5%)	26 (54.2%)	36 (50.7%)	
Contraindicating WBC level				
- <2.0 x 10^9/l	23 (92.0%)	32 (72.7%)	55 (79.7%)	0.119
- <1.5 x 10^9/l	1 (4.0%)	10 (22.7%)	11 (15.9%)	
- <1.0 x 10^9/l	1 (4.0%)	2 (4.5%)	3 (4.3%)	
Contraindicating platelet count number				
- <200 x 10^9/l	3 (12.0%)	5 (11.4%)	8 (11.6%)	0.802
- <100 x 10^9/l	14 (56.0%)	28 (63.6%)	42 (60.9%)	
- <50 x 10^9/l	8 (32.0%)	11 (25.0%)	19 (27.5%)	

	MTX prescription to 1–5 patients a year	MTX prescription to >5 patients a year	Total	p value
Contraindicating anaemia level				
- <6 mmol/l	8 (44.4%)	17 (45.9%)	25 (45.5%)	0.995
- <5 mmol/l	7 (38.9%)	14 (37.8%)	21 (38.2%)	
- <4 mmol/l	3 (16.7%)	6 (16.2%)	9 (16.4%)	
Recommendation 6				
Blood monitoring interval after start of MTX				
- Once after 2–3 weeks	12 (38.7%)	21 (32.3%)	33 (34.4%)	0.672
- Every 2–3 weeks	13 (41.9%)	24 (36.9%)	37 (38.5%)	
- Every 1–1.5 months	5 (16.1%)	15 (23.1%)	20 (20.8%)	
- Every 2–3 months	1 (3.2%)	5 (7.7%)	6 (6.3%)	
Blood monitoring interval after stable MTX dose				
- Every month	13 (41.9%)	15 (23.1%)	28 (29.2%)	0.299
- Every 2 months	6 (19.4%)	15 (23.1%)	21 (21.9%)	
- Every 3 months	11 (35.5%)	32 (49.2%)	43 (44.8%)	
- Every 6 months	1 (3.2%)	3 (4.6%)	4 (4.2%)	
Recommendation 7				
Alternative administration modes in case of MTX-induced gastrointestinal side-effects				
- Parenteral administration	0 (0%)	13 (20.0%)	13 (13.5%)	0.005*
- Splitting oral dose	14 (45.2%)	11 (16.9%)	25 (26.0%)	
- Both	8 (25.8%)	19 (29.2%)	27 (28.1%)	
- None	9 (29.0%)	22 (33.8%)	31 (32.3%)	
Recommendation 8				
First action when LT >4 x ULN				
- Check for alcohol/NSAID	18/35 (51.4%)	29/66 (43.9%)	47/101 (46.5%)	0.473
- Increase folic acid dosage	4/35 (11.4%)	6/66 (9.1%)	10/101 (9.9%)	0.708
- Decrease MTX dosage	7/35 (20.0%)	20/66 (30.3%)	27/101 (26.7%)	0.266
- Parenteral MTX	1/35 (2.9%)	1/66 (1.5%)	2/101 (2.0%)	0.645
- Discontinue MTX	25/35 (71.4%)	49/66 (74.2%)	74/101 (73.3%)	0.761
- Start UDCA/antioxidants	7/35 (20.0%)	5/66 (7.6%)	12/101 (11.9%)	0.066
Level of LT abnormalities requiring MTX discontinuation				
- >2 x ULN	9 (29.0%)	20 (30.8%)	29 (30.2%)	0.912
- >3 x ULN	15 (48.4%)	30 (46.2%)	45 (46.9%)	
- >4 x ULN	7 (22.6%)	14 (21.5%)	21 (21.9%)	
- No discontinuation	0 (0%)	1 (1.5%)	1 (1.0%)	
Recommendation 9				
Long-term MTX use				
- Unaltered continuation	19/31 (61.3%)	44/65 (67.7%)	63/96 (65.6%)	0.537
- Discontinuation	12/31 (38.7%)	21/65 (32.3%)	33/96 (34.4%)	0.800
After 1 year	4/12 (33.3%)	5/21 (23.8%)	9/33 (27.3%)	
After 2 years	6/12 (50.0%)	11/21 (52.4%)	17/33 (51.5%)	
After >2 years	2/12 (16.7%)	5/21 (23.8%)	7/33 (21.2%)	

	MTX prescription to 1–5 patients a year	MTX prescription to >5 patients a year	Total	p value
Recommendation 10				
Establishing pregnancy wish				
- In women	29/31 (93.5%)	64/65 (98.5%)	93/96 (96.9%)	0.196
- In men	18/31 (58.1%)	46/65 (70.8%)	64/96 (66.7%)	0.217
Discontinuation of MTX if pregnancy wish				
- In women	29/31 (93.5%)	64/65 (98.5%)	93/96 (96.9%)	0.196
- In men	22/31 (71.0%)	45/65 (69.2%)	67/96 (69.8%)	0.862

[a] Values are expressed as frequencies and/or percentages, and were tested with Pearson's chi-squared test. * p<0.05, significant difference between the experienced and less experienced respondents. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; GFR, glomerular filtration rate expressed as ml/min and normalized to an average surface area (size) of 1.73 m^2; LT, liver tests; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; WBC, white blood cell.

Recommendations

The 10 key WASOG recommendations are listed in Table 6.3, with the corresponding level of evidence and grade of recommendation. The mean level of agreement for the total set of recommendations amongst the 17 leading sarcoidologists was 8.7 (range 8.0–10). The percentage of sarcoidologists who indicated that they would change their clinical practice in accordance with each of the recommendations is shown in Table 6.4. Twelve per cent of the sarcoidologists reported that the total set of recommendations would change their clinical practice; the other experts reported that they were already working according to the recommendations. All sarcoidologists were in favour of implementing these recommendations in general clinical practice and would encourage fellow physicians to use these recommendations.

Recommendation 1

The indications for MTX in sarcoidosis consist of its use as a second-line treatment option in steroid-refractory cases, in the presence of steroid-associated adverse effects or as a steroid-sparing agent; or as a first-line treatment option as a MTX/steroid combination therapy or monotherapy in exceptional situations.

The evidence to support MTX as a steroid-sparing agent or alternative agent is scarce. One small (n=24) but high-quality RCT showed that sarcoidosis patients without previous treatment who took MTX 10 mg weekly required significantly lower doses of glucocorticosteroids than patients taking placebo, after 12 months of treatment (median 8.3 mg daily (0.83–21.7) and 16 mg daily, respectively, p<0.001); at 6 months, there was no significant difference between the groups.[21] A recent retrospective cohort study comparing the DMASDs MTX and AZA in sarcoidosis showed a significant steroid-sparing potency, without a difference between the two groups.[22] The steroid-sparing potency of MTX was also found in several case series.[24,26,28,46,51,52,54,56,57,63] Moreover,

MTX has been proven effective and is recommended as a steroid-sparing agent in other inflammatory diseases, such as RA, giant-cell arteritis and polymyalgia rheumatica, and can also be considered in systemic lupus erythematosus or (juvenile) dermatomyositis.[64]

Table 6.3 Multinational recommendations for the use of methotrexate in sarcoidosis.

	Recommendation	Level of evidence[19]	Grade of recommendation[19]	Agreement mean (±SD)[a]
1	The indications for MTX in sarcoidosis consist of its use as a second-line treatment option in steroid-refractory cases, in the presence of steroid-associated adverse effects or as a steroid-sparing agent; or as a first-line treatment option as a MTX/steroid combination therapy or monotherapy in exceptional situations.	2b 4	B C	8.9 (±1.1)
2	The recommended initial dosage of oral MTX is 5–15mg weekly.	4	C	9.0 (±1.6)
3	Prescription of folic acid with MTX therapy is recommended, at least 5 mg weekly or 1 mg daily.	5	B[b]	9.6 (±1.1)
4	The preadministration work-up for patients starting MTX should include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, complete blood count (CBC), creatinine, and when indicated, serology for HIV, hepatitis B/C and IGRA test for Mycobacterium tuberculosis infection.	5	D	9.1 (±1.1)
5	Before starting MTX, some contraindications should be considered: significant renal disease, significant hepatic disease other than sarcoidosis, bone marrow depression and acute or chronic infection.	5	D	9.3 (±1.2)
6	When starting MTX or increasing the dose, ALT with or without AST, creatinine and CBC should be monitored every 3–6 weeks until a stable dose is reached, and every 1–3 months thereafter; after stabilization the monitoring interval can be extended to every 6 months.	5	D	8.9 (±1.3)
7	In case of MTX-induced gastrointestinal side-effects, including mucositis, splitting the oral dose should be considered, provided the total MTX dose is ingested within a 12-h period. Parenteral administration or an alternative immunosuppressive drug should be considered in case of persistent intolerance.	5	D	8.3 (±2.0)
8	Caution is warranted if there is a confirmed increase in ALT/AST. If there are no other causes, it should lead to either MTX dose reduction or withdrawal, liver biopsy to evaluate for MTX toxicity or additional folic acid supplementation; consider an alternative immunosuppressive drug after normalization.	4	C	9.0 (±1.4)
9	Based on its acceptable safety profile, MTX is appropriate for long-term use.	5	C[b]	9.3 (±1.1)
10	MTX should not be used by men or women for at least 3 months before planned pregnancy, and should not be used during pregnancy or breast feeding (absolute contraindication).	5	D	9.5 (±0.9)

[a] The level of agreement was measured on a 10-point visual analogue scale (1, no agreement; 10, full agreement). [b] Upgraded level of recommendation based on evidence derived from rheumatoid arthritis studies. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; IGRA, interferon-gamma release assay; MTX, methotrexate.

Table 6.4 Evaluation of recommendations, with the percentage of sarcoidologists who indicated that each of the recommendations would change their clinical practice or not.

Recommendation		The recommendation will change my practice (%)	Already working according to this recommendation (%)	I will not change my practice in this respect (%)
1.	Indications for use	5.9	94.1	0
2.	Starting dosage	0	88.2	11.8
3.	Folic acid	11.8	88.2	0
4.	Preadministration work-up	5.9	88.2	5.9
5.	Contraindications	11.8	88.2	0
6.	Monitoring	0	94.1	5.9
7.	Adverse effects and administration	17.6	64.7	17.6
8.	Hepatotoxicity	0	94.1	5.9
9.	Long-term safety	0	100	0
10.	Pregnancy	0	100	0

Several case series are available for pulmonary and extrapulmonary sarcoidosis, and showed a 60–80% response to MTX in steroid-refractory cases or in the presence of steroid-associated adverse effects.[22-63] MTX appeared to take 6 months to be effective. The previously described retrospective cohort study comparing MTX and AZA found a positive effect of MTX on lung function.[22] Lower and Baughman[28] showed that 33 of 50 patients using MTX for 2 years saw their vital capacity improve by more than 15% or showed improvement in other organs. Vucinic[24] showed an improvement in forced expiratory volume in 1 second (FEV1) in 80% and in diffusing capacity for carbon monoxide (DLCO) in 65% of 91 sarcoidosis patients using MTX for 6 months. The only available RCT did not find a significant effect of MTX on lung function (vital capacity), symptoms or adverse events compared to placebo. However, the study may not have been adequately powered to demonstrate the true effect of MTX because of the small number of patients enrolled in the study.[21]

Some exceptional manifestations of sarcoidosis might respond better to nonsteroidal drugs. In these cases, MTX/steroid combination or MTX monotherapy can be considered as the first-line treatment option. However, this recommendation is mostly based on expert opinion rather than evidence. Experienced sarcoidologists in particular seemed to consider MTX as a first-choice therapy in such cases (Table 6.2). For example, first-line systemic MTX therapy, whether or not combined with glucocorticosteroids, has been reported as beneficial in uveitis after topical steroid application failed.[23,26] MTX has been proposed as a first-choice immunosuppressant in neurosarcoidosis.[65] An MTX/glucocorticosteroid combination has been reported to be beneficial as a first-line treatment option in neurosarcoidosis,[27,36,40,46,61] as many neurosarcoidosis manifestations are usually chronic and MTX appears to show increased efficacy at lower levels of morbidity.[27] Another indication is cardiac involvement, in which a first-line MTX/glucocorticosteroid combination therapy should be considered to avoid aneurysm formation because of high doses of

glucocorticosteroids.[66] Starting MTX with low-dosed glucocorticosteroids might also be beneficial for patients suffering from diabetes or overweight whose steroid dose should be kept as low as possible, as the required cumulative glucocorticosteroids dose with MTX is several milligrams lower than without MTX.[21]

Recommendation 2

The recommended initial dosage of oral MTX is 5–15 mg weekly.

The single available RCT demonstrated that an initial oral MTX dosage of 10 mg weekly had steroid-sparing efficacy,[21] whereas case series showing effectiveness of MTX used dosages of 5–20 mg weekly.[22-63] The safety profile of MTX in these cases was acceptable (see Appendix 1). Most research experience has been in the initial dosage range of 10–15 mg weekly. Eighty-five per cent of sarcoidologists reported using starting dosages of 5–15 mg weekly (Table 6.2). A lower initial MTX dosage is advisable in case of suspected bone marrow involvement in the sarcoidosis process, as evidenced by cytopenia.[67,68]

Studies comparing different MTX dosages in sarcoidosis are not available, and there is a need for future studies to compare higher and lower dosages of MTX to provide the best treatment effect with acceptable safety profile. Studies comparing different dose-escalation methods are not available for sarcoidosis either, but in RA the results of three RCTs directly comparing different dosages of oral MTX showed dose-dependent efficacy and toxicity.[64,69-71] The higher starting doses (12.5–25 mg weekly) were clearly more effective in RA patients than the lower doses (5–15 mg weekly), but were accompanied by more adverse effects.[69,70] Rapid dose escalation by 5 mg monthly was associated not only with higher effectiveness, but also with more adverse events, in comparison with escalation of 5 mg every 3 months.[71] Table 6.2 shows that 86% of the sarcoidologists recommended a maintenance dosage of MTX for sarcoidosis of 5–15 mg weekly, but 12% reported that higher dosages of up to 20 mg weekly may be warranted in individual cases. As the treatment effect and safety profile for higher dosages of MTX in sarcoidosis have not been determined, increasing the dose of MTX for sarcoidosis beyond 20 mg weekly is probably not advisable without appropriate safety studies. Evidence regarding the best escalation method in sarcoidosis is not available, but in the case of insufficient response and an acceptable safety profile we recommend considering escalation after 8 weeks to 10-15 mg weekly with a maximum of 20 mg weekly in individual cases.

Recommendation 3

Prescription of folic acid with MTX therapy is recommended, at least 5 mg weekly or 1 mg daily.

No studies on the prescription of folic acid with MTX therapy for sarcoidosis are available. A meta-analysis of nine studies in RA, including 788 patients, suggested that folic acid supplementation reduces the gastrointestinal and liver toxicity of MTX,

without reducing its efficacy.[64,72] High dosages of folic acid (>5 mg weekly) led to a significant reduction in gastrointestinal side-effects (odds ratio (OR) 0.42; 95% confidence interval (CI) 0.21–0.85),[73-76] whereas dosages of less than 5 mg weekly showed only a trend towards reducing gastrointestinal side-effects.[74] After further stratification, however, the protective effect of folic acid on gastrointestinal toxicity proved only significant in the studies that used MTX at weekly doses of less than 10 mg.[74,75] The studies analysing hepatotoxicity showed a significant protective effect of 1 mg folic acid daily or 7 mg weekly (OR 0.17; 95% CI 0.09–0.32).[73,75,76] The effect of folic acid supplementation on haematological adverse effects could not be accurately assessed because of a low incidence of events in the samples studied.[77] Almost 70% of the sarcoidologists recommended prescribing folic acid at 1 mg daily or 5 mg weekly, whereas 17% reported prescribing higher dosages.

At least 5 mg folic acid weekly is recommended for RA, taking into account the potential need for higher dosages if MTX is given in higher doses.[64] Similar prophylaxis is recommended in sarcoidosis, as data on the prescription of folic acid or data supporting the need for higher dosages to provide adequate prophylaxis in sarcoidosis are not yet available.

Recommendation 4

The preadministration work-up for patients starting MTX should include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, complete blood count (CBC), creatinine, and when indicated, serology for HIV, hepatitis B/C and interferon-gamma release assay (IGRA) test for Mycobacterium tuberculosis infection.

The work-up information needed to decide whether to start a patient with sarcoidosis on MTX can be extrapolated from data on MTX-induced toxicity. Studies investigating the risk factors for severe toxicity in sarcoidosis are lacking, but data on RA suggested that an estimated creatinine clearance less than 79 ml/min increases the risk of severe pulmonary toxicity.[64,78] Furthermore, lung abnormalities on radiograph, but not pulmonary function tests, proved predictive of MTX-induced pneumonitis.[64,79-81] Exacerbation of hepatic disease was an additional risk in obesity, diabetes and viral/alcoholic hepatitis.[64,82-85]

Recommendations in Europe and the USA about the preadministration work-up for arthritis patients all suggest CBC, creatinine, AST, ALT with or without bilirubin and ALP.[86,87] Hepatitis B/C serology, serology for HIV and chest radiographs have also been suggested as part of the pretreatment work-up.[64,87,88] Table 6.2 shows that 83–99% of the sarcoidosis experts reported AST, ALT, ALP, bilirubin, CBC and creatinine to be part of their preadministration work-up. A chest radiograph is usually available in sarcoidosis patients, as the lungs are commonly involved in the sarcoidosis process.[1,2] An additional chest radiograph as part of the preadministration work-up does not offer added value, and we therefore do not recommend routine chest radiographs. Only in cases with suspected pulmonary infection, established during clinical evaluation before the start of

MTX, an additional chest radiograph is recommended to determine a change in the features (based on expert opinion).

Sarcoidosis and tuberculosis (TB) have comparable clinical and histopathological features, both being granulomatous diseases frequently affecting the lungs. A well known feature is the increased risk of reactivating a latent TB infection or worsening of an active TB infection caused by immunosuppressive TNF-α inhibitors.[89] Therefore, screening for TB is recommended before starting TNF-α inhibitors. However, no evidence is available on the screening methods for TB in patients on MTX. One retrospective study concluded that MTX treatment was probably not associated with an increased incidence of TB in rheumatic diseases.[90] Recommendations in RA stated that screening should therefore be similar to that in the general population.[91] However, some case reports showed the occurrence of active TB in patients on long-term MTX treatment.[92] Furthermore, the American College of Rheumatology (ACR) recommended that MTX should not be initiated in the presence of active TB or latent TB infection prior to starting preventive therapy.[87] Combining the available evidence, we recommend excluding mycobacterial infection in selected sarcoidosis cases using an IGRA test such as QuantiFERON-TB Gold In-Tube (QFT-GIT) assay or T-SPOT.TB assay, which seem to be accurate methods given the presence of anergy to tuberculin in sarcoidosis, prior to initiating further immunosuppressive treatment with MTX.[93,94]

The evidence available for RA was combined with the expert opinion among sarcoidologists and processed into recommendation 4. Contraindications that should be considered before the start of MTX in sarcoidosis are discussed in more detail at recommendation 5.

Recommendation 5

Before starting MTX, some contraindications should be considered: significant renal disease, significant hepatic disease other than sarcoidosis, bone marrow depression and acute or chronic infection.

There is no evidence regarding any contraindications that should be considered before the start of MTX in sarcoidosis. Contraindications that should be considered according to rheumatology experts include significant renal disease with glomerular filtration rate (GFR) less than 30 ml/min, hepatic disorders, leucocytopenia less than 3.0 x 10^9/l, thrombocytopenia less than 50 x 10^9/l, inadequate contraception, pregnancy, history of drug or alcohol abuse, acute or chronic infection and pulmonary disease.[87] Renal and hepatic diseases, leucocytopenia, thrombocytopenia and infections were considered contraindications by 70–96% of the sarcoidologists in our survey, whereas pulmonary disease, anaemia and a history of alcohol/drugs use were less often mentioned (20–52%) (Table 6.2). In addition, GFR less than 30 ml/min was considered a contraindication by 54%, white blood cell (WBC) count of less than 2.0 x 10^9/l by 73%, platelet count of less than 100 x 10^9/l by 64% and haemoglobin (Hb) level of less than 5–6 mmol/l by 84% (Table 6.2). In general, sarcoidologists seem to take a more cautious approach than the rheumatology guidelines.

MTX is considered contraindicated by significant renal disease, as MTX is mainly cleared by the kidney.[95] Kidney involvement from sarcoidosis is rare, having been reported in 7–22% of sarcoidosis patients at autopsy, but sometimes leads to kidney failure.[96] Furthermore, renal failure can also be the consequence of hypercalcaemia and hypercalciuria, which are both frequent manifestations of sarcoidosis.[96] In these cases, AZA is recommended as the first-choice glucocorticosteroid-sparing immunomodulator (based on expert opinion).

Involvement of the liver often occurs in sarcoidosis, with liver biopsy demonstrating granulomatous disease in half of the patients.[97-101] Liver test abnormalities are seen in one-fourth to one half of sarcoidosis patients before the start of MTX; these can be the result of sarcoidosis or other liver diseases.[47,97] Treatment with MTX is not contraindicated when liver test abnormalities are the consequence of sarcoidosis involvement.[98] Treatment of inflammatory sarcoidosis activity can actually lead to improvement of liver tests.[98] A study of baseline liver test abnormalities in rheumatology patients found that values were only mildly elevated and were rarely a contraindication for starting MTX.[86] Liver test abnormalities at baseline are more common in sarcoidosis, because of liver disease from the sarcoidosis itself.[47,97] In patients with severe liver test abnormalities prior to starting MTX, one should consider a liver biopsy or radiological examination to distinguish between sarcoidosis and other liver diseases.[97] Acute and chronic hepatitis B and C infections are considered to represent contraindications.[87]

Rheumatology guidelines consider pulmonary diseases, especially interstitial lung diseases of unknown cause, to represent contraindications,[87] as pre-existing lung disease may be a risk factor for the development of MTX-induced pneumonitis.[79] In sarcoidosis, however, the main reasons for MTX prescription are pulmonary disease and respiratory functional impairment, which can be successfully treated with MTX. The presence of pulmonary disease in sarcoidosis as such is therefore not considered a contraindication to treatment with MTX, which is also reflected in the very low percentage of sarcoidologists (20%) considering pulmonary disease a contraindication (Table 6.2). Figure 6.1 shows an example of substantial improvement of parenchymal pulmonary lesions from sarcoidosis after treatment with MTX.[102] In cases of suspected or confirmed other pulmonary disease, such as acute or chronic infections, however, MTX should be considered contraindicated (based on expert opinion).

Recommendation 6

When starting MTX or increasing the dose, ALT with or without AST, creatinine and CBC should be monitored every 3–6 weeks until a stable dose is reached, and every 1–3 months thereafter; after stabilization the monitoring interval can be extended to every 6 months.

No studies evaluating the frequency of monitoring have been done for sarcoidosis, and the recommended frequency of monitoring in RA is largely based on expert opinion.[87] The limited available evidence suggests an optimal interval to detect liver

test abnormalities of 30–60 days and a decreasing incidence of MTX-induced liver damage in the first months of therapy.[64] A total of 60% of the sarcoidosis experts suggested a monitoring interval of 2–6 weeks, whereas 95% suggested an interval of 1–3 months after a stable dosage has been reached (Table 6.2).

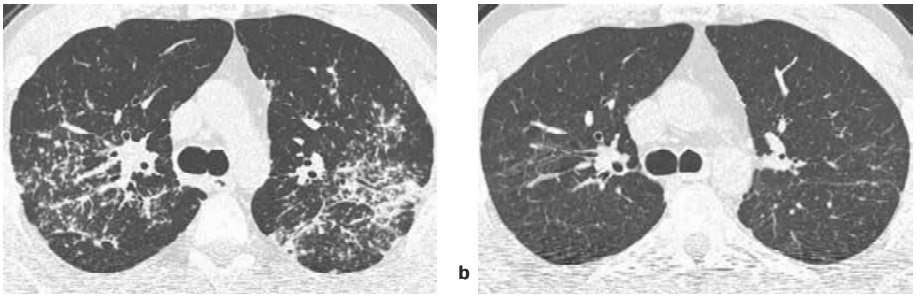

Figure 6.1 High-resolution computed tomography (HRCT) studies from a 36-year-old man with a history of 5 years of biopsy-proven sarcoidosis. Because of respiratory functional impairment, he had been previously treated with prednisone, starting at 40 mg daily. This was tapered off because of side-effects to 20 mg daily. No improvement was achieved, so treatment with methotrexate (MTX) was started. **a.** HRCT before treatment with MTX, showing multiple intraparenchymal nodules, focal pleural thickening, septal and nonseptal lines, and thickening or irregularity of the bronchovascular bundle.[102] **b.** HRCT after 6 months of treatment with 12.5 mg MTX weekly and 5 mg folic acid once a week orally, together with 10 mg prednisone daily, showing substantial improvement.

AST and ALT have been reported to correlate with the histological grades of liver disease in RA.[64,103-107] Creatinine should also be monitored, as renal dysfunction is associated with increased risk of pulmonary toxicity. A CBC is required to monitor bone marrow toxicity.[64,78] A baseline WBC count at the time of starting or increasing the dosage of MTX may be helpful to determine the follow-up interval for CBC: if baseline WBC count is low, a follow-up CBC should be performed at shorter intervals than with higher WBC count at baseline.

The 2008 ACR guidelines suggest monitoring every 1–3 months, with more frequent assessments initially.[87] As evidence regarding monitoring frequency in sarcoidosis is lacking, we have combined the recommendations extrapolated from RA with expert opinion to recommend a monitoring frequency of 3–6 weeks until a stable dose is reached and every 1–3 months thereafter. After stabilization, the monitoring interval can be extended to 6 months. Despite the observations that MTX hepatotoxicity is rarer in RA than in sarcoidosis, which can probably be explained by the underlying liver disease from the sarcoidosis itself,[28,83,84,101,107,108] we recommend a similar frequency pattern of liver testing in sarcoidosis. Severe liver disease as a result of MTX in sarcoidosis is rare.[101]

Recommendation 7

In case of MTX-induced gastrointestinal side-effects, including mucositis, splitting the oral dose should be considered, provided the total MTX dose is ingested within a 12-h period. Parenteral administration or an alternative immunosuppressive drug should be considered in case of persistent intolerance.

No studies are available comparing different administration modes in sarcoidosis. Recommendations for RA patients indicate a preference for the oral route when starting MTX treatment.[64,109] The bioavailability of MTX at higher oral doses (25–35 mg weekly) is decreased in RA patients, most probably because of limited absorption from the gastrointestinal tract, and can be improved by splitting the oral dose.[110,111] No studies are available investigating the effectiveness of splitting the oral dose in terms of reducing the gastrointestinal side-effects. Almost half of the sarcoidosis experts in our survey, however, reported using splitting of the oral dose with ingestion of the total dose within a 12-h period as an alternative administration option in case of MTX-induced gastrointestinal side-effects (Table 6.2); they reported regularly observing the disappearance of inconvenient symptoms.

Retrospective studies in RA suggest higher efficacy and less gastrointestinal toxicity with parenteral versus oral administration of MTX, which can be explained by a higher bioavailability of the parenteral form.[112-114] The efficacy and safety of routes of administration were evaluated in open-label studies, which found a significant reduction in disease activity scores following the switch from oral to parenteral administration.[109,115,116] This leads to a recommendation for RA patients to switch to subcutaneous or intramuscular administration in case of gastrointestinal side-effects, poor compliance or inadequate effectiveness.[109] The variable bioavailability of high oral MTX dosages forms another argument to consider changing to parenteral administration.[114] Almost half of the sarcoidologists in our survey reported prescribing parenteral MTX as an alternative administration route in case of MTX-induced gastrointestinal side-effects (Table 6.2).

As evidence regarding the best administration routes of MTX in sarcoidosis is lacking, evidence extrapolated from RA, combined with expert opinion, resulted in the recommendation to split the oral dose, changing to parenteral administration routes or considering an alternative immunosuppressive drug in case of gastrointestinal intolerance.

Recommendation 8

Caution is warranted if there is a confirmed increase in ALT/AST. If there are no other causes, it should lead to either MTX dose reduction or withdrawal, liver biopsy to evaluate for MTX toxicity or additional folic acid supplementation; consider an alternative immunosuppressive drug after normalization.

Sarcoidosis commonly affects the liver[97,99-101] and liver test abnormalities during MTX use may thus be due to the underlying sarcoidosis, but also due to MTX use or

some other cause.[101] Studies among RA patients have found a relatively low rate of MTX hepatotoxicity, with a reported 3–5% incidence of advanced pathological changes on liver biopsy.[83,84,107,108] Studies found that only patients with persistently elevated transaminase levels or decreased albumin levels had a toxic reaction to MTX.[103-107] Therefore, RA guidelines rely on the use of serial liver function testing to identify patients with a toxic reaction to MTX.[64] Studies amongst sarcoidosis patients found a 9% incidence rate of MTX-associated toxic effects established by liver biopsy after 1 year of MTX therapy and a 14% incidence rate after 2 years of therapy.[28,101] However, no sarcoidosis patients were reported to have severe liver disease as a result of MTX therapy.[101] The higher incidence of hepatotoxicity in sarcoidosis compared to RA may be because of the underlying liver disease from the sarcoidosis itself.[28,101] As half of the patients showed changes in their liver biopsy results that were attributed to sarcoidosis, the associated inflammatory and fibrotic changes may overlap with the changes seen in toxic reactions to MTX and could therefore have led to overestimation of MTX toxicity.[101] In sarcoidosis, the ALP level at the time of biopsy[28,101] and the number of times the AST was elevated in the year before the biopsy[101] correlated with the severity of the toxic effect of MTX. However, patients with hepatic sarcoidosis showed higher levels of various liver tests as well.[28,101] Therefore, the absolute liver test results or the number of abnormal tests are not clinically useful for predicting either liver sarcoid involvement or MTX hepatotoxicity.[28,101] Nevertheless, as serial liver testing is a noninvasive safe way to trace liver disease including MTX toxicity, it is recommended for sarcoidosis patients on MTX therapy. Baughman et al.[101] also claimed an important role for liver biopsy in screening for toxic reactions.

Studies investigating how to deal with the liver test abnormalities in sarcoidosis patients using MTX, or the level of liver test abnormalities at which MTX should be discontinued, have been scarce. Forty-six per cent of the sarcoidologists in our survey reported discontinuing MTX when liver test results exceeded the level of 3 times the upper limit of normal (ULN), whereas the remaining experts reported that they discontinued MTX at liver test results more than 2 times the ULN or more than 4 times the ULN (Table 6.2). Studies in RA recommended MTX withdrawal if there is a confirmed increase in ALT/AST of more than 3 times the ULN.[64] The majority of sarcoidologists reported discontinuing or decreasing the dosage of MTX when liver test results exceed the level of 4 times the ULN, after checking for other causes of liver test abnormalities, such as alcohol or nonsteroidal anti-inflammatory drugs use (Table 6.2). Checking for other causes is important, as, for example, RA patients on MTX treatment who are heavy drinkers are more likely to show advanced changes on liver biopsy.[108] Rheumatology experts emphasize that other causal factors, including nonsteroidal anti-inflammatory drugs, obesity with nonalcoholic steatohepatitis and alcohol, should be considered in case of persistently elevated liver tests after discontinuation of MTX.[64] Only 10% of the sarcoidosis experts reported that they first increased the dosage of folic acid to decrease the hepatotoxic effects of MTX (Table 6.2). However, no literature is available on the value of raising the folic acid dosage when liver test abnormalities

increase during MTX use. Expert opinion, however, suggests some beneficial effects. Furthermore, the sarcoidologists did not agree with the recommendation by rheumatology experts to reinstitute MTX at a lower dose following normalization of liver tests,[64] but suggested considering an alternative immunosuppressive drug after normalization.

As there is no definite evidence regarding how to deal with an increase in liver test abnormalities during MTX treatment of sarcoidosis patients, we combined recommendations extrapolated from RA with sarcoidosis expert opinion to formulate recommendation 8.

Recommendation 9

Based on its acceptable safety profile, MTX is appropriate for long-term use.

There have been no studies with long-term follow-up data to conclusively determine the long-term safety profile of MTX for sarcoidosis patients. Adverse effects because of MTX are listed in Appendix 1. As described above, gastrointestinal and liver toxicity were most frequently reported by the sarcoidologists as the reason to discontinue MTX, which was necessary in 10% of cases. However, Baughman et al. and Vucinic reported lower discontinuation rates of 0–4%.[23,24] Sixty-eight per cent of the experienced sarcoidologists reported continuing MTX unaltered in the long term (Table 6.2). Compared with AZA, MTX has comparable side-effects in sarcoidosis patients, except for a higher infection rate during AZA use.[22] Leflunomide has been proposed to have a more favourable safety profile compared with MTX,[117,118] but studies directly comparing MTX and leflunomide are lacking.

A large 6-year study found that RA patients on MTX had a lower mortality rate and reduced cardiovascular mortality.[64,119] Furthermore, discontinuation of MTX because of toxicity in RA patients is unusual[120] and MTX is less frequently discontinued than other disease-modifying antirheumatic drugs.[64,121] Long-term MTX use by RA patients was not associated with an increased risk of serious infections.[64,122] Whether MTX in RA patients is associated with a low risk of developing lymphoma has not been fully elucidated.[64,123,124]

Despite the limited available evidence, the overall safety profile of MTX in the short term seems to be acceptable. As studies to determine the long-term safety profile of MTX in sarcoidosis patients are lacking, we surmise that the safety profile will be reasonably similar to that found for RA patients.

Recommendation 10

MTX should not be used by men or women for at least 3 months before planned pregnancy, and should not be used during pregnancy or breast feeding (absolute contraindication).

No studies are available assessing the outcome of continued MTX therapy before or during pregnancy in sarcoidosis patients. A total of 99% of the experts in our survey

asked female patients whether they had a pregnancy wish, and 71% did so with male patients. A total of 99% discontinued MTX if female patients wanted to become pregnant and 70% did the same for male patients (Table 6.2).

Six studies amongst RA patients assessed the outcome of continued MTX therapy before or during pregnancy (n=101): they reported 24% miscarriages and 6% congenital malformations,[64,125-130] whereas lower percentages of miscarriages and congenital malformations were found in healthy women not using MTX.[131] No studies amongst RA patients have evaluated the effect of MTX use by men on pregnancy or fertility. Nevertheless, the recommendation for both male and female RA patients is to discontinue MTX at least 3 months before planned pregnancy.[64] For sarcoidosis patients, similar incompatibility of MTX with planned or actual pregnancy and breast feeding is indisputable, so MTX should be discontinued by both men and women at least 3 months before planned pregnancy, and should not be used during pregnancy or breast feeding.

Conclusion

Ten multinational WASOG recommendations for the practical use of MTX in sarcoidosis were developed by integrating evidence from both a systematic literature search and the expert opinions of sarcoidologists worldwide, and were shown by an evaluation study to be supported by all leading sarcoidosis experts.

This is the first study addressing evidence-based recommendations for the optimized use of MTX in sarcoidosis. A unique feature was the involvement of 113 sarcoidosis experts from all over the world in the development of the recommendations, which allowed approaches to frequently encountered issues on the use of MTX in sarcoidosis in daily practice to be collected. The broad range of participants, involving all the leading international sarcoidosis experts, should enhance the implementation of these recommendations in sarcoidosis practice worldwide.

Our systematic literature search showed that RCT evidence supporting the use of MTX in sarcoidosis was very limited. Most of the published data were derived from observational case series, some of them including a large number of patients but most including only a small sample. A Cochrane review on DMASDs in pulmonary sarcoidosis found no data on MTX available for meta-analysis.[7] Furthermore, no long-term follow-up data were available, which is actually crucial in determining the long-term benefits, given the recurring nature of sarcoidosis. For most aspects, little or no evidence was found specifically relating to sarcoidosis, which limits the strength of the proposed recommendations. On the other hand, evidence on these aspects in RA was available from several RCTs and high-quality cohort studies. We extrapolated evidence from these studies to help develop the recommendations for MTX in sarcoidosis, especially where data for sarcoidosis were lacking. As the clinical problems encountered in sarcoidosis show many similarities with those in RA, lessons learned from the use of MTX in RA are extremely valuable. Nevertheless, certain scenarios and clinical

challenges are unique to sarcoidosis, and should be considered separate from the evidence gained amongst RA patients. It is especially in these cases, therefore, that the expert opinion of sarcoidologists from all over the world was important. Moreover, the world's leading sarcoidosis experts reported a high level of agreement with the proposed recommendations, which strengthens their value.

Optimization of treatment with MTX and other glucocorticosteroid-sparing immunomodulators in sarcoidosis is important to avoid overprescription of more expensive treatment modalities, such as TNF-α inhibitors. Optimized utilization of less expensive, but effective treatment modalities is important to keep the healthcare system affordable. MTX has proved to be the cornerstone of therapy in many immune-mediated diseases,[15,16] and a survey found that 80% of physicians reported MTX to be their preferred second-line treatment option for sarcoidosis.[13,14] Therefore, the proposed evidence-based recommendations may serve to help optimize the prescription of MTX in clinical practice. We think these recommendations will be useful for both experienced and less experienced MTX prescribers.

As studies investigating the use of MTX in sarcoidosis have been scarce, there is a need for RCTs looking into the effect of MTX on various well defined outcome measures in sarcoidosis with a reasonable duration of follow-up. In addition, side-effects and safety must be well documented. When patients fail to respond to MTX or develop severe toxicity symptoms necessitating MTX withdrawal, alternative treatment options such as AZA[22], leflunomide[118] or biologicals[10] should be considered. However, specific guidelines for these treatment modalities are currently lacking. Future research should focus on establishing useful recommendations in clinical practice for these therapeutics as well.

In conclusion, we developed multinational WASOG recommendations for the use of MTX amongst sarcoidosis patients in routine clinical practice, by combining a systematic literature search with expert opinion, with the aim of promoting both evidence-based and patient-based medicine.

Mobile application

A mobile application (app) was developed for smartphone or tablet with the recommendations and useful clinical sarcoidosis cases. The app 'MTX in sarcoidosis' can be downloaded for free from the Apple Store or Google Play Store (Appendix 2).

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