



Appendix 1

**Overview of studies on the use of
methotrexate in sarcoidosis**

Randomized controlled trials

Authors	Study goal	Patients treated (n)	Patients responding (n)	Drop-outs (n)	Organ involvement	Combi/monotherapy	MTX dosage	Folic acid dosage	Adverse effects of MTX (n)
Baughman et al. (2000) ¹	Determining whether MTX can be GC-sparing in acute sarcoidosis in first year of GC therapy	16 MTX/8 placebo	Significantly lower GC dosage in second 6 months in MTX group compared to placebo (8 MTX/2 placebo); no difference in lung function, chest radiograph stage, symptoms or side-effects	Drop-outs: 7 MTX/2 placebo (p>0.20). Reasons: non-compliance, pregnancy wish, pulmonary embolism	Lung (n=8 in MTX and n=6 in placebo group), skin (n=2 and 1), eye (n=2 and 2), liver (n=1 and 1), testicular (n=0 and 1)	Combination with prednisone 40 mg daily starting dose	10 mg weekly orally	Start in case of oral symptoms or nausea	Nausea (n=1), respiratory infections (n=?), not related to MTX

Case series

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Vorselaars et al. (2013) ²	145 MTX/ 55 AZA	Not described	95 MTX/41 AZA lung, 15/5 neurological, 6/3 cardiac, 7/3 joints, 4/1 fatigue, 2/0 uveitis, 21/2 other	Combination with prednisone	10 mg weekly orally increasing to 15 mg weekly	Significant GC-sparing potency without difference between MTX and AZA, similar positive effect in lung function, comparable side-effects except for a higher infection rate in AZA (p=0.01)	5 mg weekly	MTX: gastro-intestinal 20%, hepatic functional decline 8%, infections 18%, headache 4%, malaise 8%, withdrawal due to side-effects 16%
Baughman et al. (2012) ³	365	329	Eye (all patients), lung, skin, liver, neurologic, cardiac	Monotherapy MTX (n=115); combination with prednisone 40mg daily (n=101), AZA 20mg daily, leflunomide 50-150mg daily	10 mg weekly orally	Disease resolution or stabilisation	Use not described	n=14 stopped due to toxicity, hepatotoxicity in liver biopsy (6 of 12 patients)

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Vucinic (2002) ⁴	91	73 (approximately)	Lung, eye, skin, heart, liver, spleen, bone marrow, bones, lymph nodes, neurologic, parotid and thyroid gland	Combination with GC (n=49), monotherapy MTX (n=42), previously treated with GC	10 mg weekly orally	Improvement of chest radiograph, improvement of lung function, improvement of clinical signs and symptoms of extrapulmonary disease, reduction in/termination of prednisone dosage (n=49) after 6 months of treatment.	Not standard	No patients experienced side-effects causing discontinuation of MTX
Zeitlin et al. (2000) ⁵	13	9	Sinonasal, lungs, skin, eye etc.	Combination with GC and/or AZA and/or (hydroxy)chloroquine after monotherapy with GC	Not described	Improvement of sinonasal complaints	Not described	Not described
Dev et al. (1999) ⁶	11	10	Eye (panuveitits)	Combination with GC (n=7)	12.5 mg weekly orally	Preserved or improved visual acuity, decrease in daily GC requirements	1 mg daily	Oral ulcers (n=1), alopecia (n=1), nausea (n=1)
Lower et al. (1997) ⁷	28	17	Neurosarcoidosis including cranial nerve involvement, seizures, peripheral neuropathy, lungs, skin, eye, liver	Combination with prednisone	Not described	MRI or CSF improvement, subjective improvement	Not described	Neutropenia (n=1), hepatotoxicity (n=1), severe nausea leading to discontinuation (n=1)
Lower and Baughman (1995) ⁸	50	39	Lung, skin, central nervous system	Combination with GC (n=30), monotherapy MTX (n=20)	10 mg weekly orally	>15% improvement in VC or improvement of other organs (33 of 50 patients), reduction in prednisone dosage (25 of 30 patients treated with GC) after 6 months of treatment	Not standard, only when gastrointestinal side-effects	Mouth sores, nausea, neutropenia (n=1), MTX-induced cough (n=1), hepatotoxicity (n=6)
Baughman and Lower (1990) ⁹	12	Not described	Lung (n=12), skin (n=7), liver (n=4), central nervous system (n=3)	Monotherapy MTX (n=10), previously treated with prednisone (n=2)	10 mg weekly orally	Significant improvement in VC (p<0.01), significant drop in percentage of lymphocytes in BAL (p<0.001)	Not described	None

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Lower and Baughman (1990) ¹⁰	14	13	Lung (n=14), eye, (n=6), liver (n=6), skin (n=5)	Combination with GC (n=11), monotherapy MTX after GC monotherapy (n=3)	10 mg weekly orally	Improvement of symptoms (n=13), 15% improvement in VC (n=5), of chest radiograph (n=6), >50% reduction of skin lesions (n=4), improvement of LT abnormalities (n=2), decrease in daily GC requirements (n=9)	Not described	One episode of infection
Veien and Brodthagen (1977) ¹¹	16	12	Skin (=16), lungs or hilar adenopathy (n=13), eye (n=4), liver (n=4), bone (n=1)	Monotherapy	25 mg weekly orally	Clearance of skin lesions (n=12), weekly orally clearance of uveitis (n=3)	Not described	Nausea (n=10) with discontinuation in 2, transient LT abnormalities (n=2)

Case reports

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/ monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Sakellariou et al. (2013) ¹²	1	1	Lung, central skeleton	Combination with prednisone 20 mg daily	10 mg weekly orally	Pain relief in skeleton, normalisation of inflammatory markers	7.5 mg weekly	None
Alemдароҗу et al. (2013) ¹³	1	1	Lung, lymphadenopathy, bone phalanges and adjacent soft tissue	Combination with GC	10 mg weekly orally	Regression of lymph nodes, hand findings unchanged	Not described	None
Bouaziz et al. (2012) ¹⁴	2	1	Oral	Combination with GC	20 mg and 15 mg weekly orally	Complete remission	Not described	None
Delmonte et al. (2012) ¹⁵	1 (comorbidity sickle cell disease)	1	Lung, mediastinum, lymph nodes	Combination with prednisone 25 mg daily, erythrocytapheresis	7.5 mg weekly orally	Reduction in lung infiltrates and mediastinal lymph nodes	5 mg weekly	None
Sakushima et al. (2012) ¹⁶	3	3	Spinal cord (n=2), cerebrum (n=1)	Combination with GC	Not described	Decrease in inflammatory markers of CSF and serum	Not described	None

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Comb/monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Bargagli et al. (2011) ¹⁷	2	0	Skin, bone, hypercalciuria	Combination with GC	10 mg weekly orally	No effects	Not described	None
Gautam et al. (2011) ¹⁸	1	1	Skin	Combination with prednisone 40 mg daily	7.5 mg weekly orally	Complete remission	Not described	None
Lambert et al. (2011) ¹⁹	1	1	Lung, tenosynovitis	Monotherapy	15 mg weekly orally	Complete regression of nodules and tenosynovitis	Not described	None
Kimball et al. (2010) ²⁰	1	1	Neurosarcoidosis, intrasellar lesion	Combination with GC, minimal debulking	Not described	Symptom-free	Not described	None
Kalejian et al. (2009) ²¹	1	1	Skin, bone marrow with anaemia and leucocytopenia	Combination with mycophenolate mofetil 2500 mg oral daily	17.5 mg weekly orally	Improvement of skin lesions, improvement of haematological parameters, decrease in ACE	1 mg daily	Minor
Mannam et al. (2009) ²²	1	1	Lymphadenopathy, chylous ascites	Not described	Not described	Complete remission	Not described	None
Varron et al. (2009) ²³	2	1	Spinal cord, skin, lymphadenopathy	Combination with GC (1 mg/kg daily and 0.5 mg/kg daily, respectively)	20 mg and 10 mg, resp. weekly orally	Improvement/stabilisation of estimated modified Rankin scale for functional independence	Not described	None
Suárez Zambrano and Hutton (2008) ²⁴	1	1	Neurosarcoidosis: intracerebral lesion	Combination with prednisone 1 mg/kg/daily	Not described	Improving symptoms (motor seizures and headache)	Not described	None
Morgan et al. (2008) ²⁵	1	1	Osseous vertebral sarcoidosis, skin, lung, liver, spleen, hypercalcaemia, lymphadenopathy	Combination with prednisolone 40 mg daily	10 mg weekly orally	Skin abnormalities disappeared, disappearance of back pain.	Not described	Discontinuation of MTX because of intolerance, not described which side-effects
Bradley et al. (2006) ²⁶	10	5	Spinal cord	Combination with prednisone	Not described	Decrease in daily GC requirements	Not described	Unknown
Kennedy et al. (2006) ²⁷	7	3	Liver, lung	Combination with prednisone	Not described	Normalisation of LT abnormalities, effect on lungs not described	Not described	None
Chong et al. (2005) ²⁸	1	1	Skin	Monotherapy	Not described	Partial resolution of lesions	Not described	Not described

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Gardner (2005) ²⁹	1	1	Osseous sarcoidosis	Combination with low dose prednisone	15 mg weekly orally	Resolution of osseous lesions	Not described	Not described
Braun et al. (2004) ³⁰	2	0	Sinonasal, lung	Combination with prednisolone 0.5-1 mg/kg daily	Not described	No effect. In one case MTX discontinuation because of liver toxicity	Not described	Liver toxicity (n=1)
Maust et al. (2003) ³¹	3	3	Sarcoid-associated optic neuropathy (n=3), lung (n=2)	Combination with GC	10 mg weekly orally	Preserved or improved visual acuity, decrease in daily GC requirements	Not described	Leucocytopenia (n=1) with normalization after MTX dose reduction
Moin et al. (2001) ³²	1	1	Eyelid, skin	Combination with prednisone	Not described	Resolution of inflammatory process of eyelid, decrease in daily GC requirements	Not described	None
Scola et al. (2001) ³³	1	1	Neurosarcoidosis, muscle, lung	Combination with prednisone	Not described	Complete remission of symptoms	Not described	None
Diri et al. (1999) ³⁴	1	1	Myelopathy	Combination with GC	Not described	Improvement of clinical symptoms, decrease in daily GC requirements	Not described	Not described
Mañá et al. (1999) ³⁵	1	1	Lymphadenopathy hilar and supraclavicular, vertebrae, rib	Combination with prednisone 25 mg daily	15 mg weekly orally	Improvement of clinical symptoms (pain)	Not described	None
Gedalia et al. (1997) ³⁶	7	7	Eye (n=6), lungs (n=4), joints (n=4), bone (n=3), skin (n=3), lymphadenopathy (n=3), kidney (n=1)	Combination with prednisone	10-15 mg/m ² weekly orally	Improvement of clinical and laboratory parameters, decrease in daily GC requirements	1 mg daily	None
Kaye et al. (1995) ³⁷	5	5	Musculoskeletal	Not described	7.5-15 mg weekly orally	Improvement of clinical symptoms, decrease in daily GC requirements	Not described	None
Henderson et al. (1994) ³⁸	1	1	Skin, larynx	Monotherapy	10 mg weekly orally	Improvement of cutaneous and laryngeal lesions	Not described	None

Authors	Patients treated (n)	Patients responding (n)	Organ involvement	Combi/monotherapy	MTX dosage	Effect of therapy	Folic acid dosage	Adverse effects of MTX (n)
Suda et al. (1994) ³⁹	1	1	Lungs, eye, skin	Monotherapy	7.5 mg weekly orally	Improvement of pulmonary function (FVC, chest radiograph and arterial blood gases), improvement of cutaneous lesions	Not described	Nausea, transient
Webster et al. (1991) ⁴⁰	3	3	Skin (n=3), lungs (n=2)	Combination with topical steroid treatment	15 mg weekly orally	Clear improvement of skin abnormalities (n=3), improved pulmonary diffusion capacity (n=2). Maximal effect after 6–9 months.	Not described	Knee pain (n=1)
Soriano et al. (1990) ⁴¹	1	1	Neurosarcoidosis, liver, skin, eye	Combination with prednisone	25 mg weekly intramuscular	Improvement of neurological symptoms	Not described	None
Webster et al. (1989) ⁴²	3	3	Skin	Combination with topical steroids. Previous treatment with oral GC.	15–22.5 mg weekly orally	Improvement or disappearance of skin symptoms	Not described	None
Lacher (1968) ⁴³	1	1	Skin, lung, heart	Combination with prednisone	Not described	Improvement of clinical symptoms, decrease in daily GC requirements	Not described	None

ACE, angiotensin-converting enzyme; AZA, azathioprine; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; FVC, forced vital capacity; GC, glucocorticosteroids; LT, liver test; MR imaging, magnetic resonance imaging; MTX, methotrexate; VC, vital capacity.

References

1. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. *Sarcoidosis Vasc Diffuse Lung Dis* 2000;17:60-66.
2. Vorselaars AD, Wuyts WA, Vorselaars VM, Zanen P, Deneer VH, Veltkamp M, Thomeer M, Van Moorsel CH, Grutters JC. Methotrexate versus azathioprine in second line therapy of sarcoidosis. *Chest* 2013;144:805-812.
3. Baughman RP, Lower EE, Ingledue R, Kaufman AH. Management of ocular sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2012;29:26-33.
4. Vucinic VM. What is the future of methotrexate in sarcoidosis? A study and review. *Curr Opin Pulm Med* 2002;8:470-476.
5. Zeitlin JF, Tami TA, Baughman R, Winget D. Nasal and sinus manifestations of sarcoidosis. *Am J Rhinol* 2000;14:157-161.
6. Dev S, McCallum RM, Jaffe GJ. Methotrexate treatment for sarcoid-associated panuveitis. *Ophthalmology* 1999;106:111-118.
7. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med* 1997;157:1864-1868.
8. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; 155:846-851.
9. Baughman RP, Lower EE. The effect of corticosteroid or methotrexate therapy on lung lymphocytes and macrophages in sarcoidosis. *Am Rev Respir Dis* 1990;142:1268-1271.
10. Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. *Am J Med Sci* 1990;299:153-157.
11. Veien NK, Brodthagen H. Cutaneous sarcoidosis treated with methotrexate. *Br J Dermatol* 1977;97: 213-216.
12. Sakellariou GT, Anastasilakis AD, Karanikolas D, Vounotrypidis P, Berberidis C. Central skeletal sarcoidosis: a case report with sustained remission only on methotrexate, and a literature review on the imaging approach, treatment, and assessment of disease activity. *Mod Rheumatol* 2013;23: 175-181.
13. Alemdaroglu E, Erturk A, Eroglu AG. A sarcoidosis patient with hand involvement and large pulmonary lymph nodes: results of 1-year treatment with methotrexate. *Clin Rheumatol* 2013;32(suppl):S71-73.
14. Bouaziz A, Le Scannff J, Chapelon-Abrie C, Varron L, Khenifer S, Gleizal A, Bentz MH, Barthel A, Valeyre D, Seve P. Oral involvement in sarcoidosis: report of 12 cases. *Qjm* 2012;105:755-767.
15. Delmonte L, Zamo A, Cantini M, De Franceschi L. An unusual case of sarcoidosis in an adult patient with sickle cell disease: Management with methotrexate and low dose of steroid. *Am J Hematol* 2012; 88:243.
16. Sakushima K, Yabe I, Nakano F, Yoshida K, Tajima Y, Houzen H, Maruo Y, Sasaki H. Clinical features of spinal cord sarcoidosis: analysis of 17 neurosarcoidosis patients. *J Neurol* 2011;258:2163-2167.
17. Bargagli E, Olivieri C, Penza F, Bertelli P, Gonnelli S, Volterrani L, Rottoli P. Rare localizations of bone sarcoidosis: two case reports and review of the literature. *Rheumatol Int* 2011;31:1503-1506.
18. Gautam M, Patil S, Munde P. Skin as a marker of internal disease: a case of sarcoidosis. *Indian J Dermatol* 2011;56:439-441.
19. Lambert L, Riemer EC, Judson MA. Rapid development of sarcoid tenosynovitis. *J Clin Rheumatol* 2011;17:201-203.
20. Kimball MM, Wind JJ, Codispoti KE, Jones RV, Leiphart JW. Neurosarcoidosis presenting as an isolated intrasellar mass: case report and review of the literature. *Clin Neuropathol* 2010;29:156-162.
21. Kalajian AH, Van Meter JR, Callen JP. Sarcoidal anemia and leukopenia treated with methotrexate and mycophenolate mofetil. *Arch Dermatol* 2009;145:905-909.
22. Mannam P, Boselli JM, Schulman ES. Successful treatment of chylous ascites secondary to sarcoidosis with methotrexate. *Hosp Pract (Minneapolis)* 2009;37:144-146.
23. Varron L, Broussolle C, Candessanche JP, Marignier R, Rousset H, Ninet J, Seve P. Spinal cord sarcoidosis: report of seven cases. *Eur J Neurol* 2009;16:289-296.
24. Suarez Zambrano GA, Hutton GJ. Heart-shaped lesion secondary to neurosarcoidosis. *Arch Neurol* 2008;65:1388-1389.

25. Morgan SS, Aslam MB, Mukkanna KS, Ampat G. A rare presentation of sarcoidosis, back pain and spondylolisthesis. *J Bone Joint Surg Br* 2008;90:240-242.
26. Bradley DA, Lower EE, Baughman RP. Diagnosis and management of spinal cord sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006;23:58-65.
27. Kennedy PT, Zakaria N, Modawi SB, Papadopoulou AM, Murray-Lyon I, du Bois RM, Jervoise NAH, Devlin J. Natural history of hepatic sarcoidosis and its response to treatment. *Eur J Gastroenterol Hepatol* 2006;18:721-726.
28. Chong WS, Tan HH, Tan SH. Cutaneous sarcoidosis in Asians: a report of 25 patients from Singapore. *Clin Exp Dermatol* 2005;30:120-124.
29. Gardner GC, Hunter JC. Clinical images: Radiographic healing of osseous sarcoidosis. *Arthritis Rheum* 2005;52:2225.
30. Braun JJ, Gentine A, Pauli G. Sinonasal sarcoidosis: review and report of fifteen cases. *Laryngoscope* 2004;114:1960-1963.
31. Maust HA, Foroozan R, Sergott RC, Niazi S, Weibel S, Savino PJ. Use of methotrexate in sarcoid-associated optic neuropathy. *Ophthalmology* 2003;110:559-563.
32. Moin M, Kersten RC, Bernardini F, Kulwin DR. Destructive eyelid lesions in sarcoidosis. *Ophthalm Plast Reconstr Surg* 2001;17:123-125.
33. Scola RH, Werneck LC, Prevedello DM, Greboge P, Iwamoto FM. Symptomatic muscle involvement in neurosarcoidosis: a clinicopathological study of 5 cases. *Arq Neuropsiquiatr* 2001;59:347-352.
34. Diriri E, Espinoza CG, Espinoza LR. Spinal cord granulomatous vasculitis: an unusual clinical presentation of sarcoidosis. *J Rheumatol* 1999;26:1408-1410.
35. Mana J, Gomez-Vaquero C, Dorca J, Pujol R. Vertebral and rib sarcoidosis: long-term clinical remission with methotrexate. *Clin Rheumatol* 1999;18:492-494.
36. Gedalia A, Molina JF, Ellis GS, Jr., Galen W, Moore C, Espinoza LR. Low-dose methotrexate therapy for childhood sarcoidosis. *J Pediatr* 1997;130:25-29.
37. Kaye O, Palazzo E, Grossin M, Bourgeois P, Kahn MF, Malaise MG. Low-dose methotrexate: an effective corticosteroid-sparing agent in the musculoskeletal manifestations of sarcoidosis. *Br J Rheumatol* 1995;34:642-644.
38. Henderson CA, Ilchyshyn A, Curry AR. Laryngeal and cutaneous sarcoidosis treated with methotrexate. *J R Soc Med* 1994;87:632-633.
39. Suda T, Sato A, Toyoshima M, Imokawa S, Yoshitomi A, Tamura R, Suganuma H, Yagi T, Hayakawa H, Shirai M, Chida K. Weekly low-dose methotrexate therapy for sarcoidosis. *Intern Med* 1994;33:437-440.
40. Webster GF, Razsi LK, Sanchez M, Shupack JL. Weekly low-dose methotrexate therapy for cutaneous sarcoidosis. *J Am Acad Dermatol* 1991;24:451-454.
41. Soriano FG, Caramelli P, Nitrini R, Rocha AS. Neurosarcoidosis: therapeutic success with methotrexate. *Postgrad Med J* 1990;66:142-143.
42. Webster GF, Razsi LK, Sanchez M, Shupack JR. Methotrexate therapy in cutaneous sarcoidosis. *Ann Intern Med* 1989;111:538-539.
43. Lacher MJ. Spontaneous remission or response to methotrexate in sarcoidosis. *Ann Intern Med* 1968;69:1247-1248.