Use of methotrexate in patients with sarcoidosis

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ABSTRACT

Sarcoidosis may present with symptoms related to involvement of joints, skin and lungs, as well as other organs. Corticosteroids are the basis of treatment of symptomatic sarcoidosis. Additional or alternative drugs may be required in chronic cases and when systemic corticosteroids are contraindicated. Cytotoxic agents seem to be of value in selected patients, but no controlled studies are available, and the published literature consists of small case series. Therefore, no international agreement exists regarding when these drugs should be used in patients with sarcoidosis. Methotrexate is generally the preferred agent for treatment of chronic sarcoidosis when corticosteroids have inadequate efficacy and/or severe adverse effects. In this review we discuss the available literature concerning the treatment of sarcoidosis with methotrexate.

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Introduction

Sarcoidosis is the most frequent interstitial lung disease affecting young patients. Its aetiology remains unknown; since it is a systemic disease, any organ may be involved. The course of disease is frequently favourable and the disease may resolve spontaneously. However, about one third of patients experience a chronic course, and clinically significant organ impairment may occur in some (1).

The management of sarcoidosis is complex, based on: (i) the initial localisation of the manifestations; (ii) the prognosis; (iii) when to stop therapy, implying a question of drug-free remission and risk of relapse; and (iv) when to add or switch to other drugs, either to gain corticosteroid-sparing effects or because of insufficient response to corticosteroids.

Most of these issues are beyond the scope of this paper, and the reader is referred to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and to other Granulomatous Disorders (ATS/ERS/WASOG) statement and the British Thoracic Society interstitial lung disease guidelines regarding the treatment of sarcoidosis (2, 3). Nonetheless, no clear guidelines exist for initiation or termination of corticosteroid therapy. Furthermore, there seems to be some value to using cytotoxic agents in selected patients with sarcoidosis, but no studies have clearly delineated when these drugs should be initiated. Most studies are small case series, and the total number of MTX-treated sarcoidosis patients reported in the literature is small. No randomised double-blind placebo-controlled trials have been performed.

A generally agreed-upon rule is to treat when there is evidence of functional impairment of vital organs. Corticosteroids are the mainstay of treatment of sarcoidosis, but alternative drugs are required in chronic sarcoidosis and when corticosteroids are contraindicated. Fortunately, only about 5% of patients with severe or persistent sarcoidosis appear to require treatment beyond corticosteroids (4). The agents most frequently prescribed to spare corticosteroids in patients with sarcoidosis are antimalarials and cytotoxic agents. Methotrexate (MTX) and azathioprine are the preferred cytotoxic agents.

The precise mechanism of action of MTX in sarcoidosis and other immune-mediated disorders remains unclear, and this topic is addressed in other articles of this supplement. MTX inhibits diverse cellular functions and modulates cytokine production. In a study of 12 patients with active pulmonary sarcoidosis, low doses of MTX suppressed alveolar macrophage cytokine release and lymphocytic alveolitis (5).

The use of MTX in the treatment of sarcoidosis was first reported in 1960s, and it has been widely used since the 1990s. Some early case reports described its efficacy in refractory cases

(6, 7). The dosage has varied from 10 to 25mg per week. The drug appears to require 6 months to become effective. The reported side effects are similar to those seen in rheumatoid arthritis (8). One clinical problem that arises when treating patients with sarcoidosis with MTX is to differentiate pulmonary involvement due to the disease from MTX hypersensitivity (9).

Pulmonary sarcoidosis

As stated above, the lung is most frequently involved, although a favourable spontaneously resolving disease course is seen in the majority of patients affected. A consensus on the pharmacotherapy of pulmonary sarcoidosis has been obtained by the Delphi technique (10), which resulted in expert recommendation to use MTX as the preferred agent aiming at corticosteroid-sparing effects, or even replacement of corticosteroids in the treatment of pulmonary sarcoidosis. This consensus is supported by two uncontrolled clinical trials on chronic sarcoidosis in which a favourable response to MTX was reported. The non-randomised interventional study from Cincinnati included 50 patients with sarcoidosis treated with MTX for at least 2 years. A corticosteroid-sparing effect was noted in 25 of 30 patients (83%) who had been treated with corticosteroids at the initiation of MTX. After discontinuation of MTX, the disease relapsed in 35 of 40 patients (88%) (11). In a study of 90 patients with chronic sarcoidosis, lung function improved in 80% of affected patients after 6 months of MTX therapy (12).

These studies suggest that MTX is effective in patients with chronic sarcoidosis. Similar effects have been reported in patients with acute pulmonary sarcoidosis (13). A randomised controlled trial of 10mg MTX once weekly *versus* placebo plus oral prednisolone, conducted over one year in 24 patients, showed that patients who took MTX required a significantly lower dose of prednisolone in the second 6-month period. However, the study was limited by a high dropout rate. The efficacy of MTX was not different from placebo on an intention-to-treat basis. Furthermore, the outcomes of lung function, radiographic changes and subjective clinical symptoms did not differ between groups.

One special case of pulmonary sarcoidosis is involvement of the upper respiratory tract (SURT) (14). Documented SURT occurs in 5% of patients with sarcoidosis. Wegener's granulomatosis may have a similar appearance to SURT (15). MTX is most commonly used in this condition to spare corticosteroids (16).

Extrapulmonary sarcoidosis

The treatment of extrapulmonary sarcoidosis must be adapted to the localisation and severity of organ involvement. For asymptomatic individuals treatment is usually not necessary. Topical corticosteroids, especially in skin and eye involvement, may be appropriate (17). However, in chronic cases, non-corticosteroid agents may be needed. The management of complicated sarcoidosis, as seen with cardiac involvement, must be designed for individual patients, and is beyond the scope of this review.

a) Cutaneous involvement

Skin involvement is quite common, occurring in 20 to 35% of patients with sarcoidosis. Erythema nodosum is the most impressive form. However, given the variability of the lesions, milder cases may be overlooked or misinterpreted (18).

Acute and chronic lesions on the face or elsewhere on the body may be the main or sole indication for therapy. Chronic use of corticosteroids may lead to long-term complications. After failure of topical corticosteroids or antimalarial drugs, MTX is often used as second-line therapy.

Various open-label clinical trials or case series investigating the use of MTX in patients with cutaneous sarcoidosis have been reported. One open-label clinical trial showed that 12 of 16 patients cleared their skin lesions with a weekly dose of MTX – initially 25mg, tapered to a maintenance dosage of 5–15mg weekly (19). A case series of 4 patients with chronic cutaneous sarcoidosis reported complete remission in 3 of 4 patients after a mean treatment duration of 29 months (20). All patients had been previously treated with topical corticosteroids and/or hydroxychloroquine without success. MTX doses ranged from 12.5 to 30mg/week for at least 6 months.

b) Neurologic involvement

The central nervous system is involved in up to 25% of patients with sarcoidosis who undergo autopsy, but clinically fewer than 10% of patients with sarcoidosis present with neurologic symptoms (1).

In case reports concerning patients with spinal cord sarcoidosis, inconstant benefit during therapy with immunosuppressive agents has been reported. Two out of 7 patients received MTX, with 10mg or 20mg/week for at least 18 months. Patients remained stable with limited disability (21).

c) Ophthalmologic involvement

The eye is involved in 25 to 50% of patients with sarcoidosis, with anterior uveitis as the most common manifestation (65% of patients with ophthalmologic involvements) (22). After initial treatment with topical corticosteroids, periocular injections or systemic corticosteroids, immunosuppressive agents may be used to control persistent disease. In one study of patients with chronic non-infectious uveitis, 100% of the patients with sarcoidosis responded to MTX (23), an obvious major success. In another study of 56 patients with sarcoid uveitis a response rate of >60% with MTX alone and >90% with the combination of MTX and azathioprine has been reported (24).

d) Musculoskeletal involvement

Musculoskeletal involvement in sarcoidosis may range from acute arthritis to chronic myopathy (25). Acute arthritis occurs in 10–40% of patients with sarcoidosis, particularly in the early phase of the disease. A characteristic Loefgren syndrome (arthritis, erythema nodosum, lymphadenopathy) is often self-limited and usually does not require immunosuppressive therapy. Chronic recurrent arthropathy occurs in only 1–4% of patients with sarcoidosis, but

this chronic condition rarely responds to therapy. No data are available regarding MTX treatment in this patient group. Osteitis cystoides multiplex is a rare differential diagnosis (26).

Childhood sarcoidosis

Although sarcoidosis affects most commonly young adults, sarcoidosis is relatively uncommon in children. Nevertheless, one open-label non-controlled trial assessed the effectiveness of low oral doses of MTX in children presenting with the characteristic triad of arthritis, rash and uveitis. MTX was administered to 7 children in a dose of 10 to 15mg/m^2 over a period of at least 6 months (27). Complete resolution of symptoms was noted in 5 patients after 6 months of therapy. The primary problem in the remaining 2 patients involved sequelae of uveitis.

Conclusion

The management of sarcoidosis is based mainly on empirically grown standards of care rather than on evidence from clinical trials. MTX is a well-tolerated therapeutic agent with reported clinical efficacy and corticosteroid-sparing capacity for treatment of chronic symptomatic sarcoidosis.

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