Cytotoxic agents in sarcoidosis: which one should we choose?

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Purpose of review
Sarcoidosis is a granulomatous disease which affects multiple organs. Its therapeutic management is very challenging due to the heterogeneity in disease manifestation and clinical course, as well as the potential side effects of the immunosuppressive therapy. An overview of presently available second-line and third-line systemic agents is provided.

Recent findings
Because curative treatment is currently not available for sarcoidosis, nonspecific immunosuppression with prednisone remains the first-choice therapy. However, as chronic use of corticosteroids is accompanied with severe adverse events, timely implementation of appropriate steroid-sparing cytotoxic agents is important. Commonly prescribed second-line agents in sarcoidosis are methotrexate, azathioprine, leflunomide and hydroxychloroquine. Nevertheless, the evidence supporting their use is limited. Third-line treatment options, including tumor necrosis factor-alpha inhibitors infliximab and adalimumab and the experimental therapeutic rituximab, are currently reserved for patients refractory to standard therapy.

Summary
A better insight into the advantages and disadvantages of second-line and third-line treatment is important. The long-term effects of immunosuppressive agents, the optimal starting and maintenance dosages, and the best interval and discontinuation regimens should be elucidated. Identified associations of polymorphisms with treatment response suggest a step towards personalized medicine. Future research should focus on the role for pharmacogenetic and phenotypic predictors of treatment response and toxicity.

Keywords
biologicals, cytotoxic drugs, immunosuppresion, sarcoidosis, therapy

INTRODUCTION

Sarcoidosis is a systemic disease with a wide variety of symptoms and a diverse clinical course, which is characterized by the formation of noncaseating granulomas [1]. Sarcoidosis management is very challenging due to the heterogeneity in disease manifestation, as well as the potential side effects of treatment.

Sarcoidosis can be self-limiting with spontaneous remission within 2–3 years in a majority of patients. However, a subgroup of patients may have chronic disease [2], which can be very severe or even fatal. This wide variety in clinical phenotypes yields various treatment strategies (Fig. 1). The decision to treat depends on the natural history of the disease with expected response to treatment on one hand, and the potential toxicity of available pharmacological agents on the other [3]. Self-limiting disease does not necessitate treatment. However, danger of organ failure or unacceptable loss of quality of life (QOL) constitute the main indications for therapeutic intervention. Furthermore, absolute treatment indications are cardiac sarcoidosis, severe

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KEY POINTS

- The management of sarcoidosis is challenging due to the heterogeneity in organ manifestation and clinical course, as well as the potential side effects of current immunosuppressive therapy.
- Nonspecific immunosuppression with prednisone remains the first-choice systemic therapeutic option. However, given the severe adverse events accompanying long-term treatment, timely implementation of an appropriate cytotoxic agent with steroid-sparing potency is important.
- First-choice second-line agents in sarcoidosis consist of methotrexate, azathioprine, leflunomide and hydroxychloroquine, although the available evidence supporting their use as that of prednisone is limited.
- Third-line therapy with biologicals is currently reserved for refractory patients without response to standard treatment.

pulmonary sarcoidosis, hypercalcemia, sight-threatening ocular sarcoidosis and neurosarcoidosis [4,5].

Corticosteroids remain the mainstay of first-line treatment in sarcoidosis [6,7] (Table 1). Six randomized placebo-controlled trials have been performed, showing that corticosteroids significantly improve symptoms, lung function and chest radiographs compared to placebo, which were systemically reviewed by Paramothayan *et al.* [8]. Although the positive effects of corticosteroids in sarcoidosis are proven in the short run, it remains uncertain whether corticosteroids provide a beneficial long-term effect, for example, prevention of fibrosis [9,10]. Furthermore, downsides of treatment with corticosteroids are the common side effects when administered chronically, such as osteoporosis, diabetes mellitus or obesity [11▪]. In case of intolerable side effects or inefficacy, cytotoxic agents should be considered. The most commonly used second-line and third-line systemic therapeutics and their indications are discussed in this review (Table 1).

FREQUENTLY USED SECOND-LINE AGENTS

Some sarcoidosis patients are unresponsive to the first-line therapy or experience severe side effects. In these cases, second-line therapeutics can be used as steroid-sparing agents. Mostly used second-line therapeutics are discussed in this section.

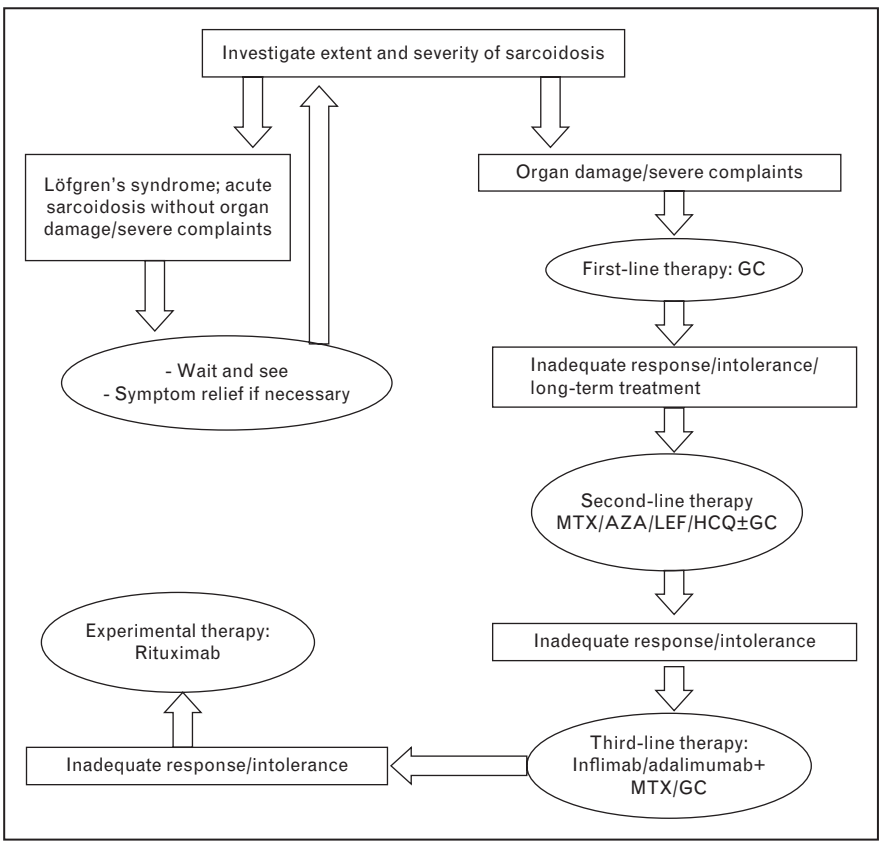

FIGURE 1. Pharmacotherapeutic management of patients with sarcoidosis. AZA, azathioprine; GC, glucocorticosteroid; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate.

Table 1. Characteristics of the most commonly prescribed pharmacotherapeutic agents in sarcoidosis

Drug	Mechanism of action	Level of evidence for use in sarcoidosis[a]	Usual dosage	Main adverse events	Comments
Prednisone	Restoration of the balance between type 1 and type 2 T-helper cell cytokines	1A	20–40 mg daily orally	Osteoporosis, diabetes mellitus, obesity, cataract	The dosage should be tapered down to a dose below 10 mg daily, if needed in combination with a steroid-sparing second-line agent
Methotrexate	Stimulation of adenosine release	1B	10–15 mg weekly orally or parenterally	Gastrointestinal, liver and renal toxicity, neutropenia, infectious and noninfectious respiratory events	Folate supplementation is necessary to prevent gastrointestinal and hepatic toxicity
Azathioprine	Purine antagonist, reduction of B and T-cell proliferation	2B	50–150 mg daily orally	Gastrointestinal and liver toxicity, neutropenia, photosensitivity, infections	Patients with low TPMT levels can develop severe toxicity, genotyping can be performed at initiation
Leflunomide	Inhibition of pyrimidine synthesis, repression of lymphocyte responses	2B	10–20 mg daily orally	Gastrointestinal and liver toxicity, silent liver fibrosis, peripheral neuropathy	
Hydroxychloroquine	Antimalarial agent, precise mechanism of action unknown	2B	200–400 mg daily orally	Gastrointestinal toxicity, retinopathy, rash, neuromyopathy	Regular complete eye examination is needed
Infliximab	Chimeric monoclonal antibody against TNF-α	1B	5mg/kg intravenously at week 0, 2, 6 with a 4 weeks interval thereafter	Allergic reaction, increased risk of serious infections, reactivation of tuberculosis, cardiac failure antibody formation	Assessment for tuberculosis at initiation. Concurrent use of MTX or other cytotoxic drugs reduces the risk of allergic reactions/antibody formation
Adalimumab	Human monoclonal antibody against TNF-α	2B	40 mg weekly subcutaneously	Allergic reaction, increased risk of serious infections, reactivation of tuberculosis	Assessment for tuberculosis at initiation. Concurrent use of MTX or other cytotoxic drugs reduces the risk of allergic reactions/antibody formation

MTX, methotrexate; TNF-α, tumor necrosis factor-alpha; TPMT, thiopurine S-methyltransferase.
[a]Level of evidence, according to the Oxford Center for Evidence-Based Medicine.

Methotrexate

Methotrexate (MTX) is a folic acid antagonist inhibiting cellular proliferation [12]. However, current evidence has shown that its anti-inflammatory mechanism of action is more likely the result of stimulation of adenosine release [12,13]. Despite limited evidence, MTX is considered to be the first-choice second-line option in sarcoidosis [14]. MTX use in sarcoidosis patients is especially based on results in rheumatic inflammatory diseases [15▪▪].

Methotrexate is useful as a steroid-sparing agent in acute sarcoidosis, as has been shown by the single available randomized controlled trial (RCT) ($n = 24$) [16]. A recent retrospective cohort study, comparing MTX ($n = 145$) and azathioprine (AZA) ($n = 55$) in sarcoidosis, showed a significant steroid-sparing potency and a positive effect on lung function of both drugs [17▪]. Recently, disease resolution or stabilization was found in 329 of the 365 patients (90%) with sarcoid eye involvement treated with MTX [18]. Large case series have also shown the use of MTX in pulmonary and extrapulmonary sarcoidosis [19–21]. A recent Japanese retrospective study showed improvement of sarcoidosis-related lesions in only 6 of the 26 patients (23%); however, MTX monotherapy was used in low dosages [22].

Typical side effects are hepatotoxicity and leukopenia, necessitating regular liver test and blood count monitoring [20]. In case of MTX-induced gastrointestinal side effects, splitting of the oral dose or parenteral administration can be considered [15▪▪]. A recent meta-analysis in rheumatoid arthritis (RA) showed that MTX was associated with a small increased risk of respiratory infections [relative risk (RR) 1.11, 95% confidence interval (CI) 1.02–1.21], without an increased risk of non-infectious respiratory events or pulmonary death compared to other agents, suggesting a lower risk than previously assumed [23▪].

Azathioprine

Azathioprine is a purine antagonist which derives its anti-inflammatory effect mainly through reducing B- and T-cell proliferation. Sarcoidosis specialists consider AZA to be the second-choice steroid-sparing agent for sarcoidosis [14]. No RCTs have been performed on AZA in sarcoidosis treatment. Reported efficacy is mainly anecdotal with three case series describing a positive outcome [24–26]. Although AZA has a similar efficacy and toxicity profile as MTX, a higher number of infections were described [17▪]. AZA is often used in cases when MTX is contraindicated or failed to induce response. One study found that half of the patients who failed to respond to MTX had a positive response when they switched to AZA [27].

Most common side effects are infections, gastrointestinal complaints, hepatic function decline and bone marrow depression [17▪]. AZA is metabolized by thiopurine S-methyltransferase (TPMT), and patients with low TPMT levels can develop severe neutropenia. TPMT genotyping is advised before starting treatment with AZA to reveal patients susceptible to toxicity [28,29].

Leflunomide

Leflunomide (LEF) represses lymphocyte responses only for actively stimulated lymphocyte clones [30]. In 2003, Majithia *et al.* [31] reported an improvement in 78% of 32 sarcoidosis patients who were treated with LEF. However, until now, no RCTs are available. A retrospective study evaluating 32 sarcoidosis patients with pulmonary and ocular sarcoidosis showed an improvement in 80% of patients on LEF monotherapy or combination therapy with MTX [32]. The most recent available study, investigating 76 sarcoidosis patients retrospectively, demonstrated a significant steroid-sparing effect of LEF, an improvement in forced vital capacity (FVC) and at least a partial response in 83% of the involved extrapulmonary organs [33]. MTX/LEF combination therapy tended to achieve a better response [33].

Reported side effects include gastrointestinal symptoms, liver test abnormalities and peripheral neuropathy [32,33]. A recently reported safety issue with LEF is silent liver fibrosis [34]. In sarcoidosis, LEF is especially used as an alternative or if needed in addition to MTX and is suggested to have comparable efficacy with less toxicity [35▪]. However, since studies directly comparing the effectiveness and side effects of LEF and MTX are lacking, future prospective trials are necessary to ground this recommendation. In RA, the occurrence of hepatotoxicity and neutropenia when using either MTX or LEF seems to be comparable [36].

Antimalarials

Antimalarials such as hydroxychloroquine and chloroquine have been used in sarcoidosis treatment over 50 years due to their immunomodulating properties, although the precise mechanism of action in sarcoidosis is unknown [37]. Although these drugs show an effect on pulmonary sarcoidosis [38] and have also been reported to be effective in neurological involvement [39], they are mostly used to treat cutaneous sarcoidosis [40]. Another application is sarcoidosis joint involvement [41], although no studies have been performed on this

subject. Common side effects are of gastrointestinal nature; furthermore, retinopathy can develop. Hydroxychloroquine is often preferred over chloroquine due to less ocular toxicity.

OTHER SECOND-LINE AGENTS

Mycophenolate mofetil (MMF), a reversible inosine monophosphate dehydrogenase inhibitor, can be considered another promising immunomodulatory agent [42,43]. Several case series of patients with sarcoidosis-associated uveitis, central nervous system and mucocutaneous involvement have shown positive results [43–46]. A recent study found significant reductions of glucocorticosteroid dosages in patients with chronic pulmonary sarcoidosis [42]. In general, MMF is well tolerated with dose-dependent and usually self-limiting mild gastrointestinal side effects, but leukocytopenia and infections can also be present [42,43,45,46].

Cyclophosphamide, a cytostatic agent, leads to inhibition of lymphocyte number and function with suppression of both cellular and humoral immunity. Case series have shown its use in neurosarcoidosis and cardiac sarcoidosis [47–51]. Adverse events consist of gastrointestinal complaints, infections, bone marrow suppression and hemorrhagic cystitis [51,52,53▪].

Thalidomide reduces tumor necrosis factor-alpha (TNF-α) release from alveolar macrophages, hereby reducing granuloma formation [54]. Its use has been described in cutaneous sarcoidosis [55–57]. Whether thalidomide is effective in pulmonary sarcoidosis remains debatable, with conflicting results being published [58,59]. The most serious adverse effect is peripheral neuropathy, often resolving after dose reduction or discontinuation [57]. The well known severe teratogenic effects of thalidomide warrant precautionary measures.

Pentoxifylline, a nonselective phosphodiesterase inhibitor, reduces inflammation by inhibition of TNF-α synthesis and activity and is effective in pulmonary sarcoidosis [60,61]. However, the frequently observed gastrointestinal side effects limit its routine use [60,61].

Apremilast, a new phosphodiesterase type 4 inhibitor that blocks the synthesis of proinflammatory cytokines, was recently found to be effective in cutaneous sarcoidosis [62].

THIRD-LINE TREATMENT: BIOLOGICALS

Some cases of severe sarcoidosis are refractory to standard first-line and second-line therapy. In this patient category, third-line therapy with biologicals has found its way into daily practice. Most used biologicals will be discussed in the following section.

Infliximab

Tumor necrosis factor-α, which is thought to be excessively produced by macrophages in sarcoidosis patients, has an important role in the cascade of granuloma formation [63,64]. Infliximab, a chimeric monoclonal antibody against TNF-α, has been studied in several manifestations of sarcoidosis. Two RCTs investigating infliximab have been performed in patients with chronic pulmonary sarcoidosis [65,66]. The largest demonstrated a significant increase in FVC of 2.5% in a study of 138 patients, with a greater improvement in more severe disease [65]. Additional subgroup analysis revealed positive effects on extrapulmonary symptoms and it may be particularly effective for lupus pernio and neurosarcoidosis [67]. A retrospective cohort study in 48 patients showed that apart from a significant improvement of 7.6% in FVC, there is also a reduction of disease activity measured by 18F-fluorodeoxyglucose PET (18F-FDG-PET) and improvement in QOL [68▪]. Furthermore, infliximab therapy has a positive effect on cognition and fatigue in sarcoidosis [69]. A recent study in 111 sarcoidosis patients treated with infliximab or adalimumab showed that patients without the TNF-α-308A variant allele (GG genotype) had a three-fold higher response rate [70▪▪].

Recently, the first long-term results of treatment with infliximab have been described. Infliximab was found to be beneficial in 14/16 (88%) patients treated for at least 12 months [71]. Another study in 26 pulmonary and extrapulmonary sarcoidosis patients described an improvement in 58.5% of the organs studied after a treatment duration up to 85 months, without major toxicity [72].

A retrospective study in 47 patients that discontinued infliximab therapy revealed a relapse rate of 62%, with 25% of the cohort relapsing within 4 months. Both high activity on 18F-FDG-PET and elevated serum soluble interleukin-2 receptor (sIL-2R) at the start of therapy predicted relapse after discontinuation [73▪▪].

Side effects of infliximab are infection risk and cardiac failure in prone patients. Prior to initiation of infliximab, all patients should be screened for current or previous tuberculosis infection, because an increased risk of tuberculosis reactivation exists [74]. Furthermore, allergic reactions to infliximab may occur, which appear to be less frequent with concurrent use of MTX or other cytotoxic drugs to reduce the risk of antibodies directed against infliximab [75]. Annual influenza vaccination and

periodic pneumococcal vaccination for all patients receiving biological agents is recommended according to rheumatology guidelines [76,77].

Adalimumab

Adalimumab is a fully human TNF-α monoclonal antibody, which was shown beneficial in cases of refractory pulmonary, eye and cutaneous sarcoidosis. It also has a positive effect on cognition and fatigue in sarcoidosis [18,69,78,79]. A recent cohort study of 26 sarcoidosis patients with uveitis showed improvement of intraocular inflammatory signs in 85% and stabilization in 15% of patients treated with adalimumab [80]. Furthermore, a case series of 10 sarcoidosis patients demonstrated a significant decrease in 18F-FDG-PET activity, without improvement in pulmonary function or inflammatory parameters [81]. In a recent RCT involving 16 patients, adalimumab was found to be effective and save in treatment of cutaneous sarcoidosis [82▪▪]. Most recently, adalimumab was shown to be effective in 75% of patients ($n = 35$), who were suffering from different sarcoidosis localizations [70▪▪]. The success rate of treatment is likely to be dependent on the adalimumab dosing regimen and the administration interval used [83].

Toxicities are usually similar to infliximab, but the risk of allergic reactions is less likely given the human nature of adalimumab [35▪]. To prevent antidrug antibody formation, concomitant MTX or other cytotoxic drug use is advised. A recent study showed a significant higher median adalimumab level and a better clinical response in RA patients using both adalimumab and MTX [84].

Rituximab

Rituximab is a monoclonal antibody targeting the B-cell-specific protein CD20. With recent findings of B cells as emerging key players in sarcoidosis [85▪▪], a rationale behind systematic B cell ablative therapy in sarcoidosis exists. Rituximab was successfully administered in ocular sarcoidosis, with a significant steroid reduction in all four patients treated [86]. More recently, the first prospective phase I/II clinical trial on rituximab in patients with pulmonary sarcoidosis ($n = 10$), refractory to steroids or second-line agents, demonstrated an inconsistent clinical response without the occurrence of severe side effects [87▪].

DISCUSSION

In this overview, we presented knowledge about the systemic treatment of sarcoidosis. Now we will discuss the gap of knowledge regarding sarcoidosis treatment and some future directions with emphasis on personalized medicine.

Limitations of current evidence

Unfortunately, little data are available to provide evidence-based guidance regarding the treatment of sarcoidosis in clinical practice. Recommendations are especially derived from extrapolations from evidence in other chronic inflammatory diseases or based on experience and eminence-based medicine [88▪].

The clinical presentation and course of sarcoidosis show a wide variety. Often the course of various organ manifestations is unpredictable. Moreover, exactly defined response criteria and clinical endpoints are lacking; therefore, pharmacological studies with well defined disease phenotypes are difficult and the definition of treatment response is challenging. The number of participants in studies investigating the efficacy of drug treatment is usually low and studies directly comparing the various treatment options are lacking. Furthermore, in general, pharmaceutical companies are less interested to conduct clinical trials in rare diseases like severe sarcoidosis. The gap of knowledge in the field of second-line and third-line therapeutics underlines the need for multicenter cooperation in research.

The review summarizes the short-term results of the immunosuppressive therapy. Information concerning the long-term effectiveness is virtually not available. This remains an important subject necessitating research attention. The question is whether systemic sarcoidosis therapy can prevent organ damage and improve QOL. Furthermore, another difficult issue is the discontinuation of treatment in stable disease. The optimal period before successful withdrawal of treatment is achievable has not been established yet. Future research is necessary to determine in which sarcoidosis patients and after what treatment duration treatment discontinuation can be considered. Moreover, attention should be paid to starting and maintenance dosages, interval and discontinuation regimens.

Future directions: personalized medicine

'Personalized medicine' is a term which is used to indicate the selection of the most appropriate pharmacological therapy for an individual patient implying maximal effectiveness with minimal side effects. As sarcoidosis can have various disease manifestations and a variable clinical course, response to pharmacological treatment is diverse. Little is known on whether specific patient and disease

characteristics can possibly predict response to currently available therapy in sarcoidosis. Apart from the exploration of the existence and value of these phenotypic predictors of response, the principles of pharmacogenetics also become increasingly important in personalized medicine. The genetic characteristics of a patient might interact with a drug, affecting its pharmacological action and leading to different treatment efficacy and toxicity [89▪]. Drug selection based on a patient's genotype has the potential to avoid unnecessary exposures to potentially toxic drugs and to aim for effective, cheaper and faster disease control [89▪]. Given the small number of participants in pharmacological studies in sarcoidosis, research into the influence of genetic variants on treatment outcome is difficult. Nevertheless, some steps towards personalized medicine in sarcoidosis have been taken. An example is TPMT genotyping, as already mentioned, which can be used in patients starting AZA therapy. The lower the TPMT activity, the higher the risk of developing toxicity, especially myelosuppression [28]. Furthermore, genetic analysis has previously revealed a number of polymorphisms in genes coding for TNF-α, with a role in the clinical and prognostic diversity of sarcoidosis [90]. The variant A allele of the TNF-α G-308A gene was shown to be more frequently present in patients with Löfgren's syndrome [90,91], whereas absence of the variant A allele (GG genotype) was associated with progression to a more severe or persistent pulmonary disease course [92]. Recently, absence of the variant A allele in sarcoidosis patients refractory to conventional treatment was shown to be associated with better response to TNF-α inhibitors, suggesting a possible role for TNF-α G-308A polymorphism genotyping when optimizing therapy [70▪▪]. In other diseases, the value of genotyping for this polymorphism and other genetic patterns has been studied more extensively. In RA, for example, multiple analyses have been made to evaluate the value of genetics when predicting treatment response to MTX and other drugs [89▪,93,94]. In sarcoidosis, the value of pharmacogenetics when tailoring pharmacotherapy needs to be further explored. Large (international) cohort studies are necessary to gain more insight.

CONCLUSION

Since curative treatment is still not available for sarcoidosis, nonspecific immunosuppression with prednisone remains the first-line therapeutic choice. In case of toxicity or inefficacy, second-line therapeutics, such as MTX, AZA, LEF and hydroxychloroquine, are proven to be effective. Third-line treatment with biologicals is currently reserved for selected patients refractory to standard therapy. Future research should focus on the role for personalized medicine, based on possible pharmacogenetic and phenotypic predictors of response, in the treatment of sarcoidosis.

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Conflicts of interest

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