Update on bioagent therapy in sarcoidosis

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Abstract

Corticosteroids are still the cornerstone of treatment for patients with sarcoidosis requiring systemic therapy. However, alternative agents and especially methotrexate may be considered for patients with refractory disease or requiring prolonged treatment with intolerable side effects. Although bioagent therapies have hitherto not clearly demonstrated superior efficacy and safety over corticosteroids in pulmonary sarcoidosis, infliximab may modestly improve lung function in patients with active disease resistant to steroids. Further studies will be needed to assess both safety and efficacy of infliximab in pulmonary sarcoidosis. Infliximab may be considered in a limited number of patients with severe extrapulmonary systemic manifestations of sarcoidosis, with careful individual evaluation of the risk-benefit ratio.

Introduction and context

Treatment decision in sarcoidosis is based on the severity or duration of disease or both (e.g., acute or chronic sarcoidosis, the latter corresponding to active disease persisting beyond 5 years from the time of diagnosis) [1]. While no treatment is necessary in a majority of patients, corticosteroid therapy is the mainstay of treatment for those who require systemic therapy. Although the dose of steroids largely varies among centres and is based on experience rather than evidence, most clinicians use approximately 0.5 mg/kg per day (30-40 mg per day) of prednisone or equivalent as a starting daily dose in chronic sarcoidosis [2]. After maximum improvement has been achieved, corticosteroid therapy is slowly tapered to maintenance therapy (10-15 mg or approximately 0.25 mg/kg daily) in order to establish the minimal dose that controls disease activity; this requires regular reassessment of pulmonary symptoms, chest radiographs, and pulmonary function [2]. The disease may be considered refractory if improvement has been documented following 0.5 mg/kg per day prednisone treatment for at least 3-6 months.

Alternative agents may be used for patients with disease refractory to corticosteroid therapy (e.g., with symptoms not controlled or worsening despite adequate corticosteroid therapy), for those requiring long-term high-dose treatment for chronic disease, or for those who cannot tolerate corticosteroid side effects. When bioagent therapy is being considered, the decision analysis approach should include the risk of long-term corticosteroid therapy at the maintenance dose and that of potentially toxic alternative therapy. Corticosteroid dependence should not be considered a treatment failure that systematically requires steroid-sparing agents; indeed, a low-dose corticosteroid treatment when well tolerated may be superior to bioagent therapies, which may cause significant, albeit different, adverse events. Whether follow-up without therapy is possible or whether therapy is mandatory should be systematically re-evaluated when considering alternative therapy. Methotrexate (10 mg/week) has demonstrated steroid-sparing activity in patients with acute [3] and chronic [4] sarcoidosis, with a cumulative risk of hepatotoxicity, and is considered the first-choice alternative to

corticosteroids; a detailed discussion of methotrexate therapy and other non-bioagent alternative drugs [1] is beyond the scope of this review. Long-term monitoring is required for both response to therapy and toxicity regardless of the drug used.

Recent advances

Two anti-tumour necrosis factor-alpha (TNF-α) therapies have been evaluated in sarcoidosis (Tables 1 and 2). Two studies using etanercept failed to show a treatment benefit in patients with either progressive pulmonary disease, using a composite endpoint of dyspnea, pulmonary function, and chest radiograph [5], or methotrexate-resistant, corticosteroid-treated ocular sarcoidosis, using the steroid-sparing effect and global ocular assessment as an endpoint [6]. Both exploratory studies suffered significant methodological limitations, especially the absence of a control group [5] and small sample size [6]. Diffusion of etanercept into tissues, especially the vitreous, may also be limited [6]. Therefore, etanercept does not seem to be effective in most patients with chronic sarcoidosis.

In contrast, two retrospective series reported symptomatic improvement in most patients receiving infliximab [7,8]. Although the level of evidence was low, efficacy was suggested in patients with chronic multiorgan extrapulmonary disease, especially lupus pernio, uveitis, and neurosarcoidosis, refractory to oral corticosteroids or with intolerable side effects [7,8]. Infliximab was also shown to be beneficial in lupus pernio [9] and chronic inflammatory eye disease in sarcoidosis, including in patients who had not responded to etanercept [10].

Nineteen patients with chronic active pulmonary sarcoidosis (stage II-IV) who had received corticosteroids for at least 3 months with suboptimal response or intolerance were included in a randomised trial [11], and 13 of them received infliximab. No significant difference was observed between groups for the primary endpoint (i.e., the relative change in vital capacity 6 weeks after initiation of treatment). No change was found in the secondary endpoints, including radiologic changes, health-related quality of life, and dyspnea scores. However, the study was underpowered due to insufficient accrual. Although not significant, the change in vital capacity in treated patients was paralleled by a trend toward improved vital capacity in the subjects in the placebo group during the open-label treatment in the second phase of the study. Of note, one patient receiving infliximab had pneumonia, and another developed recurrent cellulitis.

In a larger phase II randomised controlled trial in 138 patients with stable chronic pulmonary sarcoidosis (radiographic stage II-III) [12], infliximab therapy in addition to a stable dose of background corticosteroids or immunosuppressive therapy or both was associated with a 2.5% mean increase in forced vital capacity at week 24 versus 0 in controls (*P* = 0.038). *Post hoc* analysis identified the subgroups that benefited the most from this therapy, including those with more severe disease. The clinical relevance of the modest and transitory improvement in lung function, though statistically significant, was unclear. No improvement was obtained in secondary endpoints. Patients with phase IV or cavitary sarcoidosis or both were not included. Evaluation of severity of extrapulmonary involvement used a new, non-validated tool [12], which may not adequately reflect clinical severity as required for decision analysis [13]. The small magnitude of improvement (with potential underestimation of the treatment effect [13]) may be partly due to selection bias, with exclusion of patients with the most severe disease [13,14] and inclusion of patients with stable disease already receiving at least 10 mg/day of prednisone.

The effectiveness of infliximab therapy in chronic granulomatous disease (such as sarcoidosis and Crohn's disease) has been hypothesised to be related to its mechanism of action, whereby it binds both free TNF-α and cell surface TNF-α (the latter being involved in complement-mediated cell lysis and antibody-dependent cell-mediated cytotoxicity as well as apoptosis induction of activated lymphocytes), in contrast to etanercept, which binds soluble but not surface molecules [15].

Table 1. Available anti-tumour necrosis factor-alpha therapies

Drug	Mechanism of action	Route	Dosage
Adalimumab	Humanised monoclonal anti- TNF-α antibody	Subcutaneous	3-5 mg/kg every 2 weeks
Etanercept	Fusion protein of ligand-binding domain of human TNF-α receptor-I and human Fc fraction of IgG1	Subcutaneous	25 mg twice weekly
Infliximab	Chimeric mouse/human monoclonal IgG1 anti-TNF-α antibody	Intravenous	3-5 mg/kg, then 2 weeks later, then every 1-2 months

TNF-α, tumour necrosis factor-alpha.

Table 2. Summary of the main studies of anti-tumour necrosis factor-alpha therapy in sarcoidosis

Reference	Drug	Design	Indication	Primary endpoint	Results and comments
[5]	Etanercept	Open-label, phase II, 12 months; n = 17	Progressive stage II-III lung disease	Composite endpoint	Early termination of study for lack of efficacy Nasopharyngeal plasmocytoma and intestinal lymphoma developed
[6]	Etanercept	Double-blind randomised controlled trial, 6 months; n = 18	Ocular sarcoidosis with ongoing inflammation in the eyes Methotrexate-resistant, corticosteroid-dependent disease	Corticosteroid-sparing effect	Lack of steroid-sparing effect Lack of ophthalmology global improvement
[8]	Infliximab	Retrospective series, infliximab 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks; n = 10	Patients with drug failure or intolerable side effects Indication of therapy extrapulmonary (skin disease in 6 of 10)	Heterogeneous individual retrospective clinical assessment Steroid-sparing effect	Symptomatic improvement in 9 of 10 patients, objective improvement in all 10 patients Steroid-sparing effect obtained Angioimmunoblastic lymphoma developed
[7]	Infliximab	Retrospective series; infliximab 3 mg/kg at weeks 0, 2, 4, 6, 10 and 14; n = 12	Chronic multiorgan sarcoidosis, refractory or intolerant to corticosteroids or alternative drugs	Heterogeneous individual retrospective assessment	Some clinical or imaging improvement in all patients Low-quality evidence Recurrence of symptoms upon discontinuation of treatment Myeloma developed
[11]	Infliximab	Phase II, double-blind randomised controlled trial, 38 weeks, n = 19; infliximab 5 mg/kg or placebo at weeks 0 and 2, then infliximab at weeks 6 and 14	Chronic active pulmonary sarcoidosis, stage II-IV VC 50-80% of predicted Patients having received corticosteroids for ≥3 months, with suboptimal response or intolerance	Mean relative change in VC at week 6	Non-significant relative change in VC (15.2% ± 9.9% with infliximab versus 8.4% ± 3.3% with placebo, $P = 0.65$) No change in secondary endpoints 19 included patients (42 planned); underpowered trial One death possibly related to infliximab
[12,14]	Infliximab	Phase II, double-blind randomised controlled trial; 1:1:1 to receive placebo, infliximab 3 mg/kg or infliximab 5 mg/kg at weeks 0, 2, 6, 12, 18 and 24; n = 138	Chronic stable pulmonary sarcoidosis, stage II-III FVC 50-85% of predicted Patients receiving ≥10 mg/day of prednisone or immunosuppressive therapy or both 68% of patients with extrapulmonary involvement	Change in FVC at week 24 *Post hoc* analysis of predefined secondary endpoint ePOST	FVC improvement by 2.5% at week 24 versus 0 in controls ($P = 0.038$) *Post hoc* analysis identified subgroups that benefited most from therapy Significant improvement of ePOST score at 24 weeks, not maintained after treatment discontinuation Adverse events included pneumonia (4.4%), skin squamous cell carcinoma and epitheliod sarcoma

ePOST, extrapulmonary organ severity tool; FVC, forced vital capacity; VC, vital capacity.

Promising results have been reported in cases treated with the anti-TNF-α adalimumab [16,17], and trials are currently being conducted (NCT00311246, NCT00274352). Of note, the paradoxical development of sarcoidosis has rarely been reported during treatment with all three available TNF-α antagonists, an event potentially linked to cytokine disequilibrium [18-24].

In view of the accumulated evidence, limitations of published trials using anti-TNF-α antibodies suffer from several flaws, including an inadequate target that does not include membrane-bound TNF-α [5,6], inadequate retrospective design [7,8], inadequate patient population with stable rather than progressive pulmonary disease [12], and insufficient sample size and power [11].

Trials are under way using golimumab, a fully human monoclonal antibody directed against TNF-α (NCT00955279); ustekinumab, a human anti-interleukin-12/interleukin-23 monoclonal antibody

(NCT00955279); and abatacept, a fusion protein composed of the Fc fraction of human immunoglobulin G1 fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4 (NCT00739960), an inhibitory molecule expressed on the surface of helper T cells. One report of improvement using rituximab has been published [25], although sarcoidosis is not a B cell-driven or autoimmune disease.

Implications for clinical practice

Available evidence does not support the use of etanercept in sarcoidosis. The experience with adalimumab is too limited to draw conclusions in sarcoidosis. Infliximab may improve lung function in patients with active pulmonary sarcoidosis resistant to steroids, but with modest and clinically debatable benefit. Long-term studies will be needed to assess both safety and efficacy of infliximab in patients with intractable active disease, in whom corticosteroids are either not effective or not tolerated. Anti-TNF-α therapy should be further evaluated in patients with progressive disease, who may be more apt to benefit from therapy [12], as suggested by a preliminary underpowered negative study [11]. However, severity scores [14,26] need to be validated prospectively with regard to prognosis.

Pending further evidence, corticosteroids remain the cornerstone of therapy in sarcoidosis. The use of infliximab in sarcoidosis can be discussed on an individual basis with careful evaluation of the risk-benefit ratio, and should preferably be considered in the context of randomised clinical trials. Infliximab may be used in patients with progressive disease refractory to corticosteroids, especially in the context of lupus pernio, intractable uveitis, or neurosarcoidosis. Infliximab is unlikely to provide significant benefit in patients with severe but stable stage IV pulmonary disease. Current risk-benefit analysis suggests that infliximab be used preferably as third-line therapy (after failure of methotrexate as second-line therapy). In such a situation, it is preferable that low-dose corticosteroids be continued in association with infliximab. There are no clinical data to support the concomitant use of methotrexate and infliximab in sarcoidosis, although the possibility of blocking antibodies to infliximab during treatment prompts some clinicians to use concomitant low-dose methotrexate. Methotrexate should be preferred to bioagent therapy in patients with intolerable side effects of corticosteroids and who require maintenance of therapy; infliximab should currently not be considered the steroid-sparing agent of choice in sarcoidosis.

Although TNF-α antagonists appear to be relatively safe (with a safety profile quite distinct from that of systemic corticosteroids), concerns that anti-TNF-α therapy might increase the risk of tumour may limit the use of these agents in the future, and careful evaluation of this potential risk is warranted. Anti-TNF-α therapy increases the risk of infection, including tuberculosis [27]. Infusion reactions are usually mild [28]. Human anti-chimeric antibody may develop in patients receiving repeated infusion [29,30], with a controversial role in hypersensitivity reactions; the combination of infliximab with low-dose methotrexate may be used to limit the risk of antibody formation.

Given the well-proven effectiveness of corticosteroids in the treatment of active pulmonary sarcoidosis, newer therapies must demonstrate superior efficacy and safety in order to become the standard of care [11]. This has not been demonstrated for bioagent therapy, with the notable exception of infliximab in a limited number of patients with disease intractable with corticosteroids, especially those with severe systemic manifestations.

Abbreviation
TNF-α, tumour necrosis factor-alpha.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements

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