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The evidence for biologic immunotherapy in Sarcoidosis: A systematic review

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REVIEW

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ABSTRACT

Background

Sarcoidosis is a chronic inflammatory disease with a myriad of clinical manifestations. Treatment involves immunosuppression with corticosteroids or steroid-sparing agents. A proportion of patients does not respond to or are intolerant to therapy. Targeted immunotherapy with biologic agents has emerged as a novel approach with plausible mechanistic reasons to warrant study.

Aims

The aim of this review was to evaluate the evidence for the efficacy of biological therapy in sarcoidosis.

Methods

We conducted a systematic literature review and meta-analysis of all published randomised-controlled trials (RCT) evaluating biological therapy in sarcoidosis, using MEDLINE and Embase databases, through to September 2017. The search terms included sarcoidosis, infliximab, adalimumab, etanercept, golimumab, certolizumab, rituximab, abatacept, tocilizumab, anakinra, ustekinumab, secukinumab. Only articles reporting RCTs were selected. Improvements in respiratory disease were assessed by changes in forced vital capacity (FVC) by weighted mean difference (WMD). There were insufficient data on outcome measures in other organ systems to comparatively assess efficacy.

Results

The search identified 2,324 studies of which only 5 provided relevant and original data. This comprised a total of 364 patients, evaluating pulmonary, cutaneous and ocular sarcoidosis. One study in pulmonary disease and one study in cutaneous disease demonstrated improvements in the primary outcome. In pulmonary disease, meta-analysis of the treatment effect of anti-TNF therapy versus placebo on FVC revealed a WMD of 1.69 per cent (95 per cent confidence interval, 1.44–1.94).

Conclusion

There are insufficient data to suggest the long-term efficacy of anti-TNFα inhibitors in the treatment of sarcoidosis. This may be due to heterogeneity, small sample sizes and the lack of consistent reporting of outcome measures.

Key Words

Sarcoidosis, TNF inhibition, biological therapy, systematic review, meta-analysis

What this study adds:

1. What is known about this subject?

Targeted immunotherapy with biologic agents has emerged as a novel approach, with plausible mechanistic reasons to warrant study in sarcoidosis.

2. What new information is offered in this review?

Whilst we cannot absolutely conclude that TNF inhibitors are not effective, based upon their impact on lung function, they are unlikely to be the breakthrough therapy that was once envisaged.

3. What are the implications for research, policy, or practice?

Future research should consider alternative immunomodulatory strategies to treat this disease.

Background

Sarcoidosis is a systemic disease of unknown aetiology that is characterised by granulomatous inflammation which can develop in almost any organ system. The epidemiology of the disease remains poorly defined. Cases are reported worldwide in all races and sexes, although the incidence peaks in young adults and the disease is more frequent in people of black ethnicity.[1-3] Pulmonary involvement occurs in 90 per cent, with diffuse interstitial disease as the classical presentation.[4] Extra-pulmonary disease is seen in 30 per cent of patients, with cutaneous, ocular, reticuloendothelial, musculoskeletal, cardiac and neurological manifestations.[5]

There is no known cure for sarcoidosis. Most patients have asymptomatic non-progressive disease or experience spontaneous remission and thus do not require treatment. For those with more severe disease, treatment is aimed at reducing the burden of granulomatous inflammation and preventing organ damage.[6] Corticosteroids are the mainstay of therapy. In patients who do not respond to, or are intolerant of corticosteroids, a second-line therapeutic agent such as methotrexate or azathioprine is used.[7-11] The efficacy of current treatment regimens is poor, fostering interest in the use of new medications to treat the disease.

A number of biologic cytokine modulators are used effectively in the management of other inflammatory diseases, particularly inflammatory arthritis.[12-14] There are plausible mechanistic reasons to warrant study of targeted anti-cytokine therapy in sarcoidosis. Tumour necrosis factor alpha [TNFα] is a key inflammatory cytokine in the immunopathogenesis of sarcoidosis. Its production by monocytes and macrophages plays a pivotal role in the formation and maintenance of non-caseating granulomas. Interleukin [IL]-12 and IL-23 are upregulated in sarcoid lung tissue and skin lesions.[15,16] Increased IL-6 levels have been reported in bronchoalveolar lavage samples from patients with sarcoidosis[17] and IL-17 has been implicated in granuloma formation.[18]

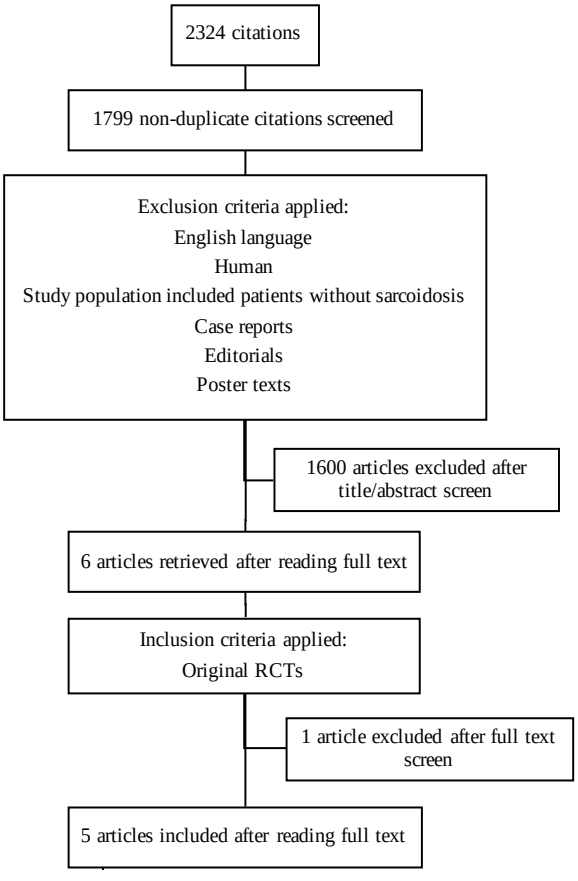
Biological therapies have been reported as being effective in the treatment of refractory organ-threatening sarcoidosis in case reports and small case series. However it is important to recognize that observational reports are limited by small numbers, publication bias and regression to the mean. Furthermore, a lack of validated outcome measures in sarcoidosis and the heterogeneity of the disease further confound these observational findings. This review aims to establish the evidence for the use of biologic agents in the treatment of sarcoidosis.

Method

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines. A comprehensive structured literature search was performed using the MEDLINE and Embase database and re-run prior to the final analysis to identify further studies that could be retrieved. The search items were: sarcoid, sarcoidosis, biologics, anti-TNF, infliximab, adalimumab, etanercept, golimumab, certolizumab, rituximab, abatacept, tocilizumab, anakinra, ustekinumab and secukinumab.

English language randomised-controlled trials [RCT] published between 1947 and September 2017 were sought. The reference lists were scrutinised to find additional pertinent trials. Cohort studies, case reports and conference abstracts were excluded. The quality of each trial was assessed using the Jadad score on a scale of 0–5.[19] A meta-analysis was performed evaluating the efficacy of TNFα inhibition in pulmonary sarcoidosis. The change in forced vital capacity [FVC] by weighted mean difference [WMD] was analysed using the available data provided. Analyses were performed using STATA version 14.

Figure 1: Flow chart of study selection process
Abbreviations: RCT = Randomised-controlled trial



Results

Literature search and study characteristics

The initial search strategy yielded a total of 2,324 articles for screening which was reduced to 6 after application of filters and screening of titles and abstracts. The search strategy is detailed in Figure 1. In total, 5 studies were original RCTs and eligible for inclusion. These were all randomised, double-blinded, placebo controlled trials, evaluating anti-TNFα inhibition. TNF inhibitors assessed included infliximab, a chimeric monoclonal antibody that blocks TNFα, adalimumab, a fully human monoclonal antibody that blocks TNFα, and etanercept, a recombinant human TNF receptor fusion protein that binds and inactivates TNF. Four studies were two arm trials whilst one study was a three-arm trial comparing TNFα, ustekinumab, and placebo. Ustekinumab is a monoclonal antibody that blocks IL-12 and IL-23. There were no RCTs examining other biological therapies.

Five studies were analysed [Table 1]. Of the five studies, two evaluated the efficacy of biological therapy in pulmonary disease, one in cutaneous disease, one in both pulmonary and cutaneous disease and the last in ocular involvement. The primary outcomes were the change in the percentage predicted FVC, the mean change in vital capacity [VC], the reduction in the Physician Global Assessment [PGA] skin score and the improvement in Ophthalmologist Global Assessment score. The number of patients included in the trials ranged from 18 to 173 and the mean age ranged from 46 years to 53 years.[15,20-23] The disease duration was reported in only 2 studies, ranging from a mean of 5.6 years to 9.8 years.[21,23] All included studies scored greater than 3 on the Jadad scale. The key points of each study are summarised in Table 1.

Key findings

There is limited data on the use of biologic agents in the treatment of sarcoidosis. Only one study demonstrated a significant benefit in treating cutaneous involvement with anti-TNF, with a significant reduction in the PGA score.[23] In pulmonary sarcoidosis, Baughman et al.[21] reported a statistically significant improvement in percentage predicted FVC with infliximab therapy, although no significant differences were observed for any of the major secondary endpoints. The remaining three studies did not report a significant benefit in their primary outcomes in both pulmonary and ocular disease.[15,20,22] The two positive RCTs were either of low quality or limited by small sample sizes. With this current evidence we are unable to conclude that there is a benefit with biological therapy in the treatment of sarcoidosis.

Etanercept

Baughman et al.[20] evaluated etanercept therapy in refractory ocular sarcoidosis. The intervention was 25mg of etanercept, or placebo, twice-a-week for six months. Eighteen patients with active ocular disease were included in the final analysis. Two out of nine patients in the treatment group and three out of nine patients in the control group met the primary endpoint, a change in Ophthalmologist Global Assessment score at six months, which was not significant. Visual acuity varied little during the study. Five patients required periocular injections [indicative of worsening disease] in the treatment group, compared to three patients with placebo. The study concluded that etanercept therapy did not result in a significant improvement in people with chronic ocular sarcoidosis.

Infliximab

The second study by Baughman et al.[21] assessed the efficacy of infliximab treatment in pulmonary sarcoidosis. One hundred and thirty-eight patients were enrolled, of which 133 completed the study. This was a three-arm trial in which participants were given placebo, 3mg/kg infliximab or 5mg/kg infliximab at weeks 0, 2, 6, 12, 18 and 24, and then followed up to week 52. The primary endpoint was the change in percentage predicted FVC at week 24. The secondary endpoints were the St George's Respiratory Questionnaire score, 6-minute walking distance [6-MWD], Borg's CR10 dyspnoea score and the proportion of Lupus Pernio PGA responders for patients with facial skin involvement. The results demonstrated a statistically significant improvement in the primary endpoint at week 24; 2.5 per cent improvement in percentage predicted FVC from baseline compared to no change in placebo group [p=0.038]. The improvement in the 3mg/kg group was similar to that in the 5mg/kg group. There was no treatment benefit in secondary endpoints and thus the clinical importance of the improvement in FVC is questionable.

Rossmann et al.[22] also assessed the efficacy of infliximab in pulmonary sarcoidosis. Nineteen people were enrolled, of which 16 completed the study. The intervention was 5mg/kg infliximab or placebo at weeks 0 and 2, followed by an open-label infusion of infliximab at weeks 6 and 14 for all study participants. The primary endpoint was the mean relative change in VC at six weeks. Secondary outcomes included spirometry, chest x-rays, levels of dyspnoea and health-related quality of life using SF-36. Both primary and secondary end points at six weeks were not met. The mean relative change in VC was higher in the infliximab group but this was not significant [15.22±9.91 per cent versus

8.39±3.33 per cent, *p*=0.65]. This may be a consequence of a loss in power from failing to meet the enrolment target of 42 patients.

Adalimumab therapy

Pariser et al.[23] assessed adalimumab in moderate to severe cutaneous sarcoidosis. Sixteen people were enrolled of which 12 completed the study. The study lasted 32 weeks and consisted of three phases [double-blind, open-label and washout]. The intervention was 80mg of adalimumab or placebo at week 0 followed by weekly 40mg adalimumab or placebo for 12 weeks, after which all participants were given open-label 40mg adalimumab weekly for a further 12 weeks. The primary outcome was defined by a PGA scale of the volume of cutaneous lesions of two or less at week 12. All participants were given a score of four at baseline. The secondary endpoints included; PGA of ≤3, PGA of 1 or 0, improvements in the area and volume of a selected target lesion, Dermatology Life Quality Index [DLQI] score, Sarcoidosis Health Questionnaire [SHQ] score, Patient Global Evaluation [PGE], and pulmonary function or radiographic findings if co-existing chest and bone involvement. At week 12, 50 per cent of participants in the adalimumab group achieved a PGA score of ≤2 compared to only 20 per cent in the placebo group, although this was not statistically significant. The only parameter that reached significance was target lesion size, with a 32 per cent reduction in area with adalimumab compared to a 54 per cent increase in the placebo group [*p*=0.02]. There was little change in pulmonary function tests. Results from the open-label phase demonstrated an improvement in several parameters compared to baseline, including a 35 per cent reduction in target lesion area [*p*<0.00], 38 per cent reduction in volume [*p*=0.02] and fall in DLQI score from 5.69 to 1.41 [*p*<0.00]. The authors concluded that adalimumab was an effective and relatively safe treatment for cutaneous sarcoidosis in this trial.

Golimumab and Ustekinumab therapy

Judson et al.[15] evaluated golimumab and ustekinumab in the treatment of pulmonary and cutaneous sarcoidosis. Of the 173 patients enrolled, 158 completed the study. Of these patients, 132 had pulmonary involvement and 58 had cutaneous disease. The intervention was either 200mg golimumab at week 0 followed by 100mg every four weeks until week 28, or 180mg of ustekinumab at week 0 followed by 90mg at weeks 8, 16 and 24, or placebo. The primary endpoint was the change in percentage predicted FVC at week 16. The secondary endpoints were FVC at week 28, 6-MWD, the St George's Respiratory Questionnaire; and the skin PGA score in patients with cutaneous disease. There was no statistically significant improvement in the primary endpoint or any major secondary endpoint in either treatment arms compared to placebo. For patients with pulmonary involvement who received oral corticosteroid at baseline, a greater proportion in the golimumab arm, but not the ustekinumab arm, were able to reduce their corticosteroid dose by at least 50 per cent during the taper-phase [golimumab 81.6 per cent, *p*=0.01; ustekinumab 57.9 per cent, *p*=0.63 compared with placebo 51.6 per cent]. In those with cutaneous involvement, there was a reduction in target lesion score [-2.3 versus -1.4, *p*=0.07] and a trend towards a greater PGA response [53 per cent responders *vs.* 30 per cent responders] with golimumab compared to placebo. The authors concluded that there was no significant benefit in golimumab or ustekinumab treatment for pulmonary sarcoidosis.

Meta-analysis of TNF inhibition in pulmonary sarcoidosis

Three studies evaluated the efficacy of TNF therapy in patients with pulmonary sarcoidosis, totalling 270 subjects [161 in TNF arm and 109 in the placebo arm]. Each study reported a different duration until primary outcome; 14 weeks, 28 weeks and 52 weeks. Two of these studies used change in the percentage predicted FVC as the primary outcome. The third study measured mean change in VC. Meta-analysis of change in FVC revealed a statistically significant WMD of 1.69 per cent [95 per cent confidence interval, 1.44-1.94] [Figure 2]. The minimal clinically important difference [MCID] for per cent-predicted FVC lies between 2 per cent and 6 per cent. Thus, although the overall benefit is statistically significant, the result falls below the MCID.[24] There was high heterogeneity between the results from these three trials, despite the entry criteria in the Judson trial[15] matching that of a subgroup in the Baughman trial.[21]

Adverse events

Four out of five studies reported on adverse events. In the infliximab study, Baughman et al.[21] reported serious adverse events in 23 per cent of the infliximab arm and 18 per cent of the placebo arm. Rossman et al.[22] reported serious adverse events in 31 per cent of the infliximab group compared to 17 per cent of the placebo group, with one death in the infliximab group caused by recurrent cellulitis and a pulmonary embolism. Pariser et al.[23] reported one serious adverse event, a pneumonia with adalimumab. Judson et al.[15] reported serious adverse events in 13 per cent and 17 per cent of the golimumab and ustekinumab arms respectively, compared to 16 per cent of the placebo group. Overall the most common event was respiratory tract infections.

Discussion

This systematic review has revealed little evidence to support the use of TNF inhibition in sarcoidosis. One study reported a significant improvement with TNF therapy in cutaneous disease. There was no benefit seen in ocular disease. Of the three studies evaluating chronic pulmonary sarcoidosis, only one reported a significant improvement in its primary endpoint. This improvement was not thought clinically relevant as all other secondary objectives were not met.

Adalimumab was effective in treating cutaneous sarcoidosis. This supports the results from previous studies, albeit not RCTs, which have shown success in therapy-resistant and chronic sarcoidosis.[25] However, the sample size in this study was small [n=16] and as such, a larger scale RCT is required to provide more evidence.

Etanercept therapy did not prove efficacious in the treatment of ocular sarcoidosis. This may be partly explained by the difference in its mechanism of action compared to anti-TNF monoclonal antibody therapy. Etanercept is a soluble form of the p75 TNF receptor and primarily binds only soluble TNFα, leaving membrane-bound TNFα partially intact. This may permit maintenance of the granuloma structure. Etanercept is not as effective in treating other granulomatous diseases such as Crohn's, whilst the risk of tuberculosis, an opportunistic granulomatous infection, is lower with etanercept therapy.[26,27]

In pulmonary sarcoidosis, our meta-analysis revealed a statistically significant improvement in FVC with TNF inhibition. However, there was high heterogeneity between the results from the three trials included, and whilst significant, the improvement in FVC fell below the MCID and is likely not clinically relevant. The only study to report a statistically significant benefit in FVC was by Baughman et al.[21] a 2.5 per cent improvement in percentage predicted FVC with infliximab. This falls at the lower limit of the MCID, with no improvement in all secondary endpoints.[21] The authors suggest this may relate to the inclusion criteria of stable pulmonary disease on background therapy, which may have diminished the response to infliximab therapy. Post-hoc exploratory analyses of patients with severe disease demonstrated greater improvements in FVC and 6-MWD.[21] Future trials in patients with more extensive lung involvement may be warranted to establish a potential threshold of disease progression after which infliximab is more effective. Rossmann et al.[22] reported a non-significant trend of improvement in VC at six weeks with infliximab. In the open-label extension, the entire cohort received a further two doses and improvement in VC continued, with the authors proposing that a longer duration of treatment may have led to more significant improvements. Judson et al.[15] reported no statistically significant improvement in percentage predicted FVC with golimumab. Sensitivity analysis suggested inefficacy may be related to an inadequate dose. There was greater FVC improvement in patients with higher golimumab trough levels. A trend towards an improved FVC in patients with a body mass index [BMI] less than 30 compared to the group with BMI greater than 30 was also reported.

More research in this area is warranted. The design of future trials evaluating TNF inhibition in sarcoidosis could consider inclusion of patients with more severe disease and ensure longer follow up. However, it is quite possible that if TNF inhibitors were effective in sarcoidosis, we would have observed a benefit. A wiser recommendation may be to direct research to other targeted therapy strategies including IL-17 and IL-6 inhibition or the use of Janus kinase inhibitors or anti-fibrotics. There are currently no RCTs looking at the efficacy of other cytokine blockers. IL-6 is thought to be involved in the initiation and maintenance of alveolitis. Increased levels of IL-6 are reported in bronchoalveolar lavage and have correlated with severity of disease and requirement for steroid therapy.[17,28] IL-17A has been implicated in granuloma formation with increased IL-17A expression and a greater proportion of circulating TH-17 cells.[18,29] There is abundant STAT1 expression in lymph node granulomas from patients with active disease, suggesting STAT1 might play an important role, thus, the interference of the JAK-STAT signalling pathway maybe a potential therapeutic target.

Conclusion

The question of whether biological therapy in sarcoidosis is effective cannot be answered with the current evidence. Whilst we cannot absolutely conclude that TNF inhibitors are not effective, based upon their impact on lung function, they are unlikely to be the breakthrough therapy that was once envisaged. Future research should consider alternative immunomodulatory strategies to treat this disease.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Table 1: Characteristics for studies included in systematic review

Name Year	No. of Pts	Country of study	Sex	Mean age ± SD [years]	Disease duration [years]	Target organ of therapy	Study design	Intervention	Duration [weeks]	Primary endpoint assessed	Result	Quality score
Baughman et al.[20] 2005	18	USA	M/F M=6%	Not stated	Not stated	Eye	RCT	Etanercept Placebo	28	Improvement in Opthalmologist global assessment score	Non-significant improvement; improvement seen in 2/9 etanercept v 3/9 placebo.	4
Baughman et al.[21] 2006	138	USA	M/F M=56%	Infliximab: 48 ± 9 Placebo: 45 ± 9	Infliximab: 7 ± 6 Placebo: 7 ± 6	Lung	RCT	Infliximab [3 or 5mg/kg] Placebo	52	Change in % predicted FVC compared to baseline	Statistically significant improvement; infliximab 2.5% v 0% placebo, p = 0.038	3
Rossman et al.[22] 2006	19	USA	M/F M=53%	Infliximab: 48 ± 2 Placebo: 49 ± 5	Not stated	Lung	RCT	Infliximab Placebo	14	Mean VC change compared to baseline	Non-significant improvement; infliximab 15 ± 10% v placebo 8 ± 3%, p = 0.65	3
Pariser et al.[23] 2013	16	USA	M/F M=20%	Adalimumab: 46 Placebo: 53	Adalimumab 9.8 Placebo: 5.6	Skin	RCT	Adalimumab Placebo	32	Physician Global Assessment score reduction	Non-significant improvement; adalimumab 50% PGA ≤2 v placebo 20% PGA ≤2	5
Judson et al.[15] 2014	173	USA	M/F M=51%	Golimumab: 50 ± 9 Ustekinumab: 50 ± 10 Placebo: 49.5 ± 9.5	Not stated	Lung & skin	RCT	Golimumab Ustekinumab Placebo	28	Change in % predicted FVC	Non-significant improvement; golimumab 1.15% p = 0.13 ustekinumab -0.15% p = 2.02 placebo 2.02%	5

Abbreviations: M = male, F = female, SD = standard deviation, RCT = randomised-controlled trial; FVC = forced vital capacity, VC = vital capacity

Figure 2: Forest plot of TNF inhibition in pulmonary sarcoidosis