REVIEW

Steroid-resistant sarcoidosis: is antagonism of TNF-α the answer?

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ABSTRACT

Steroid-resistant sarcoidosis has conventionally been treated with various drugs, including methotrexate, azathioprine, cyclophosphamide, cyclosporine, antimalarial drugs and thalidomide, with variable success. There is a compelling need for more efficient and safer alternatives to these agents. Several lines of evidence suggest a critical role of TNF-α (tumour necrosis factor-α) in the initiation and organization of sarcoid granulomas. Inhibition of TNF-α with monoclonal antibodies has therefore received attention as a potential treatment option in therapy-resistant sarcoidosis. A number of case reports and small case series describe successful treatment of refractory disease with infliximab. Preliminary evidence from an RCT (randomized controlled trial) with infliximab in pulmonary sarcoidosis suggests a modest improvement in functional and radiological parameters. In contrast, the results with etanercept have been disappointing, perhaps related to differences in the mechanism of TNF-α blockade. The experience with adalimumab in sarcoidosis is too limited to draw conclusions. An open-label study and an RCT evaluating the efficacy of adalimumab in sarcoidosis with pulmonary and cutaneous involvement respectively, have been initiated. Although TNF-α antagonists appear relatively safe, especially when compared with conventional agents, caution is warranted in view of the increased incidence of tuberculosis, which may be a particular diagnostic challenge in patients with sarcoidosis. Pending publication of the RCTs, the use of TNF-α blockade in sarcoidosis should remain in the realm of experimental treatment.

INTRODUCTION

Sarcoidosis is a multisystem disorder of unknown aetiology, most commonly occurring in young and middle-aged adults. The respiratory tract is usually affected, typically with bilateral hilar lymphadenopathy and pulmonary infiltrates [1]. Virtually any other organ system may be implicated, but the eye, skin and central nervous system are most commonly involved [2]. Spontaneous resolution of the disease is common, but progressive and disabling organ failure can occur in up to 10 % of patients. Corticosteroids are the agents of choice in the treatment of pulmonary sarcoidosis [1]. Therapy is initiated with relatively high doses of oral prednisone, usually 30–60 mg daily for the first 4–6 weeks. If the patient's condition is felt to be stable or improved, the dose is tapered by 5–10 mg decrements every 4–8 weeks to the lowest effective dose. Since relapses occur in approx. 60 % of patients, the

Key words: alveolar macrophage, inflammation, respiratory tract, sarcoidosis, steroid resistance, tumour necrosis factor-α (TNF-α).

Abbreviations: BAL, bronchoalveolar lavage; FDA, Food and Drug Administration; FVC, forced vital capacity; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; LPS, lipopolysaccharide; RCT, randomized controlled trial; SGRQ, St George's respiratory questionnaire; TNF, tumour necrosis factor; TNFR, TNF receptor; mTNFR, membrane TNFR; sTNFR, soluble TNFR.

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maintenance dose is continued for at least 6–8 months, resulting in a total treatment period of at least 1 year [2,3].

Patients with sarcoidosis occasionally cannot tolerate or do not respond to corticosteroids. Established second-line agents include methotrexate, azathioprine, cyclophosphamide, cyclosporin, (hydroxy)chloroquine and thalidomide. TNF-α (tumour necrosis factor-α) is known to play a critical role in diverse chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease and asthma. Recent evidence suggests that TNF-α may be essential for granuloma formation in sarcoidosis. TNF-α-blocking agents may, therefore, be promising therapeutic options in therapy-resistant sarcoidosis. In this review, we will briefly highlight the use of conventional agents in therapy-resistant sarcoidosis. Furthermore, we will discuss the extant experimental evidence supporting the rationale for TNF-α blockade in sarcoidosis. Finally, we will review the clinical results and reported side effects of TNF-α-blocking agents in therapy-resistant sarcoidosis.

CONVENTIONAL APPROACH TO STEROID-RESISTANT SARCOIDOSIS

Methotrexate is a folate analogue that inhibits dihydrofolate reductase, leading to depletion of tetrahydrofolate and inhibition of thymidylate synthesis, a step required for DNA replication in actively dividing cells. Methotrexate suppresses macrophage function, resulting in decreased TNF-α release in patients with sarcoidosis [4]. Several studies have demonstrated the value of methotrexate in patients with refractory disease and as a steroid-sparing agent [4]. Relapses are frequent after discontinuation of treatment, suggesting that methotrexate, similarly to other agents, suppresses but does not cure the disease [2,5]. When used in immunosuppressive doses, the most serious side effects are hepatic fibrosis and interstitial pneumonitis, which may result in pulmonary fibrosis. Other toxicities include bone marrow suppression, alopecia, skin rash, teratogenicity and gonadotoxicity [2,5]. Gastric discomfort is sometimes serious enough to mandate withdrawal. Toxicity of methotrexate can be reduced by the use of folate or folinate [6].

Azathioprine is rapidly hydrolysed in the blood to 6-mercaptopurine. 6-Mercaptopurine incorporates into DNA, inhibiting nucleotide synthesis by feedback inhibition in the early stages of purine metabolism. This ultimately prevents proliferation of rapidly dividing cells, such as activated B- and T-lymphocytes. The experience with azathioprine in sarcoidosis is limited. Small clinical trials have demonstrated that azathioprine has a potential role as a steroid-sparing agent, rather than as a single drug for treatment of pulmonary sarcoidosis [2,4,5]. Adverse effects include gastrointestinal discomfort, haematotoxicity, hepatotoxicity, increased risk of malignancy and teratogenicity [5].

Cyclophosphamide is metabolized in the liver into active alkylating metabolites, which inhibit lymphocyte proliferation. It decreases lymphocyte numbers and function, and may also have anti-inflammatory effects. It has been successfully used for the treatment of neurosarcoidosis and myocardial sarcoidosis in a limited number of patients [7,8]. Adverse effects include bone marrow suppression, haemorrhagic cystitis and bladder carcinoma, stomatitis, nausea, diarrhoea, hepatotoxicity, infertility and teratogenicity.

Cyclosporine is a calcineurin inhibitor, which exerts an inhibitory effect on T-cells. A few case reports have suggested beneficial effects on central nervous system sarcoidosis [9,10] and severe pulmonary sarcoidosis [11]. A randomized trial comparing prednisolone with or without concomitant cyclosporine therapy for progressive pulmonary sarcoidosis showed no significant difference between the two treatment groups [12]. Major adverse reactions are nephrotoxicity, hirsutism and hypertension. Caution is warranted in view of its extensive interactions with other drugs.

Chloroquine and hydroxychloroquine are antimalarial agents with immunomodulating properties that may act through inhibition of TNF-α production by macrophages [13]. They are used for the treatment of cutaneous sarcoidosis, but may also be effective in pulmonary sarcoidosis [14–16]. Ophtalmological follow-up is required for early detection of corneal lesions and irreversible retinopathy [5].

Thalidomide may also act through suppression of TNF-α production. It has proven useful for the treatment of chronic cutaneous sarcoidosis, yet its action in pulmonary sarcoidosis is less well described [17]. Adverse reactions include peripheral neuropathy, deep vein thrombosis, rash, toxic epidermal necrolysis, hypothyroidism, hepatitis and leucopenia. Its teratogenic potential is well known.

Pentoxifylline increases cAMP levels, resulting in a down-regulation of the *TNF* gene (previously known as *TNFA*) and consequently a lower production of TNF-α in mononuclear phagocytes [18]. In one small clinical trial, pentoxifylline showed promise as a steroid-sparing drug in progressive pulmonary sarcoidosis [19]. Side effects are primarily gastrointestinal in nature. Pancytopenia, toxic hepatitis, angina and hypotension occur more rarely.

RATIONALE FOR INHIBITION OF TNF-α IN SARCOIDOSIS

Sarcoid granulomas result from a specific cell-mediated immune response to an, as yet to be identified, antigenic

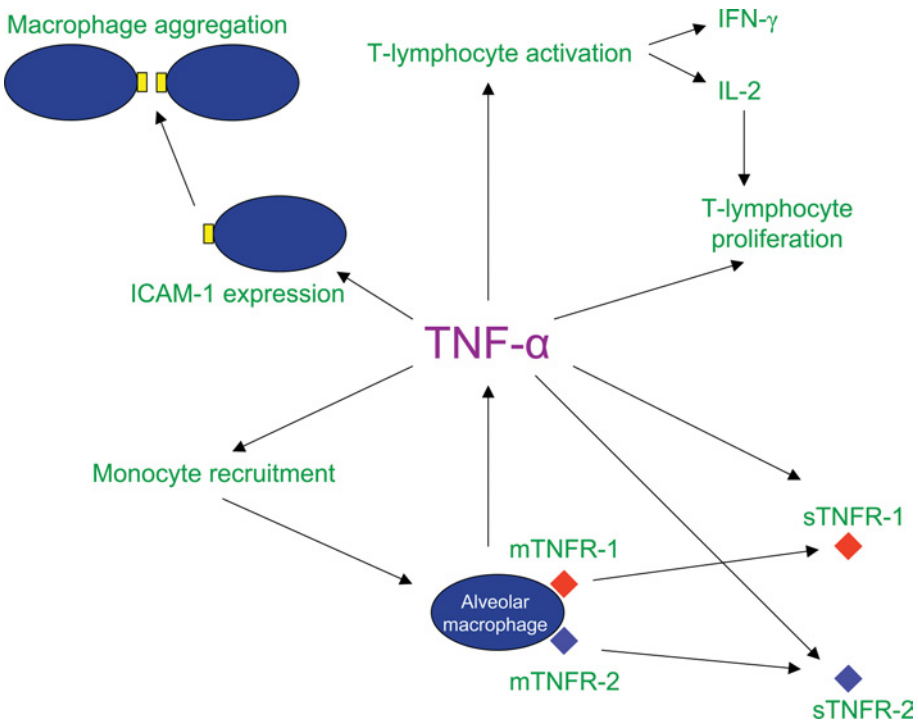

Figure 1 **Schematic representation of the effects of TNF-α in sarcoidosis**

agent. The granulomas have a tightly packed central follicle composed of macrophages, epithelioid cells and multinucleated giant cells surrounded by lymphocytes, monocytes, mast cells and fibroblasts. $CD4^+$ T-lymphocytes predominate within the follicle, whereas $CD8^+$ T-lymphocytes and B-lymphocytes are present mainly in the peripheral area. Numerous cytokines and other mediators are produced by both activated macrophages and T-lymphocytes during granuloma formation and maintenance [20].

There are several lines of evidence for a prominent role of TNF-α in sarcoid granuloma formation (Figure 1). Cultured alveolar macrophages retrieved from BAL (bronchoalveolar lavage) fluid in patients with active sarcoidosis spontaneously release high levels of TNF-α, indicating that these cells are activated *in vivo* [21]. Furthermore, levels of TNF-α produced by alveolar macrophages from patients with sarcoidosis are higher compared with healthy controls [22]. In transbronchial biopsies of patients with sarcoidosis, TNF-α co-localized with markers for macrophages (CD68), but not T-cells (CD3) and epithelial cells (cytokeratin), indicating that alveolar macrophages are the main source of TNF-α [23].

TNF-α exerts its biological activity through binding with two surface receptors expressed on a variety of cell types: mTNFR-1 and mTNFR-2 [membrane TNFR (TNF receptor) type I and type II respectively] [24]. Both receptors can be shed from the cell surface by proteolytic cleavage to form sTNFR-1 and sTNFR-2 (soluble TNFR-1 and -2 respectively), which can compete with mTNFRs. As such, they function as natural antagonists of TNF-α; however, at low concentrations, sTNFRs can enhance the effects of TNF-α by stabilizing its structure. In patients with active sarcoidosis, the production of sTNFR-1 and sTNFR-2 by alveolar macrophages is increased concomitant with TNF-α production [25]. The enhanced production of sTNFRs may serve to inhibit excessive TNF-α activity. A recent study [25] demonstrated an up-regulated expression of mTNFR1 on the alveolar macrophage surface in patients with sarcoidosis.

Ligand engagement results in the activation of intracellular signalling processes that lead to a diverse set of cellular responses, including differentiation, activation, release of pro-inflammatory mediators and apoptosis [26]. TNF-α may mediate the recruitment of peripheral blood monocytes to the alveolar spaces through the enhanced release of pro-inflammatory and chemotactic mediators [27]. Transgenic mice unable to respond to TNF-α, by virtue of increased expression of an sTNFR-1 fusion protein, had a marked inhibition of macrophage differentiation within granulomas during mycobacterial infection [28]. These results are in line with the finding that TNF-α up-regulates ICAM-1 (intercellular adhesion molecule-1) expression on the surface of alveolar macrophages *in vitro*. ICAM-1 plays a role in aggregation of alveolar macrophages and granuloma formation [27].

Several polymorphisms in the *TNF* gene have been associated with specific forms of sarcoidosis, although the

Table 1 Reports on the treatment of sarcoidosis with infliximab

?, unknown.

Authors	Study type	Organ(s) involved	Patients treated (*n*)	Patients responding (*n*)
Katz et al. (2003) [39]	Case report	Optic nerve	1	1
Pettersen et al. (2002) [40]	Case report	Brain	1	1
Meyerle and Shorr (2003) [41]	Case report	Skin and lung	1	1
Mallbris et al. (2003) [42]	Case report	Skin	1	1
Haley et al. (2004) [43]	Case report	Skin	1	1
Menon et al. (2004) [44]	Case report	Kidney	1	1
Fouchier et al. (2004) [45]	Case report	Lung	1	1
Ulbricht et al. (2003) [46]	Case report	Multi-organ	1	1
Roberts et al. (2003) [47]	Case report	Multi-organ	1	1
Yee and Pochapin (2001) [48]	Case report	Intestine and muscle	1	1
Baughman and Lower (2001) [49]	Case series	Skin ($n = 2$), lung ($n = 1$)	3	3
Pritchard and Nadarajah (2004) [50]	Case series	Eye ($n = 2$), lung ($n = 2$) and multi-organ ($n = 1$)	5	5
Doty et al. (2005) [51]	Case series	Skin, lung, liver, bone and muscle	10	10
Baughman et al. [51a]	RCT	Lung and possibly other organs involved	138	?

significance of these findings remains unclear. Seitzer et al. [29] examined polymorphisms in the *TNFA* gene (now known as *TNF* and encoding TNF-α) and the *TNFB* gene [now known as *LTA* and encoding lymphotoxin-α (TNF-β)]. Although their overall distribution was not different between patients with sarcoidosis and controls, the more uncommon *TNFA2* allele was significantly more frequent in the patients with Löfgren syndrome [29]. Furthermore, the *TNFA2* allele was more frequently present in Japanese patients with cardiac sarcoidosis than in healthy subjects [30]. However, spontaneous and LPS (lipopolysaccharide)-induced TNF-α release in BAL cells and peripheral mononuclear cells was not different between TNFA2 allele carriers and non-carriers with sardoidosis [31], questioning the clinical relevance of this polymorphism. The allele frequency of the rarer *TNF* − 857T allele, a *TNF* promoter polymorphism, was increased in Dutch and British patients with sarcoidosis [32]. The *TNF* promotor polymorphism at position −307 was more frequent in the subgroup of patients presenting with classic Löfgren syndrome [32].

Finally, conventional drugs used to treat sarcoidosis may partially or predominantly act through inhibition of TNF-α. A 4-month course of azathioprine and prednisolone was associated with significant clinical improvement and normalization of initially elevated TNF-α release in BAL fluid in patients with pulmonary sarcoidosis [33]. A total of 6 months of therapy with corticosteroids or methotrexate resulted in a significant reduction of TNF-α in BAL fluid corresponding with an improvement in vital capacity [34]. The spontaneous release of TNF-α by alveolar macrophages recovered from patients with sarcoidosis was dose-dependently suppressed *in vitro* by pentoxifylline [35]. LPS-induced TNF-α production by alveolar macrophages from patients with tuberculosis, lung cancer or chronic bronchitis was significantly reduced after the *in vitro* addition of thalidomide [36]. Chloroquine also reduced LPS-induced TNF-α release from peripheral monocytes/macrophages [37].

Taken together, these findings suggest that TNF-α may play a critical role in the pathogenesis of sarcoidosis and bolster the concept that the inhibition of TNF-α may be a key target for therapy. Several drugs have been specifically designed to inhibit the activity of TNF-α. Etanercept, infliximab and adalimumab are monoclonal antibodies directed against human TNF-α. These agents have represented major breakthroughs in the treatment of rheumatoid arthritis and Crohn's disease. Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding domain of the human TNFR linked to the Fc portion of human IgG_1. Etanercept acts as a sTNFR and thus inhibits the binding of TNF-α to its surface receptors [38]. It also binds a related molecule lymphotoxin-α (TNF-β) [24]. Infliximab is a chimaeric monoclonal anti-(TNF-α) antibody, composed of human constant and murine variable regions. Infliximab binds free TNF-α as well as cell-surface TNF-α in some situations [38]. Adalimumab is a recombinant human monoclonal anti-(TNF-α) antibody, with human-derived heavy- and light-chain variable regions and human IgG_1:κ constant regions.

CLINICAL RESULTS OF TNF-α ANTAGONISTS IN THERAPY-RESISTANT SARCOIDOSIS

Infliximab

Several case reports and a few case series on the use of infliximab for therapy-resistant sarcoidosis have been published and are summarized in Table 1.

Katz et al. [39] reported a case of progressive neurosarcoidosis with optic atrophy and visual loss despite

conventional treatment. Treatment with infliximab maintained functional vision in this case. Pettersen et al. [40] described a patient with neurosarcoidosis refractory to prednisone, azathioprine, methotrexate, hydroxychloroquine, chloroquine and cyclosporine, who responded to infliximab with improvement in cognition, behaviour and motor functioning. Meyerle and Shorr [41] reported complete resolution of cutaneous disease with stabilization of pulmonary symptoms after initiation of infliximab in a patient with cutaneous and pulmonary sarcoidosis treated previously with steroids. Mallbris et al. [42] described a case of therapy-resistant cutaneous sarcoidosis, with complete biopsy-proven regression of the dermal granulomas after combination therapy with infliximab and methotrexate. Another patient with refractory disfiguring skin disease, despite numerous systemic treatments, rapidly improved after initiation of infliximab [43]. Menon et al. [44] reported a patient treated with IFN-α (interferon-α) for hepatitis C infection, who developed hypercalcaemia and renal insufficiency as clinical manifestations of IFN-α-associated sarcoidosis. Prednisone effectively controlled hypercalcaemia, but had to be discontinued due to an increase in hepatitis C viral RNA count. Infliximab induced a rapid and persistent decline in serum calcium [44]. Another patient with refractory pulmonary sarcoidosis was successfully treated with infliximab [45]. Salvage therapy with infliximab resulted in improvement of arthritis, liver and pulmonary disease in a patient with multi-organ sarcoidosis [46]. Another case of multi-organ sarcoidosis, including pulmonary, cutaneous, ocular and cardiac involvement, refractory to conventional treatment was described by Roberts et al. [47]. After treatment with infliximab, cardiac conduction abnormalities improved, while lung function remained stable [47]. A patient with protein-losing enteropathy and proximal myopathy was successfully treated with infliximab, but the clinical course was complicated by the development of a hypercoagulable state associated with circulating anticardiolipin antibodies, which prompted the discontinuation of infliximab [48].

Baughman and Lower [49] reported two patients with lupus pernio and one with pulmonary sarcoidosis, with persistent symptoms despite corticosteroids and immunosuppressive agents, but successful outcome after infliximab. Pritchard and Nadarajah [50] described a case series of five patients with biopsy-proven and therapy-resistant sarcoidosis. Treatment with infliximab led to significant favourable effects in the absence of serious adverse effects. Doty et al. [51] reported ten patients with sarcoidosis of the skin, bone, liver, lung or muscle, resistant to conventional therapy. Nine patients experienced subjective improvement, and in all ten objective evidence of improvement was recorded either on physical examination, laboratory values or imaging studies. The adverse events were a skin eruption, oral candidiasis and the development of an angio-immunoblastic lymphoma.

So far, only one RCT (randomized controlled trial) evaluating the use of infliximab in chronic sarcoidosis with pulmonary involvement has been reported [51a]. Adult patients with histologically proven sarcoidosis, evidence of parenchymal disease on chest X-ray (stage II–III), onset at least 1 year prior to screening, FVC (forced vital capacity) between 50 and 85 % of the predicted value, Medical Research Council dyspnea score of at least grade 1 and treatment with at least 10 mg of prednisone/day or one or more immunosuppressants for at least 3 months prior to inclusion were enrolled. Patients ($n = 138$) were randomized to receive placebo or infliximab at 3 or 5 mg/kg of body weight at weeks 0, 2, 6, 12, 18 and 24. The primary end point was the change in percentage FVC at week 24. Secondary end points included SGRQ (St George's respiratory questionnaire) total score, 6-min walking distance and Borg's CR10 dyspnea score. At week 24, FVC remained unchanged in the placebo group, whereas it increased by 2.8 ± 1 % in the group receiving 3 mg/kg of body weight ($P = 0.04$ compared with placebo), 2.2 ± 1 % in the group receiving 5 mg/kg of body weight ($P = 0.12$ compared with placebo) and 2.5 ± 1 % in both groups combined ($P = 0.04$ compared with placebo). In the groups receiving 3 and 5 mg of infliximab/kg of body weight, 13.6 % and 10.8 % of patients respectively, had a clinically meaningful change in FVC (i.e. at least 10 %) compared with 4.36 % in the placebo group. Chest X-ray score changed substantially at week 24 in treated patients compared with the placebo group (mean change, -1.04, -0.85 and -0.94 in the groups receiving 3 and 5 mg of infliximab/kg of body weight and in both groups combined respectively; $P = 0.001$, 0.016 and 0.001 respectively, compared with placebo). There were no differences in SGRQ total score, 6-min walk distance or Borg's CR10 dyspnea score. As is often the case, the results of this RCT are sobering in view of the expectations raised by the earlier case reports. Nevertheless, the small benefit obtained after 6 months may be clinically more significant if it could be extended over prolonged periods, since the decay of pulmonary function in sarcoidosis generally spans many years.

Etanercept

One case report [52] has described the amelioration of therapy-resistant sarcoidosis with arthritis and skin disease after addition of etanercept (Table 2). In a separate study [53], 18 patients with ocular sarcoidosis and ongoing inflammation of the eyes, who had received at least 6 months of methotrexate and corticosteroid treatment, were randomized to receive either etanercept or placebo. The global ophthalmological assessment improved for two of the etanercept-treated patients and three of the placebo-treated patients. The authors [53]

Table 2 Reports on the treatment of sarcoidosis with etanercept

Authors	Study type	Organ(s) involved	Patients treated (*n*)	Patients responding (*n*)
Khanna et al. (2003) [52]	Case report	Skin and joint	1	1
Baughman et al. (2005) [53]	RCT	Eye	18	2
Utz et al. (2003) [54]	Open label trial	Lung	17	5

Table 3 Reports on the treatment of sarcoidosis with adalimumab

Authors	Study type	Organ involved	Patients treated (*n*)	Patients responding (*n*)
Philips et al. (2005) [55]	Case report	Skin	1	1
Callejas-Rubio et al. (2005) [56]	Case report	Multi-organ	1	1

concluded that etanercept was not associated with any significant improvement. In a prospective open-label phase II trial, 17 patients with biopsy-proven progressive stage II or III pulmonary sarcoidosis were treated with etanercept. The effect of therapy was evaluated by chest X-rays, dyspnea scores and pulmonary function tests. A total of 16 patients completed the treatment phase. Eleven patients did not respond to therapy, as shown by a deterioration in the radiographical findings and pulmonary function. Among the five patients who responded to therapy, none had a uniform improvement of all parameters. None of the baseline characteristics predicted whether patients would respond to therapy. In particular, the basal level of total TNF-α or TNF-α bioactivity in serum or BAL fluid, or released from cultured alveolar macrophages, failed to predict the subset of patients who had favourable responses. Interestingly, at 6 months the serum level of TNF-α had increased significantly and did not differ consistently between responders and non-responders. The study was terminated because of excessive treatment failures. In addition, two serious adverse events occurred. One patient developed an intestinal lymphoma and in another patient a nasopharyngeal extramedullary plasmacytoma was discovered. Utz et al. [54] concluded that their data did not support the design of a large multicentre randomized trial comparing etanercept with conventional corticosteroid therapy.

Adalimumab

Philips et al. [55] reported a case of ulcerative cutaneous sarcoidosis responding to adalimumab (Table 3). Another case report [56] described successful treatment of therapy-resistant multi-organ sarcoidosis with adalimumab. A non-randomized open-label uncontrolled study evaluating the efficacy and safety of adalimumab in progressive sarcoidosis is currently recruiting patients (Clinical Trials.gov Identifier: NCT00311246; http://www.clinicaltrials.gov). A randomized, placebo-controlled trial has been set up to evaluate the effect of adalimumab in the treatment of sarcoidosis of the skin (Clinical Trials.gov Identifier: NCT00274352).

ADVERSE REACTIONS ASSOCIATED WITH ANTI-(TNF-α) THERAPY

Opportunistic infections

The main risk of the use of infliximab is reactivation of tuberculosis. Keane et al. [57] analysed all reports of tuberculosis associated with infliximab therapy that had been received as of May 2001 through the MedWatch spontaneous reporting system of the FDA (Food and Drug Administration). Among approx. 147 000 patients treated with infliximab at that time, 70 cases of tuberculosis were reported. The reported frequency of tuberculosis in association with infliximab therapy was much higher than that of other opportunistic infections. Although the numbers of patients who have been exposed to etanercept and infliximab are similar, only nine cases of tuberculosis in patients treated with etanercept have been reported to the FDA. This discrepancy may reflect the different ways in which the two agents antagonize TNF-α. Adalimumab has also been associated with reactivation of tuberculosis [58]. The occurrence of tuberculosis observed after anti-(TNF-α) treatment may be due to the failure of granulomas to compartmentalize viable *Mycobacterium tuberculosis* bacilli, but the underlying mechanism is unclear [57]. The diagnosis of tuberculosis in patients with sarcoidosis is a challenge. First, a negative tuberculin test does not rule out latent infection, as the disease as well as preceding treatments can be responsible for a false-negative test. Secondly, the pulmonary manifestations of tuberculosis can be difficult to distinguish from sarcoid lesions.

The risk of *Listeria monocytogenes* infection appears to be increased similarly, although all reported patients with *Listeria* infection associated with infliximab (14 cases) or etanercept (one case) were receiving concurrent immunosuppressive drugs [59]. Infections with

Pneumocystis carinii and *Aspergillus* can also occur [60]. Reactivation of histoplasmosis has been described [61]. Infliximab can induce an exacerbation of Whipple's disease [62].

Immunological disorders

From the date of approval of each agent to September 2002, the FDA received several reports of leucocytoclastic vasculitis associated with etanercept (20 cases) or infliximab (15 cases). Skin lesions improved on discontinuation of anti-(TNF-α) therapy in most patients [63]. Serum sickness has been described in patients receiving infliximab for the treatment of Crohn's disease [64]. A prospective study has shown that infliximab induced anti-nuclear, anti-(double stranded DNA) and anti-phospholipid antibodies in several patients treated for rheumatoid arthritis and ankylosing spondylitis, but no relationship with clinical manifestations was observed [65]. However, a French retrospective national survey provides evidence of infliximab- and etanercept-induced systemic lupus erythematosus [66]. Shakoor et al. [67] have also reported four patients with etanercept-induced systemic lupus erythematosus. One case of a delayed hypersensitivity reaction and eosinophilic pneumonia with high titres of anti-chimaeric antibodies following infliximab infusion has been described [68]. Infliximab has also been associated with aseptic meningitis without induction of functional anti-chimaeric antibodies [69]. Agranylocytosis associated with anti-granulocyte and anti-neutrophil antibodies has been described [70].

Malignancy

The development of malignancy is an issue given the immunosuppressive nature of TNF-α antagonists. Current data suggest a higher rate of lymphomas, mostly non-Hodgkin's lymphomas, in patients receiving TNF antagonists [60]. The number of solid tumours observed during treatment with etanercept and infliximab in clinical trials was comparable with the age-, sex- and race-matched cohort obtained from the Surveillance, Epidemiology and End Results Database of the National Cancer Institute in the U.S.A. [60].

Various adverse reactions

The TNF-α antagonists infliximab and etanercept may induce new-onset heart failure or exacerbate existing disease [71]. Despite the fact that recent reports [72,73] document the efficacy of infliximab in the treatment of pustular psoriasis, this same disorder has been described as a paradoxical adverse reaction to infliximab.

CONCLUSIONS AND FUTURE PROSPECTS

Ample circumstantial evidence implicates TNF-α in the pathogenesis of sarcoidosis, but its precise role remains unresolved. The disparity between the promising effects of infliximab and the disappointing results obtained with etanercept is intriguing and underscores the complex role of TNF-α in inflammation in general and in sarcoidosis in particular. Whole-animal experiments may be ancillary for a better understanding of the pathophysiology of granuloma formation and the precise role of TNF-α in this intricate process. Unfortunately, at present, no reproducible animal model of sarcoidosis is available.

In several cases and series of patients with severe sarcoidosis, often resistant to multiple agents, treatment with infliximab (and adalimumab in two instances) has yielded promising results. These have set the stage for the phase II trials with these agents in patients not responding to corticosteroids alone. These trials are currently recruiting patients or have been completed recently. If monoclonal anti-(TNF-α) antibodies prove to be effective, it remains to be seen how they compare with the older second-line agents used in sarcoidosis. Sadly enough, none of these have been the object of well-controlled trials. It is our view that methotrexate and pentoxifylline [74], both cheap and relatively safe, have sufficient potential to warrant further investigation.

As for any immunosuppressive agent, safety considerations remain an issue. As a logical extrapolation of their mechanism of action, TNF-α antagonists are associated with an increased incidence of opportunistic infections that require protective granuloma formation for clearance. Clinicians will need to assess the potential benefits of TNF-α blockade in each individual patient and weigh up the importance of a therapeutic response against the obvious dangers of a missed diagnosis of tuberculosis.

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