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Inhibitors of Tumor Necrosis Factor (TNF) in Sarcoidosis: Who, What, and How to Use Them

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Abstract. Sarcoidosis patients with chronic disease often require prolonged treatment. Although alternatives to corticosteroids have been frequently administered in this disease, corticosteroids remain the mainstay of treatment. However disabling side effects which accompany prolonged treatment can necessitate the use of alternative, steroid-sparing agents. The tumor necrosis factor (TNF) inhibitors can be useful in treating chronic sarcoidosis. Among the biologic agents which inhibit TNF, infliximab has been studied most extensively in sarcoidosis with fewer reports available for adalimumab and etanercept. This review will summarize the available evidence to identify the best candidate to receive an anti-TNF regimen as well as the relative benefits and side effects of the three anti-TNF biological agents for treating sarcoidosis. A stepwise approach is proposed to improve the likelihood of disease improvement for patients who experience an inadequate response to an anti-TNF agent. *(Sarcoidosis Vasc Diffuse Lung Dis 2008; 25: 76-89)*

Key words: sarcoidosis, infliximab, adalimumab

I. Introduction

The use of biologic agents which block tumor necrosis factor-alpha (TNF) can provide effective treatment for the diverse manifestations of sarcoidosis (1, 2). Treatment strategies with anti-TNF agents are evolving as more data and experience are available for patients with a variety of diseases including rheumatoid arthritis, Crohn's disease, and sarcoidosis.

Three major anti-TNF agents are approved for use in rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis (3-6). The main reason to use them is the anti-inflammatory effect. In rheumatoid arthritis infliximab also demonstrated a reduction of oxidative stress markers (7).

Many published reports tout the efficacy of infliximab for the treatment of sarcoidosis. In addition to isolated case reports and series, two double blind randomized trials have been published showing benefit for infliximab in chronic pulmonary sarcoidosis. One additional study showed no effectiveness for another anti-TNF agent (8-13). Both etanercept and adalimumab have also been reported useful in treating sarcoidosis (2, 14-16). In this review, we will discuss the issues surrounding the use of anti-TNF agents in sarcoidosis. Specifically we will concentrate on who is an appropriate candidate for therapy, how

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the drugs should be prescribed and monitored, and what options exist for patients with inadequate responses.

II. Systemic Treatment Options in Sarcoidosis

A. Indications and Drug Options

Failure of patient response to conventional therapy or the presence of unacceptable side effects from other available drugs, especially prednisone (17) constitute the most common reasons for prescribing an anti-TNF agent for sarcoidosis. At the time of initial sarcoidosis diagnosis, the major treatment decision centers around whether to prescribe corticosteroids (1). In general the decision to treat or not is guided by the presence of functional impairment particularly pulmonary or cardiac involvement, neurosarcoidosis, or hypercalcemia (18). In contrast to many other disorders, the presence of active inflammation does not always indicate poor prognosis (19) and not every sarcoidosis patient requires medical treatment (1). Some conditions, such as neurologic and cardiac involvement, are frequently associated with chronic disease for which steroid sparing agents are often prescribed at initial evaluation (20, 21). In addition patients who present with significant respiratory impairment frequently require long term therapy. In these cases to minimize corticosteroid usage and toxicity, one might consider concurrent usage of a steroid sparing agent, such as methotrexate, with corticosteroids (22).

Figure 1 summarizes an approach to systemic therapy in sarcoidosis patients (1, 23). When systemic therapy is considered, corticosteroids remain the first choice (24, 25). Hydroxychloroquine can be beneficial for some manifestations, such as cutaneous disease and hypercalcemia (26-28). However, it has not been as effective for pulmonary disease as cytotoxic agents (23, 29). Methotrexate has been the most widely studied cytotoxic drug for sarcoidosis (20, 30-32). Other cytotoxic agents, including azathioprine and leflunomide, have been reported efficacious in smaller case series (33, 34). Despite these agents, a group of patients will experience persistent disease for which an anti-TNF agent, such as infliximab, should be considered.

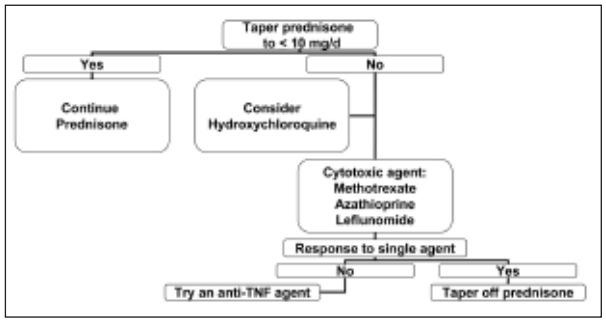

Fig. 1. Approach to patient requiring systemic therapy for sarcoidosis. Adapted from Baughman et al (1)

B. Anti-TNF Agents: Types and Mechanism of Action

Three biological agents with anti-TNF activity are commercially available. Although all three drugs are classified as anti-TNF inhibitors, the mechanism of action and route of administration vary among the three drugs. As noted in Table 1, both infliximab and adalimumab are monoclonal antibodies targeted against TNF-alpha. In contrast, etanercept is a direct TNF receptor antagonist. Differences in routes of administration can in part explain differences in onset and duration of action and side effects. Although all three drugs have proven efficacy in rheumatoid arthritis and psoriasis, responses have varied by drug type in Crohn's disease. Future sections will discuss specific dosing, onset of action, response rates, and side effects for each anti-TNF agent administered in sarcoidosis.

C. Side Effects of Anti-TNF Therapy

The side effects of anti-TNF agents include medication reactions such as anaphylaxis to infliximab as well as local reactions to etanercept or adalimumab (35). In addition, all three agents are associated with increased risks for opportunistic infections, especially tuberculosis (36). This risk is higher for infliximab than for etanercept, but it has been reported with prolonged use of all three agents (36-38). An increase in other granulomatous infections, such as deep seated fungal infections (39), and bacterial infections (40, 41) can also be encountered.

Screening for prior tuberculous infection with a detailed history and PPD is required prior to administering anti-TNF therapy. Although a PPD test is recommended, many patients with sarcoidosis will

Table 1. Biological Agents with anti-TNF Activity

Drug	Mechanism of Action	Administration	Effectiveness			
			Rheumatoid Arthritis	Crohn's Disease	Psoriasis	Sarcoidosis
Etanercept	TNF receptor antagonist	Subcutaneous	Yes	No	Yes	No
Infliximab	Chimeric monoclonal antibody	Intravenous	Yes	Yes	Yes	Yes
Adalimumab	Humanized monoclonal antibody	Subcutaneous	Yes	Yes	Yes	Insufficient Information

be anergic. Use of antigen-specific gamma interferon enzyme linked immunoassay is more specific than tuberculin skin testing in immunosuppressed patients (42). Latent tuberculosis is a relative contraindication to anti-TNF therapy since chemoprophylaxis in patients with latent tuberculosis may not prevent emergence of active tuberculosis during anti-TNF therapy (43).

Worsening congestive heart failure has been reported with anti-TNF therapy (44). This side effect appears to be a class effect as it has been reported with both etanercept and infliximab (45). Another complication while on anti-TNF therapy can be the onset of demyelinating disease (46-48). This side effect can be very confusing as optic neuritis (49) can be a manifestation of sarcoidosis which has been treated successfully with infliximab (50, 51).

Antibody formation

Although the benefit/risk ratio for infliximab is positive, of particular concern has been the problem of immunogenicity ascribed to the chimeric properties of the drug. Antibody formation is associated with allergic reactions and loss of response. Infusion reactions are important immunologic events induced by the presence of a substantial concentration of antibodies against infliximab in the serum. Concomitant immunosuppressive treatment may optimize response to infliximab by preventing the formation of antibodies (5). Steroid administration prior to an infliximab infusion can further reduce the immunogenicity. Probably the most effective strategy to optimize treatment and avoid immunogenicity is maintenance therapy. If infliximab therapy can be discontinued is yet unclear but when treatment goals have been reached, we feel this should be attempted. In the case of relapse, infliximab should be restarted as maintenance long term. Practical guidelines on how to handle the problem of immunogenicity to infliximab are important for clinicians treating patients with infliximab (52).

Serum antibodies against adalimumab appeared to be present is 17% of rheumatoid arthritis patients treated with adalimumab. Concomitant methotrexate use was lower in the group with anti-adalimumab antibodies (52%) than in the group without antibodies (84%). Serum antibodies against adalimumab are associated with lower serum adalimumab concentrations and non-response to adalimumab treatment. So also in case of adalimumab a combination with low dose methotrexate is more effective than adalimumab alone. Therefore, a combination of both is recommended (53, 54).

Anti-TNF therapy can be responsible for autoimmune reactions, including systemic lupus erythematosis (55, 56). In one systematic review, 92 cases of lupus erythematosis were identified after anti-TNF therapy (56). Based on the overall usage of the drugs, no significant difference exists in the incidence rate among the three agents.

An increased rate for malignancy, including lymphoma, as been reported with infliximab therapy in Crohn's disease patients (48, 57). Interesting, this increased risk was not observed in rheumatoid arthritis patients (58). Other studies have reported an increased proportion of solid malignancies in patients treated with anti-TNF therapy (59, 60). Overall, an increased risk for malignancy seems likely, but the relative risk remains unclear.

Interestingly, there are several isolated reports of granulomatous disease consistent with sarcoidosis developing in a patient receiving anti-TNF therapy. Although most of these have been while the patient is receiving etanercept (61-63), there is one well documented case of a patient receiving infliximab (64). These reports highlight the complex inflammatory reaction in sarcoidosis and reinforce that treatment against only TNF may permit other inflammatory reactions to occur unchecked (65). Therefore, in the patient failing anti-TNF therapy, one should always consider stopping treatment.

III. Identification of Sarcoidosis Candidates for Anti-TNF Therapy

A. Severity of Illness: Randomized Pulmonary Trials

Current available information helps to identify patients that can benefit from anti-TNF therapy. A recent placebo controlled trial randomized 135 chronic pulmonary sarcoidosis patients to receive either placebo or infliximab at either 3 mg/kg or 5 mg/kg doses (9). In that trial patients were evaluated at week 24 after completing five treatments with infliximab or placebo. All patients in this trial were receiving concomitant corticosteroids or immunosuppressive therapy, with over 90% of the patients on corticosteroids either alone or with other immunosuppressants. In all three groups the average dose of prednisone exceeded 10 mg daily. Infliximab was beneficial for the treatment of pulmonary disease. The primary end point of the study, a change in the forced vital capacity (FVC) after 24 weeks of therapy, was achieved. A significant improvement in FVC was reported with an absolute value of 2.5% for the infliximab treated patients compared to the placebo-treated patients.

Subgroup analysis identified populations which were more likely to respond to therapy (Figure 2) (9). Disease features predicting response included the level of dyspnea, pulmonary quality of life, and the disease duration. The median baseline predicted FVC was 69 percent. Patients experiencing more severe impairment or longer disease duration were more likely to respond to infliximab therapy. For patients with more severe disease, the improvement in FVC exceeded 3% and all FVC percentages were significantly higher than placebo treated controls (9).

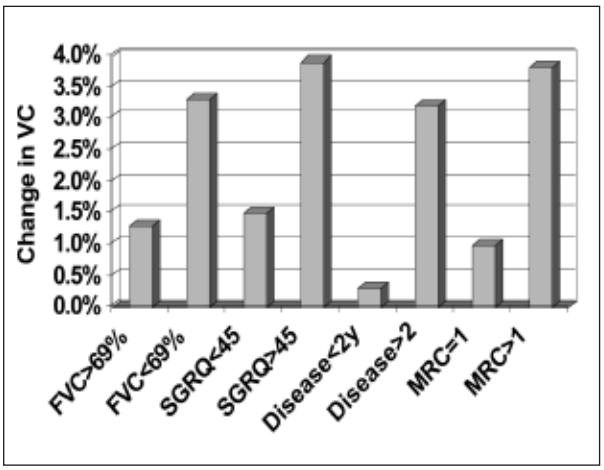

Fig. 2. The change in forced vital capacity (FVC) for infliximab versus placebo treated patients at 24 weeks. Analysis was performed looking at predefined parameters which reflected level of respiratory impairment: FVC above and below FVC of 69% (median for the study); above or below a Saint George Respiratory Questionnaire (SGRQ) score of 45 (median for the study), with the higher score indicating more severe impairment; presence of disease for more or less than two years; and a level of dyspnea using the Medical Research Council (MRC) scale of one to four, with four being the most impaired. Patients with more severe or longer disease had a larger response to infliximab therapy ($p<0.05$ compared to placebo for all four comparisons) (9).

The observation that more significant improvement occurred in those with patients with lower initial vital capacities was supported by another randomized trial by Rossman et al (10). In this smaller trial a 6% improvement in the absolute vital capacity was reported for the infliximab treated group. The median FVC was less than 59 percent for the infliximab treated patients compared to 65 percent for the placebo treated patients. These reported differences are not statistically significant; however, this study was relatively small and underpowered to detect a less than 10 percent difference between the groups. This larger response reported in more impaired patients supports the concept that the more severe the disease, the more likely the patient will respond to therapy.

B. Laboratory Data: C-reactive Protein

Reports suggest that C-reactive protein (CRP) can predict response to infliximab therapy in rheumatoid arthritis, ankylosing spondylitis, Crohn's

disease, and psoriatic arthritis (66-70). In the infliximab trial by Baughman et al, response rates were analyzed according to CRP values with the cut-point of 0.8 mg/dl (71). Approximately one-third of sarcoidosis patients had CRP values greater than 0.8 mg/dl. This frequency mimics that reported for sarcoidosis patients diagnosed in Finland, Japan or the Netherlands (72-74). In sarcoidosis patients with an elevated CRP, treatment with infliximab was associated with a greater improvement in the vital capacity, six-minute walk distance, and physician global assessment scores.

C. Extrapulmonary Disease

Although most of the data assessing infliximab efficacy in sarcoidosis evaluates pulmonary patients, case reports and series suggest that anti-TNF therapy may be effective in extrapulmonary sarcoidosis. Several case reports confirm that infliximab has been effective for managing neurologic manifestations including small fiber neuropathy and chronic cutaneous disease such as lupus pernio (8, 11, 75-78). Neurologic disease can be difficult to treat and the use of anti-TNF therapy has been successful in refractory cases (79). Small fiber neuropathy has been associated with chronic fatigue in sarcoidosis patients (80) and treatment with anti-TNF agents can reverse neuropathy and improve fatigue (81). Severe, chronic skin lesions associated with sarcoidosis can also respond to these agents (82). Anti-TNF treatment has been efficacious for the treatment of refractory ocular disease (83). In one series of chronic ocular sarcoidosis, infliximab was effective when other drugs, including etanercept, had failed (51).

In the infliximab trial by Baughman et al for chronic pulmonary disease, extrapulmonary disease was identified in over 60% of cases (9). A physician assessment score was used to follow the response of each organ during therapy. Significant improvement was noted in patients treated with infliximab compared to placebo (84). After 24 weeks of therapy, the improvement in extrapulmonary disease was greater than 40% compared to placebo.

D. Genetic Markers of Response

In rheumatoid arthritis, polymorphisms of the TNF alpha gene can be useful to predict response to therapy. One area of interest has been the -308 position of TNF alpha. Mugnier et al compared rheumatoid arthritis patients with the A/A or A/G genotype versus those with the G/G genotype at the -308 position. Those patients with the genotype GG were more likely to respond to infliximab (85). Others have confirmed that the GG genotype was associated with better response to infliximab for patients with rheumatoid arthritis or ankylosing spondylitis (86). However, not all groups have been able to identify an increased rate of response for those with the GG genotype at position -308 (87). Perhaps this reflects the rarity of these genotypes which occur in only approximately 20% of patients studied (85, 88). Position -857 is another site of interest on the TNF alpha gene. Polymorphisms at that site have been associated with variable responses to the TNF receptor antagonist etanercept (88).

Literature suggests that in sarcoidosis polymorphisms of the TNF alpha gene can affect predisposition for the disease as well as prognosis (89). In particular, TNF alpha -308 genotype GA and AA are associated with Lofgren's syndrome (90-92), a form of the disease with a high rate of spontaneous remission which is very unlikely to require chronic therapy. Some investigators have suggested that polymorphisms at this position could influence the level of TNF released by macrophages (93). However, in a study of alveolar macrophages retrieved by bronchoalveolar lavage in active sarcoidosis patients, polymorphisms at -308 had no influence on the amount of TNF released (94). In addition, a significant increase in the rare TNF -857T allele was found in 25% of sarcoidosis patients versus 14.1% of the control subjects (95). To date no correlation has been reported for TNF polymorphisms at -308 and -857 and response to infliximab in sarcoidosis.

E. Summary: Factors Associated with Improved Response

Those factors associated with a better response to anti-TNF therapy are summarized in Table 2. Patients with more severe pulmonary disease including reduced FVC and severe dyspnea, more impaired quality of life, as well as longer duration of disease are more likely to respond to treatment (9). Evidence also suggests that patients with chronic extrapulmonary disease despite ongoing therapy may experi-

Table 2. Factors Associated with Improved Response to anti-TNF Therapy

Confirmed Factors
• Lower vital capacity
• Significant dyspnea
• Impaired quality of life
• Longer duration of disease
• Refractory extrapulmonary disease
Factors associated from observations in other conditions
• Higher C-reactive protein level
• Tumor necrosis factor-alpha -308 G/A or A/A genotype

ence an even higher rates of response (84). Table 2 also includes two factors associated with response to anti-TNF agents in rheumatoid arthritis patients. In the rheumatologic literature, there are reports that patients with elevated CRP values and/or TNF -308 genotype GG may be more likely to respond to treatment. These potentially useful markers need to be verified in prospective sarcoidosis trials.

IV. Decision of Which Anti-TNF Agent to Prescribe

A. Anti-TNF Agents in Other Inflammatory Diseases

Although as noted in Table 1 all three commercially available anti-TNF agents have been reported effective in treating some patients with sarcoidosis (8-10, 15, 16), etanercept and infliximab have been more extensively studied. Table 1 summarizes the mechanism of action, route of administration, and effectiveness in rheumatoid arthritis, psoriasis, and Crohn's disease for infliximab, etanercept, and adalimumab.

Although all three agents can be useful in treating granulomatous inflammation, response rates and side effects can differ by disease state and agent. For example, infliximab is effective in Crohn's disease (70, 96), however, in a large, double blind placebo controlled trial of active Crohn's disease, etanercept was ineffective (97). The risk of reactivation of *M tuberculosis* is significantly higher for infliximab than for etanercept (36, 39). There are several possible reasons for the differing response rates (98). Firstly, these drugs differ by mechanism of neutralizing TNF. The route of administration varies with higher peak doses achieved with intravenous administration. It has been proposed that higher immediate dosing leads to intracellular suppression of TNF, which is a crucial step in granuloma formation (98). Furthermore infliximab may have a unique affect of causing inflammatory cell apoptosis which releases TNF (99). Etanercept does not generate this apoptotic response (99).

B. Infliximab in Sarcoidosis

As previously discussed, two randomized, double blind placebo trials have been performed in pulmonary sarcoidosis. Baughman et al. found a significant improvement in the FVC of patients receiving infliximab compared to placebo. Rossman et al. also found a greater improvement with infliximab. Response to infliximab for sarcoidosis can occur within two months after initiating treatment (9). Even in sarcoidosis patients with chronic disease, improvement in chest roentgenograms and CT scans can occur rapidly.

In open label as well as randomized trials (9-13), many patients with various manifestations of extrapulmonary sarcoidosis can respond to infliximab. Case reports suggest that this agent can be beneficial in neurosarcoidosis as well as ocular disease. Uveitis can complicate sarcoidosis, but it is less frequently reported in Crohn's disease or rheumatoid arthritis. In a recent trial of ocular sarcoidosis, 13 of 14 patients responded to infliximab therapy (51). These responses included three patients who previously failed etanercept. Additional studies also suggest that this agent can be extremely useful in the management of this potentially devastating complication (100-102). Although adalimumab has also been successfully used in the treatment of uveitis (103), this benefit is not a class effect as patients receiving etanercept have developed acute uveitis (83, 104). Also, etanercept was no better than placebo in treating chronic uveitis either idiopathic (105) or due to sarcoidosis (106).

C. Etanercept in Sarcoidosis

Etanercept, a soluble TNF receptor antagonist, has been reported effective in sarcoidosis case reports (15, 107). An open label trial of pulmonary sarcoidosis by Utz et al was abandoned after the majority of 17 patients failed to respond (108). While

five patients improved on therapy, eleven patients deteriorated with either progressive symptoms or worsening chest roentgenograms. One patient developed hypercalcemia and renal failure, and an additional patient withdrew after three months of therapy.

A double blind, placebo controlled, randomized trial of chronic ocular sarcoidosis was performed in patients who had received at least six months of methotrexate (106). After randomization to either etanercept or placebo, patients were evaluated using both a global assessment by a blinded ophthalmologist and a comparison of concomitant corticosteroid use. Approximately one third of patients receiving either etanercept or placebo improved during the six months of study. Similar to the results in Crohn's disease, etanercept does not seem an effective option in most sarcoidosis patients.

D. Adalimumab in Sarcoidosis

Adalimumab, a humanized monoclonal antibody targeted against TNF, has been effective in treating Crohn's disease. The required doses are higher than those needed to treat rheumatoid arthritis (109, 110). As noted, the increased dose of an anti-TNF agent may lead to higher intracellular levels and hence suppression of the granuloma (98). In the report of adalimumab for Crohn's disease, the recommended rheumatoid arthritis dose of 40 mg every two weeks was associated with a less than 30% response by week four. However, after 80% of patients increased their doses to 40 mg every week, over 50 percent of patients responded by week 12 (111). Subsequent studies of Crohn's disease patients have evaluated higher induction doses with the highest responses reported in patients receiving 160 mg on week one followed by 80 mg on week two (110). Further studies support a maintenance dose of 40 mg weekly (109).

Adalimumab has been also reported effective in treating sarcoidosis patients (16). A retrospective review of sarcoidosis patients from one institution reported benefit with each of the anti-TNF agents (2). These patients, who required treatment for progressive disease despite corticosteroids and cytotoxic treatments, received adalimumab at initial doses of 40 mg every other week. Some patients increased doses to every week. Table 3 summarizes the definitions of response to treatment. Approximately 30% of patients receiving adalimumab responded. Although this response rate was similar to that reported with etanercept, it was lower than the 80% response rate seen with infliximab. Adalimumab has been effective for Crohn's disease patients with allergic reactions to infliximab (111) and in some sarcoidosis patients intolerant to infliximab.

At the University of Cincinnati Sarcoidosis and Interstitial Lung Disease Clinic and ild care centre of the Maastricht University Medical Centre, we have instituted a more aggressive dosing regimen of adalimumab for treating sarcoidosis. The response rate to this more aggressive regimen has been higher, with more than half of patients responding. However the time to response is longer than the 2-6 weeks usually required for infliximab (9, 10). This may reflect a more rapid onset of action with the intravenous route of administration. Despite the slower response rate with adalimumab, patients responding to the drug have often tolerated long term therapy.

E. Summary: Which Agent to Prescribe

Based on the current literature, the best anti-TNF agent for treatment of sarcoidosis appears to be infliximab. However, adalimumab may be an acceptable alternative, with higher doses and more frequent dosing used. Certain factors, including toxicity, may influence this decision. Patients developing allergic reactions to infliximab, a chimeric monoclonal antibody, have been successfully treated with the humanized monoclonal antibody adalimumab (111). Moreover, infliximab or adalimumab may be more effective and less toxic when given with methotrexate (5, 54). Since some insurance carriers prefer one anti-TNF agent, reimbursement may also be a factor. Patient preference must also be considered since adalimumab can be self administered while infliximab requires intravenous infusion under direct supervision by a health care team.

V. Response Assessment to Anti-TNF Therapy

Assessing response to anti-TNF therapy is summarized in table 3. Patients can experience an inadequate treatment response because of disease wors-

Table 3. Response to anti-TNF Therapy

Adequate
• Improvement of condition
• Stability but able to reduce glucocorticosteroids *
Inadequate
• Deterioration
• Stability but unable to reduce glucocorticosteroids *
Toxicity
• Adequate response
• Inadequate response

* Reduce dose of glucocorticoids to <10 mg per day of prednisone or its equivalent

ening, but inadequate responders also include stable patients that are unable to reduce their corticosteroid doses. For most patients the inability to reduce the dose of glucocorticoids to less than 10 mg a day of prednisone or equivalent is considered an inadequate response. In some situations, a higher or lower dose may be considered acceptable. Figure 3 provides a treatment algorithm for inadequate responders.

A. Evaluation of Non-Responders

i. Toxicity

Toxicity can be encountered with either an adequate response or an inadequate response. In addition, some patients initially responding may develop disease worsening due to antibody formation, inappropriate dose and/or dose interval. Inadequate response leads to new treatment strategies. All three anti-TNF agents share certain toxicities, including worsening of congestive heart failure (44, 45). These drugs may cause allergic complications. Adalimumab and etanercept can be associated with local skin irritations including a recall reaction in areas of prior injections. The intravenously administered infliximab can create a systemic reaction, including anaphylaxis (112). Up to five percent of patients treated with infliximab discontinue therapy because of allergic reactions. The rate of anaphylaxis can be reduced by administering regular treatments or adding a cytotoxic agent (5). While cytotoxic agents can reduce the rate of allergic reactions, the effectiveness of TNF inhibitor with cytotoxic agent has not been rigorously tested. Obviously allergic reactions can be quite serious and life threatening, hence many clinicians administer a cytotoxic agent unless a contraindication exits.

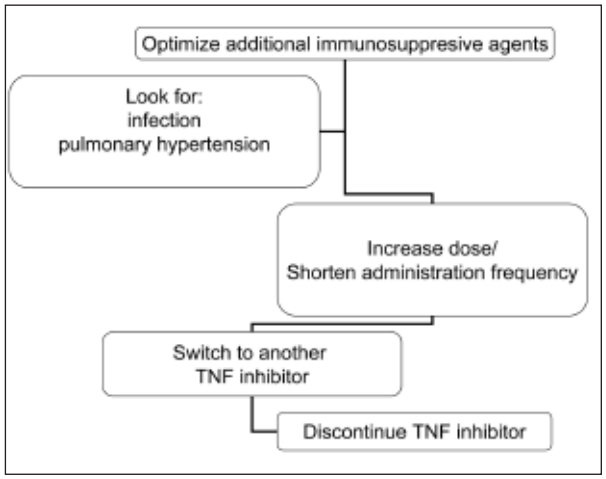

Fig. 3. An approach to a patient with inadequate response to anti-TNF therapy

ii. Secondary Disease Complications

Patients with inadequate responses to an anti-TNF therapy should be evaluated for alternative problems and complications. Infections, especially tuberculosis and fungal infections, can complicate anti-TNF therapy (36-38, 43). Although relatively rare, opportunistic infections can occur in sarcoidosis (113). Aspergillomas can occupy lung cavities of sarcoidosis patients (113, 114), and invasive aspergillosis has been reported with anti-TNF therapy for various conditions (115, 116). The risk, which appears highest in patients receiving infliximab, usually occurs within three months of initiating treatment (36). In contrast tuberculosis cases reported with etanercept usually occur a mean of 11 months after initiation of therapy (37).

Failure to respond to anti-TNF therapy may reflect other secondary disease complications including congestive heart failure or pulmonary artery hypertension (117, 118). Sarcoidosis patients treated with infliximab for pulmonary disease may experience improvement in chest roentgenograms, but still have worsening dyspnea. Echocardiography and right heart catheterization may confirm a diagnosis of sarcoidosis associated pulmonary hypertension. Infliximab has been used without worsening heart failure in patients with sarcoidosis associated pulmonary hypertension (117).

B. Treatment Options for Anti-TNF Non-responders

i. Combination Therapy: Anti-TNF Agents Plus Cytotoxic Drugs

A step wise approach has been proposed for rheumatoid arthritis patients with inadequate responses to anti-TNF agents (119). In several conditions, the combination of anti-TNF therapy plus a cytotoxic drug was superior to anti-TNF therapy alone (120-124). However, this was not reported in all situations (125, 126). In the rheumatology literature, evidence supports the use of escalating doses of methotrexate for rheumatoid arthritis (127). However higher doses could cause more toxicity, especially with chronic therapy (128). Sarcoidosis patients often have underlying hematologic abnormalities as part of their disease (129, 130). Therefore, one approach has been to prescribe combination therapy rather than higher doses. One such combination, leflunomide with methotrexate (34), appears advantageous due to less combined toxicity compared to higher doses of either agent alone. In a randomized rheumatoid arthritis trial, this combination was safe and more effective than either agent alone (131). In general a low dose methotrexate is recommended, in part to avoid antibody formation (52).

ii. Alternative Dosing Strategies

If combined immunosuppression has been maximized with inadequate response, anti-TNF dose adjustments may be beneficial. The pharmacokinetics of both infliximab and adalimumab have been well studied (119). Pharmacokinetic studies in rheumatoid arthritis and Crohn's disease indicate that effect of infliximab on TNF is both dose and time dependent. In patients with high levels of circulating TNF, infliximab given at doses of 10 mg/kg every four weeks leads to virtually undetectable TNF levels (132). Although neutralizing antibodies to infliximab may block effectiveness (133, 134), the use of higher doses can overcome antibody production (135). Unless neutralizing antibodies are present, the maximal dose of infliximab appears to be 10 mg/kg administered every four weeks. The maximum dose of adalimumab needed to block all circulating TNF remains unknown.

The original infliximab dosing report for sarcoidosis was 5 mg/kg administered initially, two weeks later, and then every four weeks (8). In subsequent reports this loading dose remains unchanged; however, the timing of the maintenance dose varies from every four weeks to twelve weeks. In the infliximab trial by Baughman et al, patients were randomized 1:1 to receive either 3 mg/kg or 5 mg/kg. After the initial two doses, maintenance dosing was every six weeks (9). The response rate was similar with either the 3 mg/kg or 5 mg/kg. In extrapulmonary disease there was no response rate difference between the two doses.

Higher trough levels of infliximab have been achieved by reducing the interval rather than increasing the dose (119). These higher trough levels are associated with improved response to the drug (136, 137) and lower levels of anti-infliximab antibody formation (138). No increased toxicity has occurred with the higher doses (9, 139). A single institution analysis of sarcoidosis patients who failed to respond to infliximab at doses of 3-5 mg/kg every six weeks responded to every four weeks 5 mg/kg dosing (140). As previously noted, adalimumab appears more effective for treating granulomatous diseases when higher loading and maintenance doses are given.

iii. Switching to a Different Anti-TNF Inhibitor

The decision to switch to another TNF inhibitor has not been studied systematically in sarcoidosis. Some patients who have failed etanercept for ocular sarcoidosis have been successfully treated with infliximab (51). Because of allergic reactions, switching from infliximab to adalimumab has been successful for some patients (2).

VI. Anti-TNF Treatment Duration

The duration of anti-TNF therapy for a responding patient remains unclear. In the study by Baughman et al., therapy was discontinued after 24 weeks and the patients observed for an additional 28 weeks. For some patients benefit persisted for up to 28 weeks after the last dose, while other patients deteriorated (9).

Unfortunately investigators of other diseases have not provided clear answers either. Studies of Crohn's disease and ankylosing spondylitis suggest

that intermittent therapy targeted to symptoms is associated with more toxicity and less overall efficacy than maintenance treatment (96, 141, 142). The rate of disease relapse after therapy discontinuation in rheumatoid arthritis appears high. In one study of 172 patients in clinical remission, only nine patients were able to discontinue drug without relapse (143). Longer follow-up data is needed to determine the rate of disease relapse in sarcoidosis patients. One may need to treat the patients for years instead of a shorter period such as in rheumatoid arthritis. There is the risk that if therapy is discontinued, a relapse of sarcoidosis may occur. Moreover, if one resumes infliximab the risk of antibody formation is higher than before. Thus far, the results in sarcodiosis are comparable with Crohn's disease, spondilitis ankylopoetica and rheumatoid arthritis.

VII. Conclusion

The use of anti-TNF agents infliximab and adalimumab has become a standard therapy for selected chronic sarcoidosis patients. Factors associated with improved response to anti-TNF agents include more severe pulmonary disease, chronic extrapulmonary disease, longer disease duration, and impaired quality of life. Although tantalizing, the role of pharmacogenomics requires more exploration in predicting which sarcoidosis patients or which specific agent should be chosen for anti-TNF therapy. The dose and even more important the dose interval are prominent factors influencing the effect of treatment. Moreover, to increase the benefit/risk ratio and avoid antibody formation a combination with low dose methotrexate or other cytotoxic agent is recommended. Of the available agents, infliximab appears to be the most effective. Adalimumab may prove an effective alternative but the onset of action is longer and higher doses may be necessary.

For the nonresponding patient who has been received an adequate trial of anti-TNF therapy, the drug should be discontinued and a search initiated to find complicating issues including antibody formation, infections, pulmonary artery hypertension, etc. Patients with inadequate responses may benefit from combination therapy with a cytotoxic agent or alternative dosing. The rate of relapse after drug withdrawal remains unknown.

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