Tumor necrosis factor-alpha inhibitor treatment for sarcoidosis

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Abstract: Sarcoidosis is a chronic multisystem disease of unknown etiology, characterized by noncaseating granulomatous infiltration of virtually any organ system. Treatment is often undertaken in an attempt to resolve symptoms or prevent progression to organ failure. Previous studies have suggested a prominent role for tumor necrosis factor-alpha (TNF-α) in the inflammatory process seen in sarcoidosis. TNF-α and interleukin-1 are released by alveolar macrophages in patients with active lung disease. Corticosteroids have proved to be efficacious in the treatment of sarcoidosis, possibly by suppressing the production of TNF-α and other cytokines. Three agents are currently available as specific TNF antagonists: etanercept, infliximab, and adalimumab. Although data from noncomparative trials suggest that all three have comparable therapeutic effects in rheumatoid arthritis, their effects in a granulomatous disease such as sarcoidosis are less consistent. In this review, current data on the effectiveness are summarized.

Keywords: sarcoidosis, infliximab, etanercept, adalimumab, anti-TNF alpha

Introduction

Sarcoidosis is a systemic granulomatous disorder of indeterminate origin, manifested by the presence of noncaseating granulomas of virtually any organ system. Although precise epidemiological studies have not been undertaken, there are several reasons why we might infer that an infective agent or agents might be the trigger(s), including spatial, seasonal, and occupational clustering (Bowman et al 2003).

There are two aspects of the granulomatous response of sarcoidosis: the initial event, leading to granuloma formation, and the evolution of the response as either resolution or chronic disease. In studies of patients with an acute form of the disease, a high proportion of CD4-positive lymphocytes have been identified in bronchoalveolar lavage (BAL) fluid (Pinkston et al 1983). These T cells are activated, as shown by their increase of interleukin-2 (IL-2) receptors and the spontaneous release of IL-2 by these cells. IL-18 has also been reported as possibly playing a central part in sarcoid granuloma formation (Shigehara et al 2001). This activation is associated with macrophage activation, interferon production, and formation of the granuloma, and has been cited as an example of the Th-1 response (Baumer et al 1997). In more than 60% of sarcoidosis patients, the granulomatous response resolves during the following 2–5 years. The events leading to resolution include an influx of CD-8 positive lymphocytes. The maintenance of the granuloma may be through the IL-12, and resolution is associated with the cytokine IL-10, which suppresses the inflammatory response (Moller et al 1996). The cytokines associated with chronic disease include IL-8, IL-12, and tumor necrosis factor-alpha (TNF-α) (Ziegenhagen et al 1997).

TNF-α and sarcoidosis

TNF-α is a 17.5-kd protein that plays a significant role in antigen-stimulated, cell-mediated immune responses and in the development of noncaseating granulomas in
a variety of diseases (Tracey 1994; Chensue et al 1995). In sarcoidosis, alveolar macrophage-derived TNF-α participates in the induction and maintenance of granulomas (Kunkel et al 1989). High levels of TNF-α and high levels of TNF-α released from alveolar macrophages seem to correlate with disease progression (Marques et al 1999). In light of its inhibitory activity against TNF-α, pentoxifylline has been proposed as a therapeutic agent for sarcoidosis and patients exhibited a favorable response, so other pure and potent TNF-α antagonists, such as the new biological anti-TNF-α, would be an alternative for the treatment of sarcoidosis.

The TNF-α inhibitors have distinct efficacy profiles. Whereas all 3 available agents (etanercept, infliximab, and adalimumab) have demonstrated efficacy in the treatment of RA, efficacy in other inflammatory arthritides and granulomatous diseases such as Crohn’s disease, Wegener’s granulomatosis and sarcoidosis varies (Haraoui 2005a, 2005b). There are no trials comparing efficacy among different anti-TNF-α in sarcoidosis.

Multiple reasons for this discrepancy have been theorized. They all target the same molecule, but in a different way. Infliximab is a humanized mouse monoclonal antibody, adalimumab a fully human monoclonal antibody and etanercept a construct comprising two human p75 TNF-α receptors coupled to the Fc portion of a monoclonal human antibody. Etanercept, adalimumab and infliximab have different binding characteristics, with infliximab and adalimumab binding to both soluble and membrane-bound TNF and etanercept binding primarily to soluble TNF (Scallon et al 2002). These differences in binding may manifest as differing effects on complement activation and apoptosis. Infliximab and adalimumab may lyse in vitro TNF-producing cells via activation of complement (Reinold 2003) and also appears to induce apoptosis of immune/inflammatory cells (Lügering et al 2001). Other differences in the efficacy profiles of these drugs are likely related to the pathophysiology of the diseases (eg, role of lymphotoxin) as well as drug characteristics (eg, dosing, pharmacokinetics, or immunogenicity).

Clinical use and adverse effects
There are no clinical trials comparing efficacy among different TNF inhibitors in patients with sarcoidosis. The choice of agent therefore depends on other factors, including patients’ convenience, access to treatment, and patients’ preferences. Infliximab requires infusion intravenously every four to eight weeks, performed by a health care professional. The usual dose is 3 mg/kg body weight; some patients require higher doses. Etanercept and adalimumab are self-administered by subcutaneous injection. Etanercept is given at a dose of 25 mg twice weekly or 50 mg weekly, and adalimumab is given at a dose of 40 mg every 2 weeks.

Common minor adverse events include injection site reactions with etanercept and adalimumab and infusion reactions with infliximab. Rare serious adverse events include optic neuritis, exacerbations of previously quiescent multiple sclerosis, aplastic anemia, and interstitial lung disease; lupus-like syndromes and hepatotoxicity may also occur. Serious infections are a particular concern, especially respiratory and skin infections (Scott and Kingsley 2006). TNF inhibitors should be stopped in the presence of serious infections. Susceptibility to intracellular pathogens may be increased, and primary tuberculosis and reactivation of prior tuberculosis are specific problems; and, as a rule, patients should be screened for tuberculosis before the initiation of therapy. The overall risk of cancer is controversial (Scott and Kingsley 2006). The only systematic review, which focused on randomized, controlled trials involving infliximab and adalimumab, but not etanercept, reported a dose-related increased risk of cancer (Pettersen et al 2002). In contrast, national registries have not yet found an increase in solid cancers after treatment with TNF inhibitors. An increase in lymphomas has been reported with all TNF inhibitors. However, because there is a preexisting association of lymphomas with severe RA and systemic inflammation, the exact contribution of therapy with TNF inhibitors is difficult to dissect. Given these uncertainties, it seems sensible to use extreme caution when considering the use of TNF inhibitors in many patients with a history of malignant disease, or even to avoid them altogether, and to warn patients that the risk of cancer with this form of therapy remains unknown. Since infliximab increases mortality when used to treat severe heart failure in patients without arthritis, TNF inhibitors should be used cautiously, if at all, when mild heart failure is present, and are best avoided when heart failure is severe. Nonetheless, there is no evidence that TNF inhibitors increase the risk of new-onset cardiac failure in patients with RA. Patients are usually advised not to conceive while taking TNF inhibitors and to avoid these treatments during pregnancy or lactation. To date, no actual adverse events have been described in those pregnancies that have occurred in patients taking TNF inhibitors. Table 1 summarizes the dose, route of administration, and most prevalent adverse effects.

Because the experience with anti-TNF in patients with sarcoidosis is still limited, multicenter trials are needed to validate the safety and efficacy in these patients. Currently, there is insufficient data to support anti-TNF as first-line
therapy for sarcoidosis or neurosarcoidosis, but is definitely an option in refractory cases. The optimal dose, duration of therapy, and long term toxicity of anti-TNF in patients with refractory sarcoidosis are yet to be determined in prospective trials.

**Treatment with anti-TNF in different manifestations of sarcoidosis**

To present the scientific evidence of anti-TNF-α treatment in patients with sarcoidosis we have made a division according to the organ affected.

**Cutaneous sarcoidosis**

Cutaneous sarcoidosis occurs in up to one third of patients with systemic sarcoidosis. Recognition of cutaneous lesions is important because they provide a visible clue to the diagnosis, and are an easily accessible source of tissue for histologic examination. Because lesions can exhibit many different morphologies, cutaneous sarcoidosis is known as one of the “great imitators” in dermatology. Specific manifestations include papules, plaques, lupus pernio, scar sarcoidosis, and rare morphologies such as alopecia, ulcers, hypopigmented patches, and ichthyosis (Katta 2002).

Treatment of cutaneous lesions can be frustrating. For patients with severe lesions or widespread involvement, the most effective treatment is systemic glucocorticoids. Other medications may be used in refractory cases, including such agents as hydroxychloroquine, methotrexate, and thalidomide.

A growing number of publisher reports suggest that anti-TNF-α therapies may be effective in the treatment of numerous inflammatory skin diseases including sarcoidosis (Alexis and Strober 2006). The majority of these reports are in the form of individual case reports and small case series. Tuchinda and Wong (2006) reported a patient with chronic progressive cutaneous sarcoidosis, unsuccessfully treated with systemic steroid and immunosuppressive agents, who responded significantly to etanercept as monotherapy.

Khanna and colleagues (2003) described a patient with lupus pernio, resistant to corticosteroids and disease modifying antirheumatic agents, who responded to the addition of etanercept.

Doty and associates (2005) reported their experience with infliximab in ten patients with sarcoidosis, five with disfiguring lupus pernio lesions; the response was dramatic. Heffernan and Anadkat (2005) reported a case of recalcitrant cutaneous sarcoidosis with multiple and disseminated violaceous papules and plaques which achieved 90% clearance by week 6 with intravenous infliximab therapy. Roberts and colleagues (2003) described a woman with systemic sarcoidosis with cutaneous manifestations in form of a mass in a right eyelid that resolved between the third and fourth dose of infliximab. Haley and associates (2004) reported a patient with severe mutilating cutaneous sarcoidosis (lupus pernio), who showed partial response to courses of a wide spectrum of immunomodulators and cytotoxic therapies who developed significant side effects due to prolonged high-dose corticosteroids, and responded rapidly to infliximab. Pritchard and Nadarajah (2004) reported five patients, one with sarcoid skin nodules that disappeared after 2 days of infliximab infusions. Sweiss and colleagues (2005) described 9 patients, three with cutaneous manifestations (one with mass lesions of the lip and nose, one with extensive psoriasiform rash and one with extremely painful bilateral lower extremity ulcerative sarcoidosis requiring high-dose narcotics for pain control), without response to corticosteroids and methotrexate and mycophenolate mofetil that resolved with infliximab. Another individual case has been described with response to infliximab (Baughman and Lower 2001; Mallbris et al 2003; Meyerle and Schorr 2003).

Finally, there are 2 cases of cutaneous sarcoidosis responding to adalimumab, one with ulcer on lower extremity that persisted despite of treatment with prednisone, hydroxychloroquine and methotrexate and resolved nine weeks after the initiation of adalimumab (Philips et al 2005) and other one with reddish-purple nodules on the face and shins and numerous hyperpigmented patches and erosions on the legs (Heffernan and Smith 2006).

**Table 1 Principal characteristics of anti-TNF drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Adverse effects (common for all anti-TNF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>3–5 mg/kg</td>
<td>Infusion intravenously every four to eight weeks</td>
<td>Local erythema Increased risk of infections</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg</td>
<td>Subcutaneous injection, twice weekly</td>
<td>Increased risk of tuberculosis reactivation</td>
</tr>
<tr>
<td>Etanercept</td>
<td>50 mg</td>
<td>Subcutaneous injection, weekly</td>
<td>Congestive heart failure Desmyelinating diseases</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg</td>
<td>Subcutaneous injection every two weeks</td>
<td>Neoplasm</td>
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</table>

**Abbreviation:** TNF, tumor necrosis factor.
Patients with cutaneous sarcoidosis who are refractory to corticosteroids and/or steroid-sparing agents, or those who develop significant drug toxicity, may be candidates for treatment with TNF inhibitors. The optimal dose, duration of therapy, and long-term toxicity of anti-TNF in patients with refractory cutaneous sarcoidosis are yet to be determined in prospective trials.

Neurosarcoidosis

Central and peripheral nervous system involvement is estimated to be 5%, but other studies have reported a prevalence of 15%–16%. The clinical course may be acute, subacute or chronic with insidious onset (Lower et al 1997; Marangoni et al 2006). A growing number of papers, specially reports in form of individual case reports, suggest that anti-TNF-α therapies may be effective in the treatment of neurosarcoidosis.

Carter and colleagues (2004) presented a 41-year-old woman who presented with headaches, fatigue, diffuse myalgias and arthralgias, galactorrhea, and short term memory problems; an elevated serum prolactin level was detected. A magnetic resonance image (MRI) of the brain showed an enlarged pituitary gland and transphenoidal resection revealed multiple noncaseating granulomas. Prednisone and methotrexate was administered. Two months later, the patient developed left homonymous superior quadrant hemianopsia. A repeat MRI of the brain showed multiple areas of prominent enhancement, including the suprasellar and parasellar region, intracranial prechiasmal optic nerves and optic chiasm, intracranial fifth nerve bilaterally, cavernous sinus, and infundibulum. After a total of five treatments of intravenous cyclophosphamide, while on prednisone 10 mg daily, the patient developed acute bilateral vision loss caused by recurrence of her optic neuropathy. She was started on intravenous infliximab 5 mg/kg at 0, 2, 6 weeks, and then every 8 weeks. After 5 months, and a total of five treatments of infliximab, the patient symptomatically improved, with decreased headaches and arthralgias and no new visual symptoms or worsening of her visual acuity.

Solberger and colleagues (2004) reported a patient with a biopsy-proven progressive neurosarcoidosis involving the hypophysis, the right vestibulocochlear nerve, the spinal cord, and the peripheral nervous system, refractory to corticosteroids and azathioprine, in whom infliximab was associated with a markedly improved clinical outcome.

Petterdensen and colleagues (2002) described a man who developed biopsy-proven sarcoidosis 16 years previously, initially involving the skin (lupus pernio), and subsequently the liver (granulomatous hepatitis), knees (synovitis), lungs (hilar lymphadenopathy), and brain (left temporal lobe lesion with associated focal seizures). His neurosarcoidosis was complicated by an episode of prolonged status epilepticus. Despite undergoing radiation therapy to the left temporal lobe and receiving full courses of prednisone, azathioprine, methotrexate, hydroxychloroquine, chloroquine, and cyclosporine, he experienced progressive neurologic involvement with confusion, disorientation, aggressive behavior, and right hemiparesis, dysmetria, dysdiadochokinesis and truncal ataxia. MRI revealed multiple supratentorial granulomas, including a large, left medial temporal lobe lesion with associated vasogenic edema. Despite receiving regular rehabilitation therapy and medications to control seizures and aggressive behavior, he remained confused and disoriented. Infliximab was administered IV at a dose of 5 mg/kg and was repeated at 2 and 6 weeks. Within 1 week of receiving the first dose of infliximab, the patient experienced a marked reduction in agitation. At 6 weeks, his right hemiparesis and hyperreflexia resolved and his right facial weakness, right appendicular ataxia, and truncal ataxia improved. Repeat MRI revealed reduced volume of all lesions and almost complete resolution of surrounding edema.

Doty and colleagues (2005) reported their experience with infliximab in ten patients with sarcoidosis, one with neurosarcoidosis with headache, seizures and paresthesias in whom MRI demonstrated parenchymal and meningeal enhancement in frontal lobe region. Infliximab was associated to prednisone and 3 months later the clinical symptoms showed improvement.

Katz and colleagues (2003) presented 2 patients with optic disc swelling secondary to neurosarcoidosis; one of them requiring treatment with infliximab: a woman with headache, chronic visual loss, papilledema, and optic atrophy characteristic of chronic intracranial hypertension. MRI showed bifrontal cerebral edema with a plaque frontal pachymeningeal enhancement. Her visual loss progressed despite conventional therapies, and maintained with infliximab.

On the other hand, Guilpain and colleagues (2004) reported a patient with optic bilateral neuropathy secondary to granulomatous infiltration of nerve optic, where therapy combining prednisone, methotrexate and infliximab was started without significant improvement of visual acuity.

Finally, Pritchard and Nadarahaj (2004) described a report of five patients, one with a myelopathy secondary to neurosarcoidosis, with a pronounced response to treatment with infliximab. There is no case with neurosarcoidosis and etanercept or adalimumab.
Currently, there is insufficient data to support infliximab as first-line therapy for neurosarcoidosis, but it does hold promise as a potential second-line therapy. It definitely is an option in refractory cases. The combination of infliximab and methotrexate is recommended if this therapeutic strategy is employed for neurosarcoidosis.

**Ocular sarcoidosis**

Ocular disease is a common feature of sarcoidosis (Jabs and Johns 1986; Usi et al 2002). The manifestations include anterior, intermediate, and posterior uveitis. The intermediate and/or posterior uveitis is often chronic and can be associated with a loss of vision (Dana et al 1996). In addition to the inflammation, lumpy or flat glial membrane, known as snowbanking, over the pars plana of the ciliary body transforms intermediate uveitis into pars planitis. The pars plana has been used as a specific landmark for inflammation. Inflammation in that area is associated with chronic disease and represents a difficult management issue for the ophthalmologist. Sarcoidosis is one of the more important causes of pars planitis. The treatment for uveitis includes therapy with corticosteroids, used topically, periocularly, and/or systemically (Krystolik et al 1998). However, the long term local and systemic use of corticosteroids is often associated with side effects, including cataracts and glaucoma. Because of these complications, alternatives to steroid therapy are often sought for the treatment of chronic uveitis. Among the immunosuppressive drugs, methotrexate has been commonly used (Dev et al 1999; Samson et al 2001). Although methotrexate is useful in many patients, incomplete control of the uveitis can sometimes occur. In these cases treatment with anti-TNF-α may be an option.

Baughman and colleagues (2005) studied the effectiveness of etanercept in the treatment of patients with ocular sarcoidosis who have persistent disease despite treatment with methotrexate for at least 6 months. Patients were randomized to receive either etanercept, 25 mg, or an equal volume of physiologic saline solution subcutaneously twice a week for 6 months. All patients were maintained with methotrexate therapy throughout the study. The primary end point of the study was the change of the ophthalmologist examination after 6 months of therapy. Anterior uveitis was present in 16 patients, posterior uveitis in 5 and pars planitis in 9. Etanercept was well tolerated. However, it was not associated with a marked improvement in this group of patients with chronic ocular sarcoidosis.

There are various reports about treatment of sarcoidosis with infliximab. Saurenmann and colleagues (2006) described the efficacy of anti-TNF-α (etanercept 11 patients and infliximab 13 patients) in children with persistently active uveitis despite treatment with at least 1 standard immunosuppressive drug. One patient had sarcoidosis and received infliximab. Infliximab resulted in better clinical responses with less ocular complications than etanercept.

Benitez del Castillo and colleagues (2005a) evaluated the long term efficacy and safety of infliximab as treatment for noninfectious posterior uveitis in 7 patients (5 diagnosed with Behçet’s disease, 1 with chronic idiopathic multifocal choroiditis and one diagnosed with sarcoidosis). Three intravenous doses of 5 mg/kg of infliximab was administered at weeks 0, 2 and 6, and was repeated in patients undergoing a relapse of uveitis after initial remission. Improvement was defined as amelioration of visual acuity or disappearance of retinal exudates and/or vitreous opacities. All patients were followed up for at least 36 months and at the end all eyes had improved in term of signs of inflammation.

Baughman and colleagues (2005b) reported their experience with infliximab in chronic ocular inflammation in 14 patients with various underlying ocular conditions including 7 patients with sarcoidosis. All patients had persistent inflammation despite systemic immunosuppressive agents and all but 1 experienced marked improvement. Four patients who had previously received etanercept with either no response or subsequent relapse responded to infliximab.

Lindstedt and colleagues (2005) described the effect of additional treatment with anti-TNF-α therapy in a case series of 13 patients with serious sight threatening uveitis (6 with Behçet’s disease, one with sarcoidosis). Infliximab treatment resulted in an effective suppression of ocular inflammation in all patients. In patients with non-Behçet’s disease uveitis visual acuity in 6 out of 8 improved or was stable. Pritchard and Nadarajah (2004) report 5 patients, 2 with chronic granulomatous uveitis and 1 with several organs affected by sarcoidosis including uveitis, who showed rapid improvement after the infusion.

For ocular sarcoidosis refractory to conventional treatment, infliximab must be considered as second-line treatment; with the actual evidence indicating infliximab resulted in better clinical responses with less ocular complications than etanercept.

**Pulmonary sarcoidosis**

The lungs are affected in more than 90% of patients, usually presenting as interstitial disease. Symptoms are dry cough, dyspnea, and chest discomfort. Pulmonary sarcoidosis has an unpredictable course that may result in spontaneous
remission or lead to progressive loss of lung function with fibrosis. There are four stages of pulmonary sarcoidosis. Patients with stage I or II disease may have no symptoms, whereas stages III and IV can be characterized by progressive dyspnea, loss of lung function, and fibrosis. Airway involvement can occur and may result in airflow limitation, persistent cough and, in severe cases, bronchiectasis. Spontaneous remission can be expected in 55%–90% of patients with stage I disease, 40%–70% with stage II disease, 10%–20% with stage III disease, and 0% to 5% with stage IV disease (Baughman 2004; Wu and Schiff 2004).

Corticosteroids are the mainstay of treatment for sarcoidosis. Alternative drugs are required in chronic resistant sarcoidosis and/or in conditions where systemic corticosteroids are contraindicated. Immunosuppressive agents (chlorambucil, cyclophosphamide, methotrexate, cyclosporine, azathioprine), anticytokine agents (thalidomide, pentoxifylline), and antimalarials (chloroquine, hydroxychloroquine) have been used in such situations. Chlorambucil and cyclophosphamide have been used in anecdotal cases of pulmonary sarcoidosis as corticosteroid-sparing agents. Therapy with anti-TNF-α may be an option in these situations (Fazzi 2003).

Ulbricht and colleagues (2003) described a patient with severe sarcoidosis involving the lung and liver. Various treatment regimens with azathioprine, methotrexate, cyclophosphamide, and pentoxifylline failed to control the disease and therapy with infliximab was commenced. Arthritis, pulmonary and liver involvement improved, and they were able to taper the corticosteroid treatment to a lower-dose regimen with no need for additional immunosuppressive treatment.

Pritchard and Nadarajah (2004) reported five patients, including a woman with pulmonary sarcoidosis with dyspnoea, arthralgias and fatigue. This patient was receiving prednisone 40 mg daily and methotrexate 7.5 mg weekly when infliximab was started. Dyspnoea and arthralgia improved 1–2 months after treatment. A computed tomography (CT) scan of the thorax before and after 6 months of treatment with infliximab showed improvement in the enlarged hilar lymph nodes.

Roberts and associates (2003) presented a case of multisystem sarcoidosis that was refractory to treatment with multiple immunosuppressive agents. Treatment with infliximab, as part of combination therapy, was added. At the time that infliximab therapy was started, patient’s lung function was stable on a regimen of systemic steroids and azathioprine and its addition provided no further benefit.

Sweiss and colleagues (2005) described 9 patients, 4 of them with systemic and pulmonary affection that were treated with infliximab. All cases showed partial or complete resolution of adenopathy, and shortness of breath improved.

A prospective, open-label, phase-2 treatment trial with etanercept in pulmonary sarcoidosis has been published recently (Utz et al 2003). Study hypotheses included the following: (1) patients treated with etanercept will clinically improve or remain stable, obviating the need for corticosteroid treatment; and (2) patients responding to etanercept will exhibit higher pretreatment lung TNF-α expression as well as the suppression of lung TNF-α expression during treatment compared to nonresponders. Fourteen patients demonstrated stage II, and 3 demonstrated stage III disease. Five of 17 patients were treatment successes, while another patient withdrew from the study after 3 months. Eleven patients did not respond to therapy. The fact that patients did not respond to therapy was secondary to the deterioration seen both in radiographs and in the results of pulmonary function tests. Serum TNF-α was present at low but measurable levels at baseline. Interestingly, enzyme-linked immunosorbent assay measurements at 6 months demonstrated significant increases in total serum level of TNF-α. No consistent differences were observed in either TNF-α level or bioactivity comparing those patients whose conditions had improved or those in whom the disease had progressed while receiving etanercept.

Another phase 2, multicenter, randomized, double-blind, placebo-controlled study has been conducted in 138 patients with chronic pulmonary sarcoidosis (Baughman et al 2006). Eligible adult patients had histologically proven sarcoidosis, diagnosed at least 1 year prior to screening, evidence of parenchymal disease on chest radiograph and a forced vital capacity (FVC) 50%–85% of the predicted value. Patients must have been treated with at least 10 mg/day of prednisone or equivalent or one or more immunosuppressants for at least 3 months prior to screening. Patients were randomized to receive intravenous infusions of infliximab or placebo at weeks 0, 2, 6, 12, 18, 24, and followed through week 52. The primary endpoint was the change from baseline to week 24 in percent of predicted FVC. Infliximab therapy resulted in a statistically significant improvement in percent of predicted FVC at week 24. Finally, we recently described a patient with pulmonary and pleural sarcoidosis resistant to treatment with prednisone and methotrexate who resolved with adalimumab (Callejas-Rubio et al 2005).

In patients with progressive stage II or III pulmonary sarcoidosis, there are a preponderance of treatment failures using etanercept as a single agent. It is not clear whether there
exists a small subset of patients with pulmonary sarcoidosis who respond to therapy with etanercept alone. In patients with refractory or recurrent pulmonary sarcoidosis, infliximab and probably adalimumab must be considered as an alternative treatment.

Renal sarcoidosis
The kidneys may be involved in sarcoidosis in various ways. Because the granuloma epithelioid cells may produce calcitriol, sarcoid patients commonly have hypercalcuria, nephrocalcinosis, and stone disease and may develop hypercalcemia. The renal interstitium may be involved with granuloma formation. An association with renal neoplasms, notably papillary carcinomas, has been described. The glomeruli may be involved in sarcoidosis and IgA nephropathy, membranous IgG deposits, or even extracapillary crescent formation may occur (Gobel et al 2001). Although corticosteroids are effective in advanced tubulo-interstitial nephritis due to sarcoidosis, long term treatment is necessary to preserve renal function and to delay the onset of end-stage renal disease (Rajakariar et al 2006). Steroid-dependant or refractory cases may respond to other immunosuppressants including anti-TNF-α agents.

There are two case reports of treatment with infliximab in renal sarcoidosis. Thumfart and colleagues (2005) described the case of a boy presenting with severe arterial hypertension and acute renal failure caused by an isolated sarcoid granulomatous interstitial nephritis. Renal function improved initially with prednisone treatment but later, the patient showed signs of severe steroid toxicity and progressive renal failure. Monthly treatment with infliximab was started, resulting in steady improvement in renal function and resolution of renal granulomata. In addition, antihypertensive medication could be reduced.

Ahmed and associates (2007) present a patient with acute renal failure due to isolated granulomatous infiltration of the renal parenchyma. Renal biopsy showed granulomatous interstitial nephritis with noncaseating granulomas. There was no evidence of extrarenal sarcoid involvement. Prednisone of 60 mg daily resulted in significant improvement in renal function. Because of recurrent flares on steroid taper and steroid toxicity, treatment with infliximab was instituted and resulted in stabilization of renal function. Steroid-dependant or refractory renal sarcoidosis cases may respond to infliximab.

Other manifestations
Fouchier and colleagues (2004) reported a patient with persistent, refractory symptomatic pulmonary sarcoidosis, complicated by a congenital muscular disease: McArdle’s disease (a glycogen storage disease caused by myophosphorylase deficiency). As the desaturations during mild exercise caused by the sarcoidosis aggravated the negative consequences of his muscle disease and he failed to respond adequately to corticosteroids and methotrexate, the patient was treated experimentally with infliximab. The results were favorable: after 17, 21, and 36 months there was an improvement in various lung function parameters, and his fatigue was reduced.

Menon and associates (2004) reported a patient treated with interferon-α who developed hypercalcemia and renal insufficiency as presenting clinical manifestation of sarcoidosis. Prednisone therapy was effective in controlling hypercalcemia but had to be discontinued due to an increase in hepatitis C viral RNA count. Infliximab was used as therapy. The patient received three doses of infliximab (5 mg/kg) and achieved a rapid decline in serum calcium to normal levels in 7 days; the serum calcium level has remained normal 3 months after the last infusion.

Yee and Pochapinet (2001) described a woman with sarcoidosis presenting with severe protein-losing enteropathy, hypoalbuminemia, and proximal myopathy who had not responded adequately to corticosteroid therapy and whose clinical course was further complicated by acute tubular necrosis and renal failure requiring long term hemodialysis. Enteropathic and myopathic symptoms resolved after infliximab therapy, and the serum albumin level also improved.

Mandel and colleagues (2005) describe a case report of a patient with sarcoidosis with parotid gland swellings who did not respond to standard therapy. Despite the use of various immunosuppressive agents, the swellings failed to resolve over a three-year period. The patient’s condition was treated successfully with infliximab. Finally, Hobbs (2005) presented the first documented evidence that intraarticular injection of etanercept is clinically beneficial and well tolerated in the setting of sarcoid arthritis.

Table 2 summarizes the studies of anti-TNF-α on different manifestations of sarcoidosis.

### Table 2 Summary of studies of effects of anti-TNF on sarcoidosis

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Anti-TNF considered</th>
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<tbody>
<tr>
<td>Cutaneous sarcoidosis</td>
<td>Infliximab and adalimumab</td>
</tr>
<tr>
<td>Neurosarcoidosis</td>
<td>Infliximab</td>
</tr>
<tr>
<td>Ocular sarcoidosis</td>
<td>Infliximab</td>
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<tr>
<td>Pulmonary sarcoidosis</td>
<td>Infliximab and adalimumab</td>
</tr>
<tr>
<td>Renal sarcoidosis</td>
<td>Infliximab</td>
</tr>
</tbody>
</table>

**Abbreviation:** TNF, tumor necrosis factor.
Conclusions
Corticosteroids are the mainstay of treatment for sarcoidosis. Nevertheless, alternative drugs, such as anti-TNF-α may be required in chronic resistant sarcoidosis and/or in conditions where systemic corticosteroids are contraindicated.

Three agents are currently available as specific TNF-α antagonists: etanercept, infliximab and adalimumab. Although date from noncomparative trials suggest that all 3 have comparable therapeutic in rheumatoid arthritis, their effects in granulomatous diseases as sarcoidosis probably are more variable. Most of the information available comes from isolated clinics cases or series of cases, and as these type of papers usually suffers from the publication bias, the results must be taken with precaution. Infliximab, and probably adalimumab, appears to be more effective in the treatment of different manifestation of refractory sarcoidosis, and would probably be the anti TNF of election in these patients.

Additional studies are needed to better define these differences and optimize the clinical utilization of these agents.

Disclosure
The authors report no conflicts of interest.

References
Anti-TNF treatments for sarcoidosis


