Effectiveness of infliximab in treating selected patients with sarcoidosis

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Summary

Objective: To assess the effectiveness of infliximab (Remicade) in the treatment of patients with sarcoidosis who either do not respond to corticosteroids and other conventional drugs or develop unacceptable side effects to these drugs.

Design: A clinical, non-randomized, off-label study.

Setting: Sarcoidosis clinic at a university teaching hospital.

Patients: Twelve biopsy-proven sarcoidosis patients, nine women and three men ranging from 45 to 70 years of age with chronic multisystem sarcoidosis refractory to corticosteroids or alternative treatment.

Intervention: Infliximab was infused at a dedicated ambulatory infusion center. The initial dose was 3 mg/kg body weight and subsequent doses were given at weeks 2, 4, 6, 10, and 14. All patients received at least six infusions.

Results: All 12 patients improved significantly. One patient had a mild allergic drug reaction that responded to antihistamine. One patient, after 3 months of stopping infliximab treatment, died of a ruptured blood vessel in the abdomen. At autopsy a plasma cell dyscrasia was found.

Conclusion: Infliximab is safe and effective in treating those patients with multisystem sarcoidosis who are either refractory or develop side effects to a standard regimen of corticosteroids and immunosuppressive agents.

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Introduction

There is no cure for sarcoidosis. Corticosteroids are universally used for suppressing the progressive and harmful granulomatous inflammation associated...
with the disease. Unfortunately, many develop intolerable side effects that become more of a problem than the illness itself. In such a situation, a number of alternative drugs, including immunosuppressive agents (azathioprine, cyclophosphamide, methotrexate), immune modulators (pentoxifylline, thalidomide), non-cytotoxic anti-inflammatory agents (chloroquine, hydroxychloroquine), and radiation have been used. These drugs are not consistently effective and many have serious side effects. Thus, the search for an ideal drug for the treatment of sarcoidosis continues. Recent studies have shown that tumor necrosis factor-α (TNF-α) plays an important role in perpetuating the granulomatous inflammation. Infliximab, a tumor necrosis factor antagonist, blocks the effect of tumor necrosis factor and exerts a beneficial effect by controlling sarcoidosis. We present the results of 12 patients with multisystem sarcoidosis who were treated with infliximab.

**Patients and methods**

Between 2001 and 2003, 12 patients with sarcoidosis at the Ambulatory Health Care Center of the Keck School of Medicine received infliximab. These patients had clinical as well as histological evidence of sarcoidosis. They were either refractory to treatment with corticosteroids and/or alternative drugs or had developed severe side effects, including depression, psychosis, suicidal tendency, brittle hyperglycemia, unmanageable obesity, and osteoporosis. All patients had a negative tuberculin test. They were also screened for latent tuberculosis by a detailed past medical, family, and social history, including travel to countries where tuberculosis is endemic. All patients were examined and evaluated by one physician. Infliximab was administered in an outpatient infusion clinic. The initial dose was 3 mg/kg body weight and subsequent doses were given at weeks 2, 4, 6, 10, and 14; all patients received at least six infusions. Additional doses were given at 8-week-intervals for those who did not respond or for those who had an initial response and then a relapse. In most of the patients, corticosteroids were reduced or discontinued. Methotrexate was continued during infliximab therapy.

**Results**

The clinical, radiological, and histological, features of 12 patients are summarized in Table 1. All patients had chronic sarcoidosis of at least 3 years duration. The following representative patients are described in detail.

**Case 1 (Case #1 in Table 1)**

In 1986, this 29-year-old Caucasian woman developed skin lesions and hilar lymphadenopathy. A hilar lymph node biopsy confirmed the diagnosis of sarcoidosis. First, her skin lesions were treated with topical steroids. Later when the lesions worsened, she was given oral prednisone and hydroxychloroquine. Prednisone was discontinued because of weight gain, psychological problems, and insomnia. Over the next 10 years, the patient was treated with methotrexate, triamcinolone injections, thalidomide, and cyclophosphamide. In 2002, her skin lesions became more prominent and disfiguring. From June to August, the patient received three infusions of infliximab at 3 mg/kg body weight and methotrexate 10 mg once per week. She tolerated the first two injections well; however, after the third injection, she developed itching and mild urticaria, both of which were alleviated by an antihistamine. After the fourth injection, her skin lesions had subsided by 85%;
<table>
<thead>
<tr>
<th>Number</th>
<th>Age at Dx</th>
<th>Age at Tx</th>
<th>Gender</th>
<th>Race</th>
<th>Clinical features at Dx</th>
<th>Biopsy</th>
<th>Treatment failure</th>
<th>Indication for Infliximab</th>
<th>Chest X-ray</th>
<th>Subjective response</th>
<th>Objective response</th>
<th>Complications</th>
<th>Follow-up</th>
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<tr>
<td>1</td>
<td>29</td>
<td>35</td>
<td>F</td>
<td>W</td>
<td>Skin lesions</td>
<td>Extensive skin lesions, depression</td>
<td>Mediastinal LN</td>
<td>Pred, HCQ, AZA, CPM, Thal</td>
<td>Progressive skin lesions</td>
<td>Stage I</td>
<td>Depression subsided</td>
<td>Complete disappearance of skin lesions</td>
<td>None</td>
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<tr>
<td>2</td>
<td>58</td>
<td>61</td>
<td>F</td>
<td>W</td>
<td>Fever, EN Dizziness, memory loss, ataxia</td>
<td>Liver &amp; skin lesions</td>
<td>Pred, HCQ, AZA, CPM</td>
<td>Progressive neurological lesions</td>
<td>Stage I</td>
<td>Dizziness subsided</td>
<td>CT improved</td>
<td>Died of abdominal bleed. Autopsy showed plasma cell dyscrasia</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>53</td>
<td>M</td>
<td>W</td>
<td>Cervical LN</td>
<td>Lupus pernio</td>
<td>Cervical LN</td>
<td>Pred, HCQ, Thal, MTX</td>
<td>Extensive skin lesions</td>
<td>Stage I</td>
<td>Improved neurological symptoms</td>
<td>Skin lesions cleared</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>64</td>
<td>F</td>
<td>W</td>
<td>Cough, bilateral hilar LN Ataxia, spinal cord involvement</td>
<td>Mediastinal LN</td>
<td>MTX (poor candidate for steroids)</td>
<td>Progressive neurological lesions</td>
<td>Stage I</td>
<td>Improved ataxia</td>
<td>MRI improved</td>
<td>None</td>
<td>Receiving 15 injections. Remains off all drugs for 3 months</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>51</td>
<td>F</td>
<td>W</td>
<td>Skin lesions and dry cough Bone pain</td>
<td>Skin</td>
<td>Bone lesions</td>
<td>MTX, HCQ</td>
<td>Bone pain and fatigue subsided</td>
<td>Bone scan improved</td>
<td>None</td>
<td>Bone lesions returned. Resumed infliximab with improvement. Remains off infliximab for 2 years Stable off infliximab for 22 months. However, remains on Pred and MTX</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>61</td>
<td>M</td>
<td>W</td>
<td>Dyspnea, cough Dyspnea, fatigue</td>
<td>Lung</td>
<td>Persistent dyspnea</td>
<td>Pred, MTX, HCQ</td>
<td>Stage II</td>
<td>Improved dyspnea</td>
<td>Lung function improved</td>
<td>None</td>
<td>Stable off infliximab for 22 months. However, remains on Pred and MTX</td>
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<tr>
<td>7</td>
<td>57</td>
<td>70</td>
<td>F</td>
<td>AA</td>
<td>Dyspnea, subcutaneous nodules Bone pain, skin lesions</td>
<td>Skin</td>
<td>Persistent dyspnea, bone pain</td>
<td>Pred, MTX, HCQ</td>
<td>Stage III</td>
<td>Improved dyspnea</td>
<td>Improved skin lesions</td>
<td>None</td>
<td>Dyspnea and skin lesions reappeared. Infliximab resumed after 15 months Died of abdominal bleed. Autopsy showed plasma cell dyscrasia</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>49</td>
<td>F</td>
<td>AA</td>
<td>Skin lesions</td>
<td>Dyspnea, progressive skin lesions</td>
<td>Skin</td>
<td>Persistent skin lesions</td>
<td>Pred, MTX, HCQ</td>
<td>Stage III</td>
<td>Improved dyspnea</td>
<td>Improved skin lesions</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>52</td>
<td>M</td>
<td>H</td>
<td>Abdominal pain, hypercalcemia, skin lesions Dyspnea</td>
<td>Abdominal pain, splenomegaly, skin lesions</td>
<td>Cervical LN</td>
<td>Pred, HCQ, pentoxifylline</td>
<td>Abdominal pain improved</td>
<td>Stage II</td>
<td>Improved cervical LN and hypercalcemia</td>
<td>None</td>
<td>None</td>
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<tr>
<td>10</td>
<td>55</td>
<td>60</td>
<td>F</td>
<td>AA</td>
<td>Uveitis, optic neuritis Elevated liver enzymes</td>
<td>Liver</td>
<td>Pred, AZA, MTX</td>
<td>Worsening liver function tests</td>
<td>Stage 0</td>
<td>Fatigue improved</td>
<td>Alkaline phosphatase level decreased</td>
<td>None</td>
<td>Still on infliximab</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>53</td>
<td>F</td>
<td>AA</td>
<td>Uveitis, optic neuritis Poor vision, dizziness</td>
<td>None, elevated ACE level</td>
<td>Pred, MTX, HCQ</td>
<td>Worsening vision</td>
<td>Stage I</td>
<td>Fatigue improved</td>
<td>Vision improved</td>
<td>None</td>
<td>Remains off treatment after 6 injections</td>
</tr>
<tr>
<td>12</td>
<td>58</td>
<td>64</td>
<td>F</td>
<td>W</td>
<td>Uveitis, optic neuritis Poor vision, dizziness</td>
<td>None, elevated ACE level</td>
<td>Pred, MTX, HCQ</td>
<td>Worsening vision</td>
<td>Stage I</td>
<td>Fatigue improved</td>
<td>Vision improved</td>
<td>None</td>
<td>Remains off treatment after 6 injections</td>
</tr>
</tbody>
</table>

Abbreviations: AA = African American, W = white, H = Hispanic, M = male, LN = lymph node, Pred = prednisone, HCQ = hydroxychloroquine, MTX = methotrexate, Thal = thalidomide, AZA = azathioprine, EN = erythema nodosum, CT = computed tomography, ACE = angiotensin converting enzyme. Note: Infliximab dose is 3 mg/kg body weight.
after the sixth injection, the skin lesions had almost completely disappeared (Fig. 1a–f). Hilar adenopathy and the lung function remained unchanged.

**Case 2 (Case #2 in Table 1)**

In 1999, this 58-year-old Caucasian woman developed fever, weight loss, erythema nodosum, and sub-cutaneous nodules (Derrier–Roussey syndrome). A biopsy of one of the nodules showed non-caseating granulomas. No treatment was given. In March 2001, the patient was found to have involvement of the liver and splenomegaly. A splenectomy was performed to exclude lymphoma. However, perihilar lymph nodes and a liver biopsy showed non-caseating granulomas. In September 2002, the patient developed dizziness, memory loss, ataxia, and tingling in her hands and feet. A CT of the brain showed changes consistent with the diagnosis of neurosarcoidosis. Prednisone 60 mg per day and methotrexate 20 mg once per week were started. In January 2003, her skin lesions returned and she developed hypercalcemia. Methotrexate was discontinued and azathioprine 100 mg/day added. With the onset of depression, the prednisone dose was reduced. Infliximab 3 mg/kg of body weight was started. Between March and October 2003, she received six infusions. Skin lesions subsided, serum calcium and alkaline-phosphatase levels became normal, neurological symptoms improved, serum angiotensin converting enzyme level came down from 185 to 167 IU, and CT of the brain improved (Fig. 2a,b). She responded to infliximab therapy and remained well for about 3 months before developing a fatal abdominal hemorrhage due to a superior mesenteric artery dissection. Autopsy revealed a plasma cell dyscrasia.

![Figure 2](link) Computerized tomography of brain (a) before and (b) after infliximab therapy (#2 in Table 1).

**Case 3 (Case #3 in Table 1)**

In 1965, this 18-year-old Caucasian man was found to have bilateral hilar adenopathy on a chest X-ray film. A cervical lymph node biopsy showed non-caseating granulomas. No treatment was given. In 1970, he developed lupus pernio. At first, the rash was treated with topical corticosteroids. The patient declined to take prednisone. A trial of methotrexate failed to halt the progression of the rash. Hydroxychloroquine, azathioprine, doxycycline, and thalidomide were tried. None of the drugs succeeded; either the patient developed side effects or the drug was ineffective. In August 2001, infliximab 3 mg/kg body weight was started. His lupus pernio cleared after eight infusions (Fig. 3a,b). The skin lesions recurred after 3 months and infliximab was resumed. He received a total of 13 infusions and remains off therapy. The patient developed high ANA titers that fluctuated spontaneously. The ANA pattern remained homogenous. There were no changes in liver or kidney functions. Sedimentation rate, CRP, and rheumatoid factor remained normal.

**Case 4 (Case #4 in Table 1)**

In 2001, this 61-year-old Caucasian woman developed a dry cough. A chest X-ray film showed bilateral hilar adenopathy. Mediastinal node biopsy revealed non-caseating granulomas. Since she had no symptoms, no treatment was given. In 2002, the patient became ataxic. An MRI revealed intramedullary lesions in the cervical and thoracic spinal cord. The clinical course was consistent with neurosarcoidosis. She was started on methotrexate 20 mg once a week. Because of her obesity, glaucoma, depression, and a family history of diabetes mellitus, prednisone was not given. Despite a 6-month course of treatment with methotrexate, her neurological symptoms worsened. In addition to ataxia she developed muscle weakness. In November 2003, she was started on

![Figure 3](link) Lupus pernio: before and after infliximab treatment (#3 in Table 1).
Infliximab 3 mg/kg body weight. After six infusions her neurological symptoms improved. The MRI in Fig. 4 shows the radiographical evidence of improvement.

**Case 5 (Case #5 in Table 1)**

In 1995, this 42-year-old Caucasian woman developed shortness of breath. In 1996, a skin biopsy established the diagnosis of sarcoidosis. In 1997, her dyspnea worsened and a chest X-ray film was consistent with stage III pulmonary involvement. She was treated with prednisone for approximately 2 years. In 2000, her symptoms progressed to include fatigue, bone pains, and low-grade fevers. Prednisone was reduced and methotrexate 20 mg once per week was added. A bone scan in January 2001 and a whole body gallium scan showed lesions in the femoral shaft, the hip bones and the skull. A 2-year trial of methotrexate failed to improve her symptoms. In February 2002, she was started on infliximab. After the third infusion, her bone pain subsided and the systemic symptoms of low-grade fever and fatigue subsided. A bone scan showed marked improvement (Fig. 5a,b). After eight infusions, infliximab was discontinued but methotrexate was continued. In March 2003, 3 months after infliximab was discontinued, her symptoms returned. Her bone marrow became hypermetabolic and areas of inflammation appeared in the left sacral and right orbital areas. She was given another course of infliximab with improvement.

**Discussion**

Infliximab is a chimeric (mouse/human) IgG-1 anti-TNF-α monoclonal antibody that binds to soluble transmembrane TNF-α with high affinity and forms a stable complex that blocks the union of this cytokine with its receptor. Inhibition of TNF-α is achieved in vitro with infliximab concentrations of 0.2–10 μg/ml.1 Infusions of 3 or 10 mg/kg Infliximab at weeks 0, 2 and 6 produce predictable, effective serum drug concentrations and are superior to placebo.2 The frequent development of anti-infliximab antibodies requires the use of methotrexate in combination, rather than monotherapy with infliximab.3,4 Infliximab also kills the cells that express TNF-α through antibody-dependent and complement-dependent cytotoxicity.4 Clinical studies in rheumatoid arthritis have established a standard regimen.3,5,6 If patients do not respond to the standard dose or have an initial response followed by a relapse, then they may have a better response if the interval between infusions is decreased or the dose is increased.2,7 TNF-α plays a role in the pathogenesis of many chronic inflammatory diseases. TNF blocking therapy with infliximab or etanercept is effective in many diseases including rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, and psoriatic arthritis.8-10 TNF-α also plays an important role in modulating the granulomatous inflammation of sarcoidosis.11,12 High levels of tumor necrosis factor are found at the site of inflammation.13 Corticosteroids, methotrexate, and azathioprine suppress TNF-α production by alveolar macrophages in...
sarcoidosis. In sarcoidosis, there are no guidelines regarding the indications, dose, and duration of therapy, and assessing response of the disease to infliximab. A limited number of sarcoidosis patients have been treated with infliximab.15–22 Our study was not a prospective, controlled, double-blind study; infliximab was not compared with prednisone or any of the other drugs used in controlling sarcoidosis. Infliximab was used because of the presence of one or more of the following:

1. Patients with sarcoidosis who failed to respond to corticosteroids.
2. Patients who responded favorably to corticosteroids but did not wish to continue because of severe side effects.
3. Patients who developed either side effects to or failed treatment with chloroquine, hydroxychloroquine, azathioprine, methotrexate, or cyclophosphamide.
4. Patients who could tolerate only methotrexate in small doses, but whose severity of the disease required adding another drug that the patient could not tolerate. Although infliximab was effective in suppressing the granulomatous inflammation, the illness recurred in four patients, 2–6 months after the initial course of six infusions had ended.
5. Patient who required a second course of infliximab infusion to control bone pains.

Infliximab was effective not only in controlling the skin lesions of sarcoidosis, but also in favorably influencing bone, pulmonary, neural, and lymph node involvement due to sarcoidosis. In Patient #9, hypercalcemia responded to infliximab, although the drug was given for enlarged lymph nodes. There were only a few side effects attributable to infliximab. No patient developed side effects warranting discontinuation or interruption of treatment. Increased autoantibody production has been reported with the use of infliximab.3,4,6 Repeated treatment with the drug may lead to the development of human antichimeric antibodies (HACA). We did not measure such antibodies. The development of HACA can be associated with hypersensitivity reactions after the drug infusion.23 In patient #3 anti-nuclear antibody levels increased but these elevations were transient and were not associated with other hematologic or immunologic changes. None of the patients experienced significant allergic or anaphylactic reaction. None developed any serious pulmonary or extrapulmonary infections, although an increased risk of opportunistic infections (including tuberculosis and fungi) has been reported in patients treated with infliximab.6,24–26

An increased incidence of lymphoma and malignancy has been reported in patients with rheumatoid arthritis and sarcoidosis who received infliximab, but it is unclear if the risk was related to the primary illness or previous immunosuppressive treatment or infliximab.27–29 One of our patients (#2) developed myeloma after termination of infliximab therapy. We believe it was unrelated to both sarcoidosis and infliximab.

In conclusion, infliximab is effective in controlling different manifestations of sarcoidosis that are resistant to conventional therapy. It is particularly beneficial in progressive, inexorable cutaneous sarcoidosis that is poorly responsive to, or is non-responsive to corticosteroids and immunosuppressive agents. It appears that in order for the drug to be active it would need to be given intermittently over a long period of time. Often, a recurrence of symptoms may be seen upon discontinuation of the drug, which may necessitate another course of treatment. Once the aggressive inflammation is brought under control, the disease can then be kept subdued with methotrexate, hydroxychloroquine, or azathioprine. It is an expensive drug. Furthermore, long-term impact of the drug in patients with sarcoidosis who have a complex immunopathogenesis is not known. The drug is likely to find its niche in controlling overwhelming granulomatous inflammation affecting the vital organs like the eyes and the central nervous system.

References

2. St Clair E, Fasenmade A, Wagner C, et al. The relationship of hypercalcemia responded to infliximab although the drug was given for enlarged lymph nodes. There were only a few side effects attributable to infliximab. No patient developed side effects warranting discontinuation or interruption of treatment. Increased autoantibody production has been reported with the use of infliximab.3,4,6 Repeated treatment with the drug may lead to the development of human antichimeric antibodies (HACA). We did not measure such antibodies. The development of HACA can be associated with hypersensitivity reactions after the drug infusion.23 In patient #3 anti-nuclear antibody levels increased but these elevations were transient and were not associated with other hematologic or immunologic changes. None of the patients experienced significant allergic or anaphylactic reaction. None developed any serious pulmonary or extrapulmonary infections, although an increased risk of opportunistic infections (including tuberculosis and fungi) has been reported in patients treated with infliximab.6,24–26

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References


