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Miscellaneous

Long term follow-up of infliximab efficacy in pulmonary and extra-pulmonary sarcoidosis refractory to conventional therapy

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ABSTRACT

Introduction: Infliximab, a humanized, chimeric, monoclonal antibody against tumor necrosis alpha (TNF-α), has been shown to reduce the pulmonary and extra-pulmonary manifestations of sarcoidosis, however, there is little information regarding sustained efficacy with long-term use of infliximab. We retrospectively investigate whether a reduction in disease response is maintained, over a prolonged course of therapy (up to 85 months) with infliximab, and report on adverse events associated with its use.

Methods: Subjects with multi-organ sarcoidosis were prescribed infliximab, between January 2000 to June 2010 due to failure of conventional therapy and were identified from the Drexel University College of Medicine sarcoidosis clinic. Retrospective patient reported symptom and objective clinical data analyses of pulmonary and extra-pulmonary findings were evaluated pre-infliximab and post or concurrent infliximab therapy. Any adverse events or reasons for discontinuation during infliximab therapy were reported.

Results: Twenty-six patients with biopsy proven sarcoidosis received anti-TNF therapy and met the criteria for study inclusion. Clinical evidence of sustained resolution or improvement was demonstrated in 58.5% of all organs assessed ($p = < 0.001$). No clinical change in disease activity was seen in 35.8% of all organs evaluated. Despite infliximab treatment, 5.7% had progressive disease activity. Adverse events were seen in 57.7% of patients treated with infliximab over a 46.2 month average duration of therapy. Three (12%) patients had an adverse event that required permanent discontinuation.

Conclusions: Infliximab is efficacious in the treatment of extra-pulmonary sarcoidosis and the efficacy is maintained with prolonged treatment. In patients with pulmonary sarcoid, sustained improvement in pulmonary imaging was seen after initiation of infliximab, however, post-treatment pulmonary function testing was not conclusive. Long-term infliximab therapy was well tolerated for our study group.

Introduction

Sarcoidosis is a multi-organ disorder which is histologically characterized by non-caseating granuloma formation. The etiology of sarcoidosis remains unclear, however, in patients with sarcoidosis, tumor necrosis factor alpha (TNF-α) is known to play a crucial role in the formation and maintenance of the non-caseating granuloma and production of this cytokine by alveolar macrophages is substantially elevated [1]. In addition, TNF-α elevations have been shown to correlate with sarcoid disease activity and progression [2].

Corticosteroid therapy is usually considered to be first line therapy for patients with sarcoidosis. Often clinical remission can be obtained without further escalation in immunosuppressive therapy [3]. In patients with refractory disease, multiple therapies have been reported including methotrexate, hydroxychloroquine, azathioprine, cyclophosphamide, pentoxifylline and thalidomide [4–9]. None of these immunosuppressive agents have been validated with randomized controlled trials and currently there are no FDA approved agents for the treatment of refractory, non-remitting pulmonary, or extra-pulmonary sarcoidosis.

Abbreviations: TNF, tumor necrosis factor; MRI, magnetic resonance imaging; CT, computerized tomography; PFT, pulmonary function test; LN, lymph node; CNS, central nervous system; IFX, infliximab; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; DLCO, carbon monoxide diffusing capacity; MTX, methotrexate; HCQ, hydroxychloroquine; AE, adverse events; HPV, human papilloma virus; PPD, purified protein derivative

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Because of TNF-α's known role in sarcoidosis, anti-TNF therapy has been an attractive therapeutic option [10]. Infliximab, a humanized chimeric monoclonal antibody against TNF-α, is currently approved by the FDA for the management of rheumatoid arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis [11–16]. Infliximab specifically binds to TNF-α, rendering this cytokine biologically inactive thereby inhibiting its contribution to granuloma formation.

Prior studies, which evaluated infliximab efficacy in sarcoidosis, have predominately reported data on short-term outcomes. Our retrospective study investigates infliximab efficacy in patients with sarcoidosis refractory to conventional therapy and reports unique data on long-term outcomes of patients treated with this anti-TNF agent.

Materials and methods

Study approval was obtained through the Institutional Review Board at Drexel University Office of Regulatory Research (approval number 19,544). Subjects (18–85 years of age) with documented single or multi-organ sarcoidosis were retrospectively identified from our sarcoidosis clinic using office records, dating from January 2000 to June 2010, as data sources. Inclusion criteria included patients with sarcoidosis who were started on infliximab due to failure or intolerance of conventional therapy, which was defined as corticosteroid and/or disease modifying anti-rheumatic drug therapy such as methotrexate. Failure of therapy was determined by either a pulmonologist or rheumatologist and defined as either clinical or symptomatic progression of disease despite non-biologic therapy. All patients included in the study had biopsy proven sarcoidosis. Exclusion criteria included those patients without documentation of biopsy proven sarcoidosis, as well as incomplete documentation that precluded an adequate investigator analysis of disease response before or after infliximab initiation. Two separate investigators agreed upon a patient's exclusion.

Data were retrospectively collected for patients who underwent serial follow-up with history and physical examination conducted by a consistent examiner experienced with the diagnosis and management of sarcoidosis. The duration of infliximab use was noted for each patient, as well as the use of immunosuppressive therapy prior to and concurrent with infliximab therapy.

Pulmonary and extra-pulmonary (ocular, cutaneous, lymphatic, musculoskeletal, cardiac, neurologic, sinus, liver and renal) data were collected. Prior magnetic resonance imaging (MRI) or computerized tomography (CT) scans were reviewed to assess organ disease burden prior to and after initiation of infliximab. In addition, available chest radiographs were evaluated to assess lymphadenopathy attributed to sarcoidosis. Documented physician evaluation was reviewed to establish sarcoid burden in cutaneous and ocular sarcoidosis. Based on this documented objective data, a patient's clinical response was interpreted as resolved, improved, unchanged, or progressed after starting infliximab therapy. Each organ with documented sarcoid involvement was graded in this manner. Those organs defined as "resolved" demonstrated complete resolution of clinical disease activity. "Improved" disease was used to describe the organs that had reduced sarcoid burden or reduced frequency in disease activity but still had evidence of disease. Organs labeled as "unchanged" demonstrated disease activity that was clinically no different than prior to infliximab initiation. Patients with organs interpreted as "progressed" displayed clinical features of progressive disease despite starting infliximab. The same grading scale was used to assess patient reported symptom response to infliximab. Patient reported, organ-specific, symptomatic response to infliximab was designated as either resolved, improved, changed or progressive, as documented by the examining physician. Pulmonary function testing (PFT) was collected in patients with documented pulmonary sarcoid. PFT data were collected retrospectively, both pre-infliximab and post-infliximab therapy.

Adverse events during infliximab therapy and any reasons for discontinuation of infliximab therapy were reported. All data collection was completed by physician investigators and verified by the principal investigator.

Statistical analysis

Wilcoxon Signed Ranks Test (nonparametric) analysis was utilized to compare improved and resolved versus worsened disease outcome by organ system affected. This comparison was calculated for data pertaining to objective clinical and subjective symptom outcomes. The same statistical tool was utilized to compare PFT data prior to and after infliximab therapy in patients with pulmonary sarcoidosis.

Results

Forty-two patients with sarcoidosis received infliximab infusions. Sixteen patients were excluded due to incomplete data ($N = 10$), absence of confirmatory biopsy ($N = 5$), or incomplete infliximab dosing ($N = 1$). Poor patient follow-up was the cause of incomplete data collection and thereby prevented consistent documentation to retrospectively review. Twenty-six patients met the criteria for study inclusion. African Americans and males were the prominent groups represented in the study cohort (81% and 62%, respectively). The average duration of disease activity was 14.9 years (Table 1).

Objective disease activity, measured by imaging of the involved organ or physician assessment (for cutaneous and ocular sarcoid analysis), was most represented in the lung, skin, lymph node and central nervous system (57.7%, 42.3%, 42.3%, 30.8%, respectively; Table 2). Clinical improvement was most pronounced in patients with cutaneous sarcoidosis, demonstrating sustained clinical resolution (36.4%) or improvement (63.6%) in all of the patients with sarcoid lesions treated with infliximab (Table 2, $p = 0.005$). Patients with documented neurosarcoid

Table 1
Demographic and Sarcoidosis Characteristics of the Study Population.

Mean Age, Years (Range)	51 (35–69)
Ethnicity, *N* (%)	
African American	21 (81)
Caucasian	4 (15)
Other	1 (4)
Gender, *N* (%)	
Female	10 (38)
Male	16 (62)
Average age of initial sarcoidosis diagnosis (yrs.)	38.0 (22–54)
Average disease length (yrs.)	14.9 (6–50)
Ineffective immunosuppression prior to IFX, *N* (%)	
Corticosteroids	24 (92.3)
Methotrexate	20 (76.9)
Hydroxychloroquine	23 (88.5)
Etanercept	1 (3.8)
Concurrent immunosupp-ression at IFX initiation, *N* (%)	
Corticosteroids	16 (61.5)
Methotrexate	15 (57.7)
Hydroxychloroquine	12 (46.2)
Average duration of IFX therapy (months)	46.2