

Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease

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Abstract Objective

To study the potential effectiveness of tumor necrosis factor α (TNF- α) inhibitor treatment for pulmonary fibrosis associated with a collagen vascular disease, CVD (rheumatoid arthritis, RA and systemic sclerosis, SSc) refractory to conventional treatment.

Methods

Four patients (three men with RA, one woman with SSc) were treated with infliximab. All patients received 3mg/kg of infliximab at intervals 0, 2 and 6 weeks, and then maintenance infusions every 8 weeks afterwards for at least a 12-month period. Patients had active disease despite treatment with corticosteroids and other immunomodulatory agents.

Results

Treatment was well-tolerated from all patients. Pulmonary fibrosis remained stable during treatment in terms of symptoms, pulmonary function tests (PFTs) and High resolution computed tomography (HRCT) appearance. As expected, a clinical response was observed in joint symptoms in patients with RA as evaluated by the DAS28 (Disease Activity Score, the 28 joint version).

Conclusion

This study suggests that inhibition of TNF- α with infliximab may stabilize the progression of pulmonary fibrosis associated with CVD. Prospective, controlled trials are necessary to determine the efficacy of infliximab in pulmonary fibrosis associated CVD.

Key words

Infliximab, pulmonary fibrosis, collagen vascular disease, rheumatoid arthritis, scleroderma, treatment.

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Introduction

TNF- α is a potent proinflammatory mediator that can modulate the function and development of most nucleated cells, including those involved in chronic inflammatory lung disease (1, 2). A number of studies, involving animal models and patients, have demonstrated that TNF- α is upregulated in fibrosing alveolitis (2). Furthermore, blockade of TNF- α in animal models results in reduction of inflammation and subsequent fibrosis (3). Therapeutic TNF blockade has been successfully used for treating various conditions including rheumatoid arthritis (RA) and Crohn's disease (4). Infliximab is a chimeric monoclonal human mouse antibody that binds with high affinity and specificity to both the soluble and membrane-bound forms of TNF- α . Infliximab has demonstrated efficacy in reducing the signs and inflammatory symptoms of RA and in inhibiting joint erosion in clinical trials. In addition, infliximab has been shown to significantly inhibit joint space narrowing (5). It has been recently reported that it could be also effective in patients with refractory sarcoidosis and in cases of severe manifestations of Behçet's disease (6, 7).

Collagen vascular diseases (CVD) comprise a heterogeneous group of disorders, which includes RA and systemic sclerosis. Treatment options for patients with pulmonary fibrosis associated with CVD are limited. There are two case reports in literature suggesting evidence that inhibition of TNF- α may be on benefit to patients with fibrosing lung conditions in the setting of RA (8, 9). In this report we describe the use of the anti-TNF- α monoclonal antibody, infliximab, in three patients with RA and one woman with systemic sclerosis and pulmonary fibrosis.

Methods

Patients and treatment

Four patients were included in this uncontrolled, open label, prospective study.

All patients selected had a severe active disease and non-responding to corticosteroids and/or other immunosuppressive therapies, including methotrexate.

Patients were eligible for this study if their respiratory symptoms (dyspnea, cough) had become worse with an associated deterioration of > 10% of forced Vital Capacity (FVC) and/or diffusing capacity for carbon monoxide (TLco) > 15% in lung physiology.

They received infliximab in the recommended dose of 3mg/kg during weeks 0, 2, 6, and thereafter every 8 weeks.

Patient evaluation

Patients were evaluated at baseline and after 6 and 12 months of treatment. The assessment of clinical response of pulmonary fibrosis was based on:

- a) symptomatology (dyspnea, cough);
- b) Pulmonary function tests (PFTs);
- c) imaging by high resolution CT scan (HRCT) and DTPA scan.

Furthermore, the assessment of clinical response of RA was done using the DAS28 (Disease Activity Score, the 28 joint version) (10, 11).

HRCT evaluation: The HRCT slices were evaluated at five predetermined levels: the aortic arch, the tracheal carina, the pulmonary hilae, the pulmonary venous confluence, and 1-2 cm above the right diaphragm. The scans were performed with 1mm thickness and 1 to 2 sec scanning time during breath holding at end of inspiration. Mean total extent of involvement of any interstitial abnormality at each of the previously described levels, (expressed as a percentage of the area affected at each given slice) at the level of 5% was recorded. Mean values of these percentages per patient represented the Total Interstitial Disease Score (TID). This HRCT scoring was also applied in previous studies with good correlations with parameters of lung function (12). Individual slice scores and TIDs were recorded from the HRCT at the beginning of the study before the administration of treatment. Lung parenchyma involvement was classified as 0-20%: mild (grade 1), 21-40%: moderate (grade 2), > 40%: severe (grade 3).

^{99m}Tc-DTPA scan: An aerosol of Tc-^{99m} diethylenetriamine pentaacetate (DTPA) was produced using a Venticis II radioaerosol delivery system (CIS bio international, Cedex, France). The radioaerosol delivery system was ad-

Table I. PFTs and HRCT scores before and after infliximab treatment in different time points.

| | Patient 1 | | | Patient 2 | | | Patient 3 | | | Patient 4 | | |
|--------------|-----------|------|-------|-----------|------|-------|-----------|------|-------|-----------|------|-------|
| | 0 mo | 6 mo | 12 mo | 0 mo | 6 mo | 12 mo | 0 mo | 6 mo | 12 mo | 0 mo | 6 mo | 12 mo |
| FVC%pred | 77.3 | 78.9 | 79.2 | 83.1 | 78.2 | 79.5 | 73.1 | 76.2 | 74.1 | 74.5 | 76.2 | 75 |
| TLCO%pred | 42.1 | 38.4 | 39.1 | 57.3 | 65.2 | 67.1 | 55.1 | 64.1 | 58.1 | 56.1 | 54.2 | 53.3 |
| TID score | 46.6 | 36.6 | 47.5 | 33.3 | 31.6 | 29.1 | 31.6 | 31.6 | 33.3 | 42.5 | 39.1 | 35 |
| GGO* | 5 | 0 | 5 | 13.3 | 3.3 | 0 | 12.5 | 10 | 10 | 19.1 | 9.1 | 5 |
| reticulation | 31.6 | 36.6 | 42.5 | 20 | 28.3 | 29.1 | 19.1 | 22.5 | 22.5 | 25 | 30 | 26.6 |
| DTPA(min) | 23 | | 26 | 27 | | 35 | 36 | | 38 | 34 | | 38 |

FVC: Forced vital capacity; TLco: Diffusing capacity for carbon monoxide.

ministered to patients for 4 minutes. A dynamic study consisting of 30 one-minute frames were then acquired by GE Millennium MPS γ -camera (GE, Milwaukee, Wisconsin, USA). The half-time of clearance was estimated in minutes for each lung and the average value was obtained. A clearance half-time of < 40 min was regarded as abnormal. A clearance half-time of less than 20 min (50% of normal) was categorized as very rapid (13).

Results

The treatment was well tolerated in all our patients without adverse reactions. Results are shown in Table I. Patient 1, is a 62-year-old man, ex-smoker, with a ten-year history of seropositive RA with a 5-year history of respiratory symptoms. He was treated with interferon gamma-1b (IFN- γ -1b) (200 mg sc thrice a week). After one year of treatment and stabilization of PFTs and TID score (from 45.5 remained at 46) the patient discontinued the drug because of intense flu-like syndrome. He was then treated with infliximab for 12 months. His initial DAS28 score was 6.8 and decreased to 3.6 after 12 months of treatment. In addition, morning stiffness decreased from 2 hours to less than 30 minutes. The patient already had a HRCT appearance with already extended disease and a predominant reticular pattern in addition to limited macrocystic disease (honeycombing). There were also ground glass opacities extending at approximately 10% of each slice level. After 6 months of treatment, HRCT revealed complete resolution of ground glass opacities but the reticular pattern remained un-

changed (TID score from 46 decreased to 36). After 12 months of treatment, HRCT showed coarsening of the reticular pattern with replacement of fine reticulation or microcystic disease with honeycombing. Reticular changes had extended to previously unaffected areas (TID score remained stable at 47%) (Fig. 1). The patient reported stabilization in dyspnea, cough and exercise tolerance, with stabilization in PFTs. Before starting infliximab, PFTs showed a restrictive pattern with a forced vital

capacity, FVC% pred 78.9 which remained at 79% and transfer factor of the lung for carbon monoxide, TLCO % pred, from 38.4 to 39.1%. Abnormal DTPA clearance half-time ($t_{1/2} < 40$ min) was before (23 min) and after treatment (26 min).

Patient 2 is a 64-year-old man, current smoker (30py) with a two-year history of seropositive RA, initially treated with methotrexate and prednisolone, and one year history of pulmonary involve-

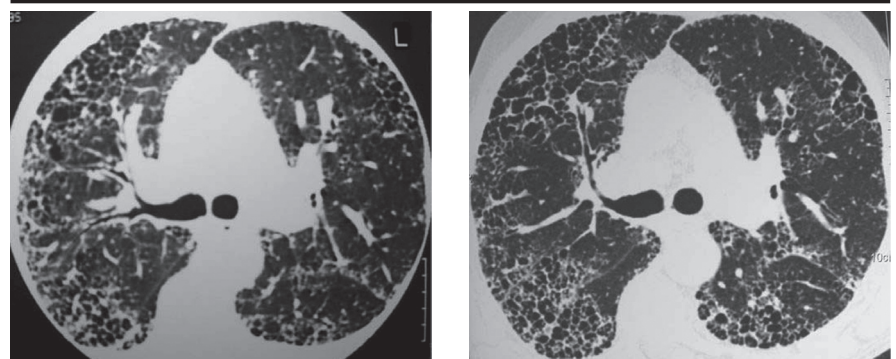


Fig. 1. Patient 1: Comparing consecutive HRCT images at the level of the right upper lobe, resolution of the ground glass opacities seen on (A) are seen on the consecutive image obtained six months later (B). However, the macrocystic honeycomb component definitely seen in A has clearly extended in image (B).

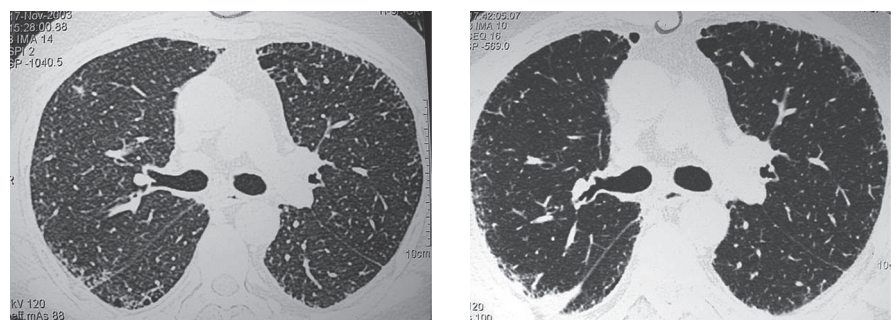


Fig. 2. Patient 2: Comparable images at the level of the right upper lobe bronchus. Subtle GGOs seen in A have resolved. Peripheral reticulation seems less intense and thick in B. Small pleural effusion on the right in B.

evaluated with a decrease in DAS28 score, from 5.78 to 4.8 after 12 months of treatment. The TID score decreased from 33 to 31 after 6 months and to 29 after one year of treatment (Fig. 2). Abnormal DTPA clearance half-time ($t_{1/2} < 40$ min) was found before (27 min) and improved after one year of treatment (35 min). PFTs remained stable while the symptomatology of this patient was slightly improved.

Patient 3, is a 70-year-old man, ex -

smoker, with a five-year history of seropositive RA, and two years history of respiratory disease. He treated with methotrexate and corticosteroids unsuccessfully. Following one year of therapy with infliximab the patient reported improvement in pulmonary symptoms, in addition to improvement in joint symptoms. The DAS28 score decreased significantly from 5.8 to 3.6. The TID score remained unchanged after the first 6 months of treatment

(31.6%) and slightly increased after one year of treatment (33.3%) (Figs. 3 and 4). PFTs, the FVC% and the TLCO % pred did not change significantly.

Patient 4 is a 58-year-old female, non-smoker, with a five-year history of systemic sclerosis with Raynaud's, esophageal and lung involvement but no skin involvement (scleroderma sine scleroderma). The pulmonary fibrosis was refractory to azathioprine and corticosteroids received for at least one year.

The TID score slightly decreased after the first 6 months of treatment (from 42.5 to 39%) with improvement of the ground glass opacities (Fig. 5). The HRCT appearance improved even after one year of therapy in both parameters (ground glass opacities and TID score) (Fig. 6). Pulmonary symptoms also improved with stabilization in PFTs after 12 months of treatment.

Discussion

This is a report of our experience in the treatment of interstitial pulmonary fibrosis with infliximab in CVD. To the best of our knowledge, this is the first report of the treatment of pulmonary fibrosis associated systemic sclerosis with an anti-TNF agent. Furthermore, three patients with pulmonary fibrosis associated RA showed stabilization of

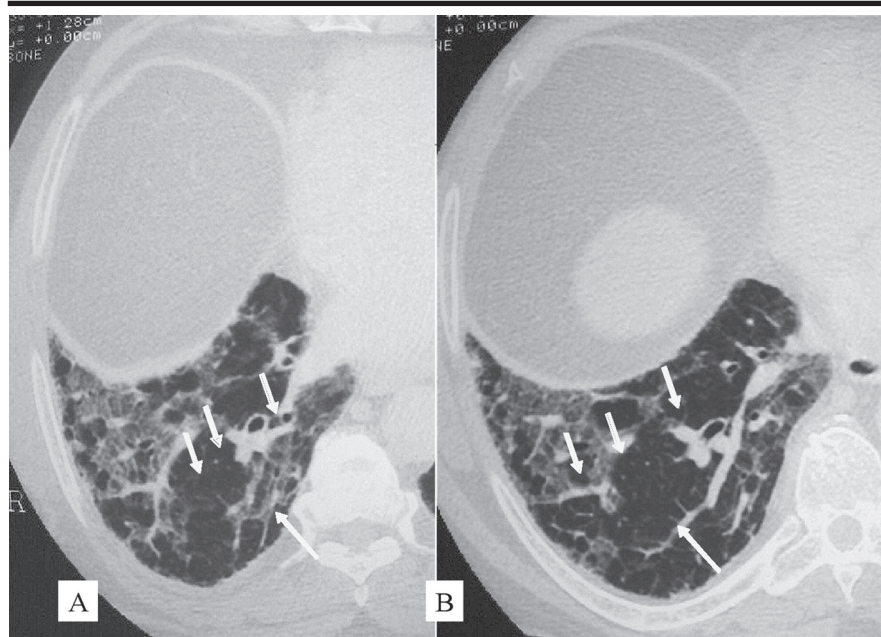


Fig. 3. Patient 3: Regional resolution of GGOs at (B) (after 6mo) compared to (A) (baseline) (arrows).

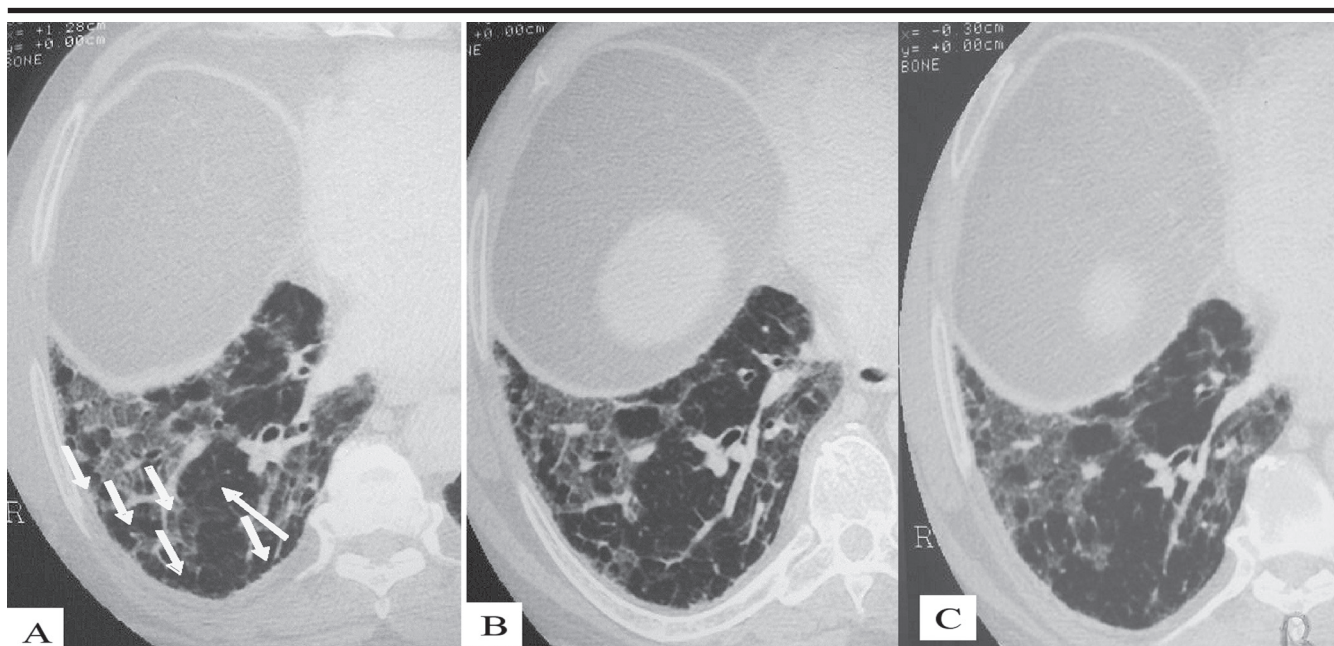


Fig. 4. Patient 3: Regional resolution of GGOs at (B) compared to (A) (arrows). Essentially stability of the disease between (B) and (C).

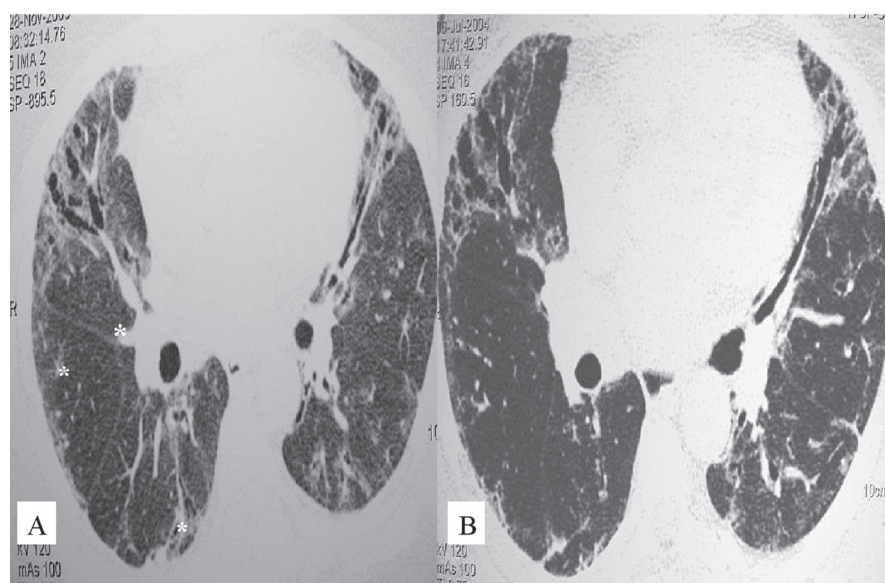


Fig. 5. Patient 4: The extensive GGOs seen in (A) (at baseline) around the bronchiectasis and the macrocystic parenchymal changes (only a few of them indicated with asterisks) have almost completely resolved in (B) (after 6 mo). There is a subtle increase in caliber both in the bronchiectatic and cystic changes in (B).

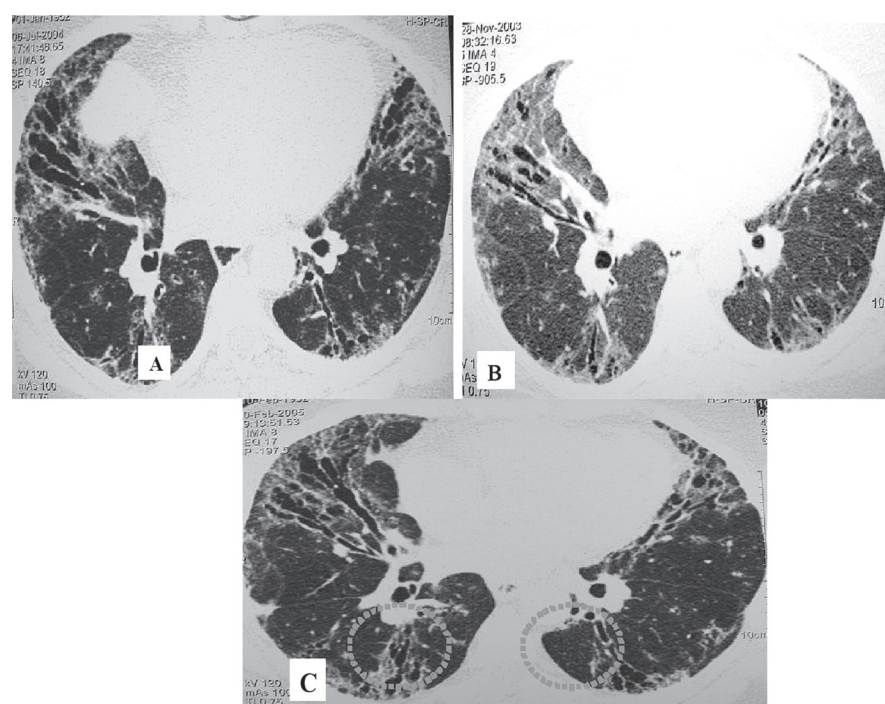


Fig. 6. Patient 4: Virtually all GGOs seen in (A) (at baseline) around the bronchiectasis and the macrocystic parenchymal changes have resolved in (B) (after 6 mo). In (C) the GGO surrounding the traction bronchiectasis in the middle lobe have resolved. Resolution of the ground glass element is also evident in the areas marked in circles (after 12 mo).

their lung disease and significant improvement of their joint symptoms. These findings suggest that infliximab can be given safely to patients with interstitial lung disease, but the impact on the disease on the disease severity is still unknown from this short report.

There are only two case reports in the literature indicating that infliximab may have beneficial effects in the treatment of RA associated with interstitial lung disease. The first, reported by Vassallo *et al.*, suggests improvement of the pulmonary symptomatology and

stabilization of pulmonary function; the authors did not provide information about the HRCT findings (8). The second, was recently reported by Bargagli *et al.*, provides more information about the HRCT abnormalities, although the patient was treated in combination with methotrexate (9). On the contrary, there is emerging experience that anti-TNF drugs could have lung toxicity (14-17). Ostor *et al.* reported three cases of patients who developed rapid fatal exacerbations of rheumatoid arthritis associated fibrosing alveolitis after taking infliximab (14). Being over 60 years old and previous lung fibrosis appear to be risk factors for developing fibrosing alveolitis in RA patients treated with TNF-blockade in four fatal cases (15). We also recommend caution in the administration of infliximab in pulmonary fibrosis, as the pathophysiology of a potential lung injury is unknown and unproven. On the other hand, we did not detect a similar phenomenon in our clinical practice and after a longer follow-up period. Randomized-controlled are needed in order to conclude about the efficacy and safety of these agents. TNF- α is a key cytokine in the early immune response of a variety of inflammatory disorders, and a critical mediator in the pathogenesis of lung fibrosis (18). The introduction of TNF- α antagonists has dramatically changed the treatment of RA; infliximab has been shown to be efficacious and well tolerated in large, randomized, placebo controlled trials in the treatment of RA. However, serious infections, including disseminated tuberculosis (TB) and opportunistic infections have been reported in patients treated with infliximab. Furthermore, it is not clear how biological therapies will affect patients over the long term (19, 20). These biological drugs suppress inflammation in RA by inhibiting the activity of the proinflammatory cytokine, TNF- α . On the other hand, chronic inhibition of this cytokine could potentially result in increased incidence of infections or tumours in some patients (20). Whether anti-TNF increases the risk of malignancies remains to be determined with no data suggesting such an effect at present. Our patients did not de-

velop infection or tumour, even after 6 months of follow-up after the 12 month treatment with infliximab.

In our study, there was one patient with fibrosing alveolitis of systemic sclerosis (FASSc) treated with infliximab. Despite the evaluation of large cohorts of patients with systemic sclerosis, the pathogenesis (21) and the optimal approach to FASSc remains elusive and for many years, idiopathic pulmonary fibrosis (IPF) and FASSc were viewed as histologically identical. The large study by Bouros *et al.* established that NSIP is much more prevalent than UIP, although, survival did not differ between NSIP and UIP/end-stage lung disease (22). Our patient was refractory to azathioprine and improved pulmonary symptoms stabilized the HRCT TID score in combination with resolution of the ground glass opacities. Lung fibrosis in RA is usually the result of UIP on histology. Although our patients had not histologically proven disease, the HRCT appearance is consistent with a fibrotic process, showing small areas of ground glass opacities. The pulmonary fibrosis associated with RA is progressive with an estimated median survival of < 4 years (23). We did not observe improvement in lung function, however, all our patients showed stabilization in the HRCT appearance with simultaneous stabilization or improvement in PFTs and symptomatology. Similar to our findings, Niden and colleagues, in an open pilot study reported tolerability in nine subjects with IPF patients. Although the subjects were severely ill (with DLCO < 30% pred), there was a functional improvement in some (24). A phase II, double-blind, parallel, placebo-controlled, randomized study of the efficacy and safety of etanercept in pulmonary fibrosis is underway. The primary endpoint of the trial is to evaluate safety and efficacy and the secondary objective is to evaluate quality of life and pharmacokinetics (25).

Our data indicate that infliximab may be a useful treatment in pulmonary fibrosis associated collagen vascular disease. Randomized-controlled clinical trials are required for the better evaluation of this agent in the treatment of these patients.

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