Case Report

Pulmonary Complications of Infliximab Therapy in Patients with Rheumatoid Arthritis

ANDREW J.K. ÖSTÖR, EDWIN R. CHILVERS, MARGARET F. SOMERVILLE, ANITA Y.N. LIM, SUZANNE E. LANE, ADRIAN J. CRISP, and DAVID G.I. SCOTT

ABSTRACT. We describe 5 patients with rheumatoid arthritis (RA) who developed pulmonary complications following infliximab therapy; 4 patients had preexisting usual interstitial pneumonia. As the pathophysiology of the pulmonary insult is unknown, we advise caution in the use of anti-tumor necrosis factor-α therapy in patients with RA with underlying lung disease of sufficient severity to withhold methotrexate treatment. (J Rheumatol 2006;33:622–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INTERSTITIAL LUNG DISEASE INFLIXIMAB
ANTI-TUMOR NECROSIS FACTOR-α THERAPY USUAL INTERSTITIAL PNEUMONIA
BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

Anti-tumor necrosis factor-α (TNF-α) therapy has had a major influence on treatment of rheumatoid arthritis (RA). The efficacy of this intervention has been demonstrated in multiple randomized controlled trials showing significant clinical benefit. The drugs are generally well tolerated; however, serious adverse events are documented, particularly infection and reactivation of *Mycobacterium tuberculosis*. We describe 4 patients with RA who developed fatal exacerbations of interstitial lung disease (ILD) and one patient with nonfatal bronchiolitis obliterans organizing pneumonia (BOOP) following infliximab treatment. The first 3 cases have been reported as a drug alert[1]. Concern is emerging regarding the respiratory complications of anti-TNF-α therapy. In view of the poor prognosis of patients with ILD complicating RA and our lack of knowledge of the underlying pathophysiology of this process, it seems wise to caution aggressive treatment in these circumstances without careful explanation, information, and detailed monitoring.

From the Rheumatology Department, Addenbrooke's Hospital, Cambridge; Rheumatology Department, Norfolk and Norwich University Hospital, Norwich; and Division of Respiratory Medicine, Department of Medicine, School of Clinical Medicine, University of Cambridge, Addenbrooke's and Papworth Hospitals, Cambridge, UK.

A.J.K. Östör, FRACP, Consultant Rheumatologist, Rheumatology Department, Addenbrooke's Hospital; E.R. Chilvers, FRCP, PhD, Professor of Respiratory Medicine, Division of Respiratory Medicine, Department of Medicine, School of Clinical Medicine, University of Cambridge, Addenbrooke's and Papworth Hospitals; M.F. Somerville, MSc, BA (Hons), Rheumatology Clinical Research Manager, Rheumatology Department, Norfolk and Norwich University Hospital; A.Y.N. Lim, MRCP, Rheumatology Specialist Registrar, Rheumatology Department, Norfolk and Norwich University Hospital; S.E. Lane, FRCP, MD, Consultant Rheumatologist, Department of Rheumatology, The Ipswich Hospital NHS Trust, Ipswich; A.J. Crisp, FRCP, MD, Consultant Rheumatologist, Rheumatology Department, Addenbrooke's Hospital; D.G.I. Scott, FRCP, PhD, Professor of Rheumatology, Rheumatology Department, Norfolk and Norwich University Hospital.

Address reprint requests to Dr. A.J.K. Östör, Rheumatology Department, Addenbrooke's Hospital, Cambridge, CB2 2QQ, UK.
E-mail: andrew.ostor@addenbrookes.nhs.uk

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CASE REPORTS

Case 1. A 67-year-old man with a 4 year history of seropositive RA developed rapidly progressive dyspnea and cough 3 weeks after administration of his third dose of infliximab. Changes consistent with early pulmonary fibrosis had been noted on a previous chest radiograph and high resolution computer tomography (HRCT) scan that showed predominantly basal and lateral reticular shadowing (Figures 1A, 2A). However, prior to starting infliximab, he had no respiratory symptoms. His concurrent medications included azathioprine 200 mg and prednisolone 15 mg daily for arthritis. Methotrexate (MTX) had been avoided due to the underlying lung disease.

On examination he was afebrile and tachypneic with a blood pressure of 124/72 mm Hg. Fine end inspiratory crepitations were audible in the lung bases. Full blood examination revealed anemia and a mild leukocytosis. Results including pulmonary function tests and arterial blood gas analysis are given in Tables 1–3. He was started on intravenous cefotaxime, erythromycin, and cotrimoxazole. A chest radiograph showed progressive change and HRCT of the chest 2 years after the original scan displayed bilateral multifocal ground-glass opacification with more extensive peripheral fibrosis and honeycomb change (Figures 1B, 2B). Bronchoscopy was normal and bronchoalveolar lavage showed scant pus cells only, with normal cytology and no bacterial growth. An open lung biopsy revealed an active inflammatory (predominantly neutrophils) and fibroproliferative process consistent with usual interstitial pneumonia (UIP; Figure 3). Detailed screening for bacterial, fungal, viral, and mycobacterial organisms including cytomegalovirus and *Pneumocystis carinii* was negative.

His condition deteriorated and he required intubation. Three doses of intravenous methylprednisolone (1.0 g daily for 3 days) were administered followed by one dose of cyclophosphamide [500 mg intravenously (IV)]. There was no clinical response and he died of progressive respiratory failure 5 weeks after the third dose of infliximab. Of note, his joint symptoms had improved taking infliximab.

Case 2. A 61-year-old woman with a 12 year history of seropositive RA and a 7 year history of mild RA-associated pulmonary fibrosis was started on infliximab therapy due to progressive joint disease. Prior to this she had min-

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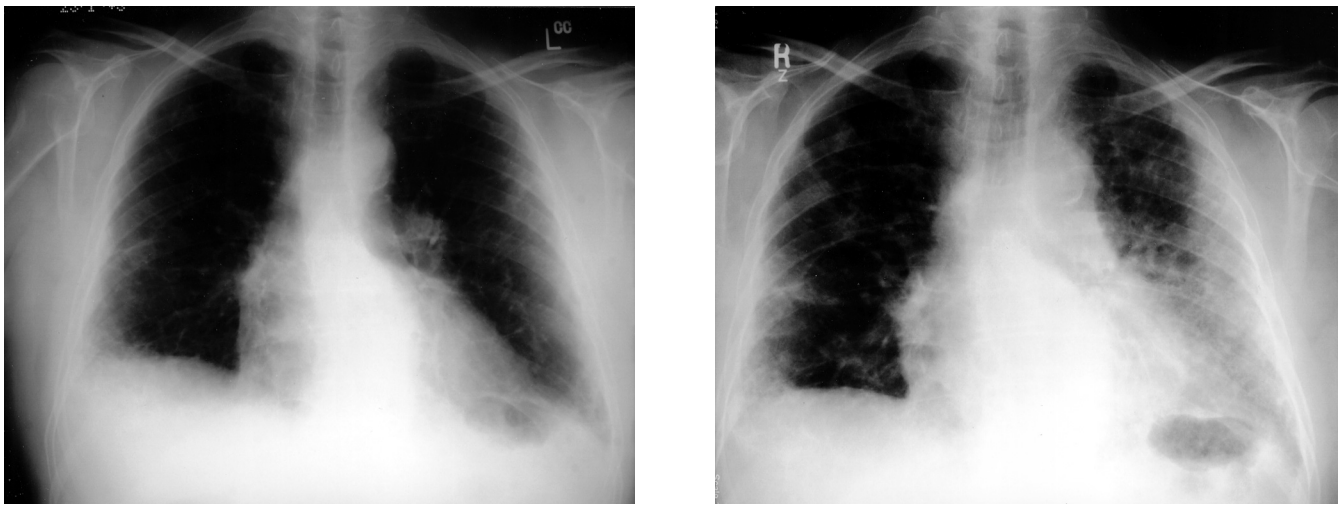
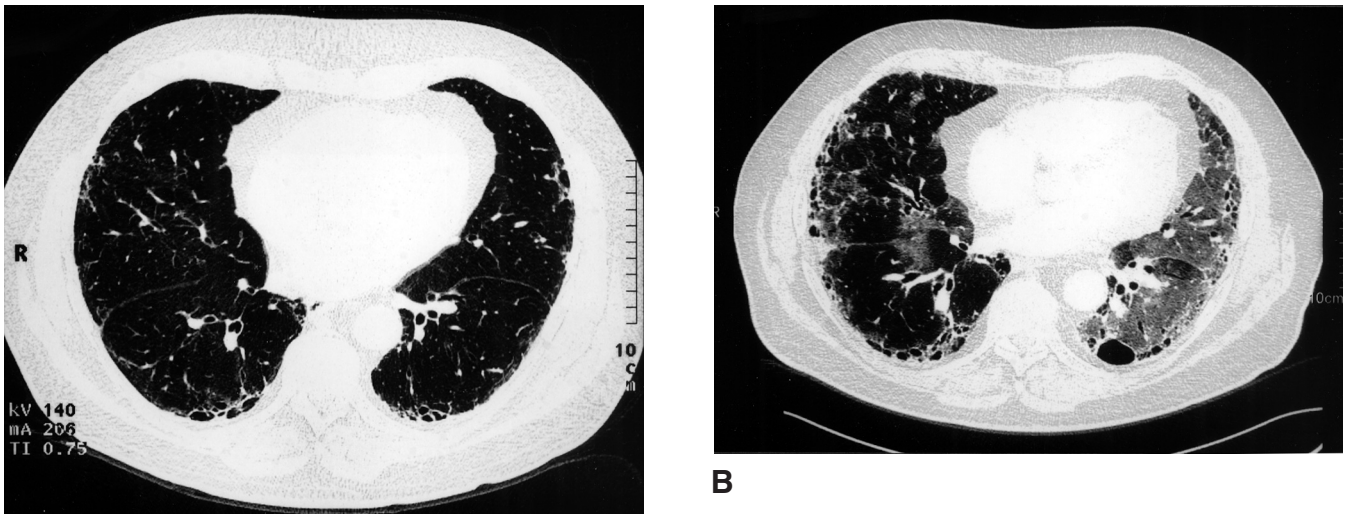


A B

Figure 1. A. Chest radiograph, Patient 1, showing early pulmonary fibrosis. B. Post-infliximab radiograph shows more extensive pulmonary fibrotic change.



A B

Figure 2. High resolution CT scans from Patient 1 show (A) predominantly basal and lateral reticular shadowing; and (B) bilateral multifocal ground-glass opacification with more extensive peripheral fibrosis and honeycomb change.

imal breathlessness, but had noted a dry cough over the preceding 12 months. Additional medications included prednisolone 7.5 mg and azathioprine 150 mg daily for the arthritis and lung disease. Several disease modifying antirheumatic drugs (DMARD) had been tried for the arthritis, without benefit, and MTX was not used due to the preexisting pulmonary disease.

Her joint symptoms responded well to infliximab; however, 3 weeks following the second infusion she complained of worsening breathlessness and dry cough. On examination she was apyrexial and tachypneic, with bibasal crepitations in the lung fields. Her chest radiograph on admission revealed widespread fine reticulonodular shadowing with dramatic change from the radiograph 18 months previously; HRCT revealed extensive peripheral fibrosis with honeycomb change and traction bronchiectasis, together with some ground-glass opacification consistent with UIP (Table 1). This had progressed markedly from her pre-infliximab scan. Exhaustive investigation for an infectious cause including blood cultures taken prior to antibiotics, sputum culture, and bronchoalveolar lavage revealed no evidence of viral, bacterial, fungal, or mycobacterial infection (Tables 2, 3). Her prednisolone was increased to 40 mg daily and she was started on cefuroxime and clarithromycin. She was discharged after 4 weeks in hospital with moderate improvement in her respiratory symptoms, but no change in her arterial blood gases. She received home oxygen therapy and the prednisolone was tapered. When reviewed 1 month later, her breathlessness had deteriorated and the prednisolone was increased to 20 mg daily followed by 3 pulses of cyclophosphamide 1 g IV given at 6 weekly intervals. She was readmitted 6 months later with endstage respiratory failure and despite further antibiotics, oxygen, and noninvasive ventilatory support she died 4 days later. A post mortem revealed features of endstage fibrotic lung disease and the accelerated and terminal phase of UIP secondary to RA (Table 1).

Case 3. A 75-year-old woman, an ex-smoker, with a 33 year history of seropositive RA and a 7 year history of associated pulmonary fibrosis was admitted with increasing shortness of breath, dry cough, and lethargy 1 week following the second dose of infliximab. She was taking prednisolone 5 mg

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Table 1. Laboratory results in 5 patients with RA who developed pulmonary complications after infliximab therapy.

Indicator	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
ESR, mm/h (pre and post infliximab)	56 to 28	40 to 78	29 to 26	50 to 69	42 to 38
RA disease activity score (pre and post infliximab)	8.11; post not performed	6.9; 5.5	7.07; 5.85	Not done	5.86 to 4.79
Eosinophil count at presentation	Normal	1.3×10^9 ($0–0.4 \times 10^9$)	Normal	Normal	Normal
Chest radiograph pre infliximab	Mild interstitial shadowing	Peripheral reticular nodular shadowing, particularly in mid and lower zones	Small volume lungs with widespread interstitial pattern	Left apical calcified granuloma and diffuse interstitial fibrosis	Normal
Chest radiograph post infliximab	Progressive pulmonary fibrosis	Dramatic deterioration since previous radiograph, with severe fibrosing lung disease. Pattern typical for UIP	Extensive bilateral reticular shadowing, with discernible progression of the original lung disease	No change from previous	Interstitial pulmonary shadowing
Chest HRCT pre infliximab	Early pulmonary fibrosis prominent posteriorly and in bases. Features consistent with UIP	Honeycomb changes posteriorly and peripherally in bases. Diffuse pulmonary fibrosis consistent with UIP	Upper lobe centri-lobular emphysema and mid and lower zone peripheral reticular nodular shadowing consistent with UIP	Not done	Not done
Chest HRCT post infliximab	Appearance consistent with severe pulmonary fibrosis/UIP	Extensive honeycombing, patchy ground-glass opacification consistent with UIP	Not done	Extensive changes of bilateral chronic ILD consistent with UIP	Widespread ground-glass opacity involving all zones and fine intra and inter-lobular reticulation at the extreme bases
Histology results	Active inflammatory fibroproliferative process in keeping with UIP (open lung biopsy)	Endstage fibrotic lung disease. Features consistent with accelerated and terminal phase of UIP (post mortem)	Not done	Honeybombing and 1 cm left apical calcification consistent with old TB. Findings consistent with ARDS on a background of diffuse pulmonary fibrosis (post mortem)	Bronchiolitis obliterans organizing pneumonia (trans-bronchial biopsy). No evidence of PCP or other infection
BAL analysis (cell counts not done)	Scant pus cells, negative cytology, no organisms, culture negative	Negative cytology, no organisms, culture negative	Not done	Histiocytes and bronchial epithelial cells, negative cytology, no organisms, culture negative	Negative cytology, no organisms, culture negative

UIP: undifferentiated interstitial pneumonia, HRCT: high resolution computer tomography, TB: tuberculosis, PCP: *Pneumocystis carinii* pneumonia, ARDS: acute respiratory distress syndrome, BAL: bronchoalveolar lavage, ESR: erythrocyte sedimentation rate.

daily for both her joint and lung disease. Azathioprine 50 mg daily was started prior to infliximab in order to reduce the development of antichimeric antibodies to this treatment. She had previously received multiple DMARD, without benefit. A chest radiograph and HRCT prior to biologic therapy revealed small-volume lungs with upper lobe centrilobular emphysema and mid- and lower-zone peripheral reticular shadowing consistent with UIP. These features had not changed over the preceding 2 years (pulmonary function test results given in Table 2).

On examination she was febrile (38.2°C), tachypneic, and had a blood pressure of 108/86 mm Hg, with fine inspiratory crackles audible throughout both lung fields. There were no focal signs of an infectious process. A chest radiograph on admission revealed small lungs with extensive airspace and reticular shadowing in both mid and lower zones. As in the previous 2 cases, extensive investigation failed to identify an infectious organism including mycobacterium and fungi and the eosinophil count was normal (Tables 2, 3). Despite IV broad-spectrum antibiotics, oxygen, and ventilatory support her lung disease progressed and she died 4 weeks after the second dose of infliximab. She did not receive intensification of her immunosuppression therapy over this period. Her family declined a post mortem. Her joint symptoms had responded to the infliximab.

Case 4. A 68-year-old female smoker with an 11 month history of seropositive RA was started on leflunomide 20 mg daily. MTX was avoided as a screening chest radiograph had revealed left apical calcified granulomata and changes consistent with pulmonary fibrosis. She described a reduced but stable exercise tolerance for 12 months (Table 2). Leflunomide was discontinued after 3 months due to persistent nausea and diarrhea. After a flare of arthritis she was started on infliximab 3 mg/kg, resulting in a prompt and marked response. Neither HRCT nor blood gas tests were performed prior to biologic therapy.

Three weeks after her third dose of infliximab she was admitted with a 7 day history of vomiting, anorexia, and chills, but no fever or new respiratory,

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Table 2. Pulmonary function tests pre and post infliximab.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Pre infliximab					
FEV1	2.67 (86%)	2.26 (86%)	0.98 (60%)	1.16 (63%)	Nil
VC	3.34 (84%)	2.54 (82%)	1.42 (71%)	1.84 (83%)	
FEV/VC	76%	89%	70%	63%	
DLCO	5.15 (57%)	3.03 (37%)	1.45 (23%)	11.2 (57%)	
Post infliximab					
FEV1	2.51 (81%)	1.5 (57%)	Nil	1.16 (62%)	2.06 (88%)
VC	2.99 (74%)	1.5 (49%)		1.64 (73%)	2.27 (83%)
FEV/VC	79%	100%		71%	91%
DLCO	4.49 (50%)	TLCO (not recorded)		5.0 (25%)	3.94 (52%)
					Repeat after resolution of respiratory symptoms:
					2.03 (87%)
					2.31 (84%)
					88%
					5.7 (74%)

FEV1: forced expiratory volume, 1s: VC: closing volume.

Table 3. Arterial blood gas analysis on admission (mm Hg).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
pH	7.46	7.45	7.50	7.43	Not done
pCO_2	39	32	31	39	
pO_2	56	64	33	58	
O_2 saturation	90% (on air)	93% (on FiO_2 24%)	70% (on air)	88% (on FiO_2 50%)	

urinary, or joint symptoms. On examination she was stable with a temperature of 38°C, pulse rate of 112/min, blood pressure of 130/70 mm Hg, and a respiratory rate of 20/min. Her previously documented fine crepitations in the lungs were unaltered, and she had no signs of localized pulmonary infection.

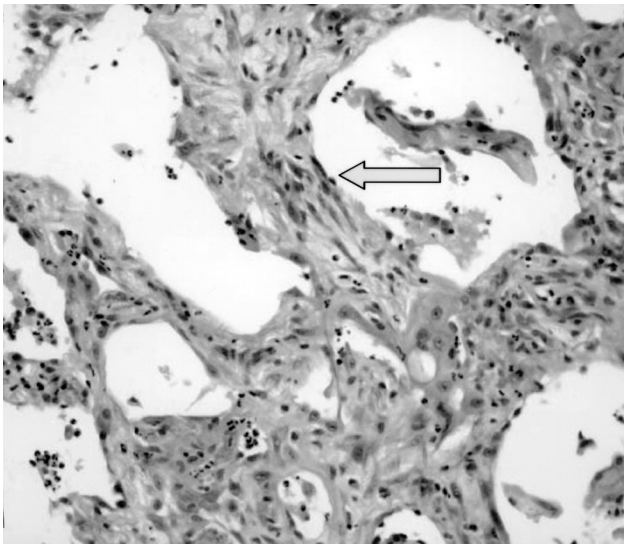

Figure 3. Lung biopsy from Patient 1 reveals diffuse interstitial fibrosis. In this field there are active fibrotic foci (arrow) as well as scattered acute inflammatory cells (neutrophils).

The white blood cell count was mildly elevated and the chest radiograph was unchanged from the initial investigation. Urine culture grew *Escherichia coli* and she was started on co-amoxiclav. Sputum and blood were repeatedly negative for Ziehl-Nielsen staining, and tuberculosis and other culture and tests for atypical pneumonia were negative.

Six days after admission she complained of worsening shortness of breath and dry cough. HRCT revealed marked basal and peripheral reticular shadowing associated with honeycombing and additional ground-glass shadowing consistent with accelerated phase UIP (Figure 4, Table 3). Despite broad-spectrum antibiotics, oxygen, and ventilatory support her respiratory symptoms deteriorated and she died 16 days post-admission. At no stage was an infectious organism isolated from her respiratory tract including bronchoalveolar lavage (Table 1). Post mortem was limited to the lungs at the request of the family, and confirmed the clinical and radiological diagnosis (Table 1).

Case 5. A 49-year-old female nonsmoker with a 32 year history of seropositive RA was started on infliximab for ongoing arthritis despite azathioprine 100 mg and prednisolone 5 mg daily. There was no history of lung disease and her pre-infliximab chest radiograph was normal. Shortly after the third dose of infliximab she developed sudden onset dyspnea, dry cough, and night sweats. She was started on erythromycin, with mild symptomatic improvement. On examination, fine late inspiratory crepitations were audible at both lung bases with no other significant abnormal physical finding. Her chest radiograph and HRCT revealed patchy bronchocentric ground-glass shadowing, but no evidence of pulmonary fibrosis (Tables 1, 2). Due to the bronchocentric appearance of the shadowing and lack of evidence to support infection, a transbronchial biopsy was undertaken. This showed several alveoli containing fibroblastic plugs and focal thickening of alveolar septa most con-

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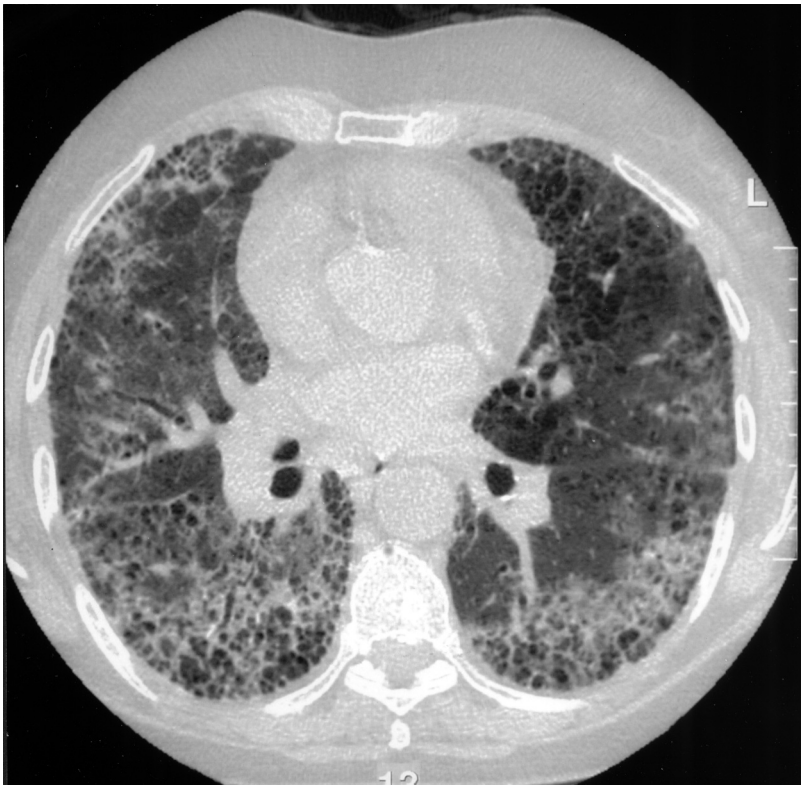

Figure 4. High resolution CT from Patient 4 shows basal and peripheral reticular shadowing associated with honeycombing and additional ground-glass change.

sistent with BOOP. Eosinophils were not a feature and bacterial and fungal stains were negative. She did not require admission and became asymptomatic 3 weeks after presentation, without specific intervention. The chest radiograph changes resolved completely within 3 months.

DISCUSSION

RA is associated with a wide variety of interstitial lung diseases. These include nonspecific interstitial pneumonia, UIP, organizing pneumonia (chronic obstructive pneumonia/BOOP), lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and diffuse alveolar damage[2]. The prevalence of ILD in patients with recent onset RA has been reported to be 8.2%[3]. The accelerated form of UIP has been reported widely in the respiratory literature and is defined as an acute, severe exacerbation of disease following a period of relative stability. In such patients pathological examination of the lungs often shows diffuse alveolar damage.

For most types of RA-associated ILD, progressive shortness of breath and a nonproductive cough are the dominant symptoms. The differential diagnosis includes typical and atypical infections and drug-induced lung disease. Nonspecific interstitial pneumonia and UIP are the commonest types of ILD in patients with RA, and in one series were associated with a mean survival of less than 4 years[4]. A reduced carbon monoxide transfer factor on lung function testing (TLCO < 54%) appears to be the key predictor of disease progression[5], and as a consequence screening for ILD in patients with RA has been suggested[3]. The unifying feature of our first 4 cases was that they were found to have RA-associated UIP.

MTX therapy, the current standard for the treatment of RA, can cause a drug-induced alveolitis and pulmonary fibrosis, and this complication is almost certainly underreported[6]. In our series concomitant azathioprine and leflunomide were used as DMARD in lieu of MTX due to concerns in patients with underlying lung disease, although the validity of this strategy remains unproven. Both drugs, however, have been associated with alveolitis[7-11]. Four out of 7 patients in one series died, the remainder improving after withdrawal of azathioprine[7].

Infliximab, a chimeric anti-TNF-α monoclonal antibody (Remicade, Schering-Plough), has been shown to both reduce the symptoms and signs of RA and arrest the radiological progression of disease[12]. Infliximab is usually combined with MTX to enhance its efficacy and to reduce the development of neutralizing anti-infliximab antibodies. An open pilot study, however, found the combination of azathioprine and infliximab to be effective in a group of 21 patients with severe refractory RA[13]. Unfortunately, one patient with RA-related vasculitis and ILD died after the third dose of infliximab secondary to streptococcal pneumonia.

In our series 3 patients taking azathioprine and one taking leflunomide developed rapidly progressive lung disease after

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the addition of infliximab. The striking feature was the temporal relationship, in that the pulmonary disease progressed shortly after only 3 or fewer doses of infliximab. The decline was inexorable in the first 4 patients, who all had RA-associated UIP. An infectious etiology for the deterioration is still possible, despite lack of isolation of an organism, and emphasizes the need for vigilance in patients taking immune-modulating drugs. The corollary is that patients may be labeled as having an infectious cause for respiratory compromise where the process may be an autoimmune or idiosyncratic pulmonary insult. We believe that this may have been the underlying process in the first 4 cases. Case 5 represents infliximab-induced BOOP, which has been associated with a variety of drugs and which may improve spontaneously.

Infliximab precipitating MTX lung disease has also been reported recently[14,15]. Similarly to our cases, worsening pulmonary symptoms developed shortly after the second or third infusion of infliximab, and one case was fatal. Two further cases of pneumonitis have been reported with infliximab as monotherapy. One patient had Crohn's disease, the other ankylosing spondylitis[16,17].

Etanercept, a TNF-α receptor fusion protein (Enbrel, Wyeth), is currently being evaluated in an open-label study in patients with UIP[18]. This treatment has been linked with the development of granulomatous lung injury[19,20]. In addition to the above evidence incriminating biologic agents in the exacerbation of RA-associated ILD, we are aware of a further patient who developed a fatal exacerbation of ILD treated with adalimumab (Humira, Abbott) who was not receiving azathioprine or MTX (J. Palit, personal communication).

Information from the British Society for Rheumatology Biologics Register (BSRBR), which prospectively collects data on all patients with RA receiving biologic therapy in the United Kingdom, reveals that after treatment with any biological agent, patients with preexisting pulmonary disease, defined as any pulmonary pathology at baseline (n = 184), had a mortality rate of 90 per 1000 person-years of followup compared with those without pulmonary disease (n = 6061), who had a mortality rate of 14 per 1000 person-years of followup. This represented a 4.4-times higher mortality rate among patients taking the biologic therapy (95% CI 1.8–10.7) (BSRBR May-August 2004 Newsletter). The odds ratio of RA patients with ILD who were treated with any biologic agent (n = 249) compared with those without ILD (n = 17) was 2.42 (95% CI 1.47–4.00). A causal relationship, however, remains unclear.

A case report has suggested that infliximab is effective in stabilizing lung function in RA-associated pulmonary fibrosis[21]. Azathioprine has also been found to be effective in treating interstitial pneumonitis associated with RA[22], and interestingly, joint disease deteriorated in this patient.

TNF-α has been implicated as a pivotal cytokine in the pathophysiology of pulmonary fibrosis[23,24]. Blockage of TNF-α abrogates silica or bleomycin-induced lung toxicity and inhibits fibrogenesis in animal models of lung fibrosis[23]. Gosset, *et al*[25] have reported significantly raised TNF-α production by alveolar macrophages in RA patients with or without pulmonary disease compared with controls. Together, these data suggest that blocking the effects of TNF-α would be beneficial in patients with RA-associated ILD. However, Elias suggests that the interaction of TNF-α with interleukin 1 or interferon-γ may modulate fibroblast proliferation[26], and that inhibition of TNF-α may result in an increased proinflammatory effect of these cytokines. Further, as infliximab binds to TNF-α expressed on the surface of CD4+ T cells and macrophages, cell lysis with local release of macrophage-derived proteolytic enzymes may also drive pulmonary damage. The inflammatory response in RA is a Th1-mediated pathway, whereas a Th2 response mediates most forms of ILD. This dichotomous response may in part explain the difference in response of one disease and not the other. The pivotal proinflammatory effect of TNF-α in RA has been well described[27].

We have described 4 patients with RA who died of progressive UIP and one case of nonfatal BOOP after 3 or fewer doses of infliximab. We caution the use of infliximab and other anti-TNF-α agents in RA patients with underlying lung disease, especially in those who have disease severe enough to raise concern regarding use of MTX. We recommend heightened vigilance for this and other pulmonary complications during postmarketing surveillance.

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