Lethal pneumonitis under leflunomide therapy

Sir, We report the case of a 62-yr-old man with a 15-month history of rheumatoid arthritis (RA) presenting with acute respiratory insufficiency. Initial diagnosis of RA was based on five of seven American College of Rheumatology (ACR) criteria. X-rays showed no joint erosions and chest radiography showed slight reticular changes. No history of smoking was reported. His drug history comprised steroids [10–25 mg/day (months 1 to 15)] and methotrexate (MTX) [15 mg/week (months 5 to 12)]. MTX was discontinued after 7 months due to increasing disease activity and leflunomide therapy (20 mg/day) was started.

Twelve weeks after initiation of leflunomide the patient presented with acute respiratory insufficiency ($pO_2 = 40.5\text{ mmHg}; pCO_2 = 30.7\text{ mmHg};$ respiratory rate $30/\text{min}$) with rapidly increasing dyspnoea for 2 days, fever and non-productive cough. At the time of presentation his medical therapy comprised prednisolone (30 mg/day), leflunomide (20 mg/day), calcium and cholecalciferol. RA disease activity was moderate. Initial laboratory studies showed: white cell count 9.1/\text{nl}, C-reactive protein (CRP) 72 mg/l, antinuclear antibodies (ANAs) and IgA rheumatoid factor (RF) negative, IgG RF, IgM RF and cyclic citrillinated peptide antibodies (CCP) highly positive, liver and kidney function normal. No micro-organisms were found in several blood, sputum and urine samples. Tests for viral infection and fungal agents were also negative. Bronchoalveolar lavage (BAL) produced a cellular liquid (320 cells/$\mu l$) with a predominance of lymphocytes (49%).

Chest radiography showed widespread interstitial opacities. High-resolution computed tomography (CT) scan showed bilateral patchy areas of ground glass attenuation, irregular reticular opacities and honeycombing.

The patient was immediately transferred to the intensive care unit. Ventilation and inotropic support were subsequently required. Despite discontinuation of leflunomide and immediate steroid pulse therapy (500 mg methylprednisolone) no improvement of the pulmonary condition was achieved. Adjunctive antibiotic treatment, immunoglobulin therapy (30 mg for 3 days) as well as cyclophosphamide (1000 mg), occasionally reported to be helpful in MTX pneumonitis [1], were ineffective. No leflunomide elimination procedure was performed. Chest radiography rapidly progressed to massive patchy acinar consolidation, alveointerstitial infiltrates and fibrosis. The patient died 30 days after presentation due to respiratory failure. Lung autopsy showed prominent fibrosis in several sections. Focally beneath the alveolar surface there were proliferations of fibromyoblasts, without fibromyxoid polyps characteristic of usual interstitial pneumonia (UIP). Within the fibrosis there were hyaline bands, most probably remnants of previous diffuse alveolar damage (DAD). In young fibrosis there was a mild inflammatory infiltration with a predominance of lymphocytes (Fig. 1). With respect to the age of the fibrotic process it seems that it developed over the same period of time. The process was diagnosed as chronic interstitial pneumonia and organization of diffuse alveolar damage.

Leflunomide is known to be an effective treatment of RA and is one of the most often prescribed antirheumatic drugs. Pulmonary side effects were not considered dangerous until September 2003 when sporadic cases of interstitial pneumonitis, including five lethal cases, were reported in Japan [2]. Pneumonitis is a potentially life-threatening complication well known with MTX [3–5]; the
mechanism by which leflunomide may induce pneumonitis or intensify the pulmonary toxicity of MTX is unclear.

RA itself can also affect the lung [6] usually leading to an interstitial pneumonia, either lymphocytic or chronic non-specific with various degrees of organizing pneumonia. None of these features was seen in the presented case. UIP and non-specific interstitial pneumonia (NSIP) could be ruled out as well. Also, the process did not fulfill the criteria of organizing pneumonia. With respect to the aetiology of DAD, infectious organisms could be ruled out by clinical investigation and special stains in tissue sections. With regard to the clinical history, MTX and leflunomide stand out. MTX can cause DAD and later on organizing DAD. The reactive proliferation seen in pneumocytes and bronchiolar cells is quite characteristic. Little is known about the pulmonary side effects of leflunomide. As there are many effects described, such as inhibition of inducible nitric oxide synthase (iNOS), prostaglandin E2 and matrix-metalloproteinase 1, but also an increase of TGF-β1 [7], leflunomide might cause pulmonary DAD and fibrosis as well.

Thus lung biopsy cannot differentiate between MTX or leflunomide pneumonitis, but supports the theory of drug-induced pneumonitis. From the clinical point of view the most reliable trigger in our patient is the leflunomide therapy. Though there are reports where pneumonitis occurred after discontinuation of MTX [8] a period of 3 months is too long to claim MTX as the only responsible drug. However, it remains unclear if the initial MTX therapy has increased the patient's risk of developing pneumonitis. The long elimination half-life of approximately 2 weeks makes a suspected leflunomide pneumonitis even more dangerous. It is therefore important to remember that leflunomide can possibly cause life-threatening pneumonitis. Immediate drug elimination using charcoal or cholestyramin therapy can possibly cause life-threatening pneumonitis.

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Immediate drug elimination using charcoal or cholestyramin should be considered in any case presenting with pulmonary symptoms. In addition the use of leflunomide should be carefully considered in patients with pre-existing lung disease or combined MTX therapy.

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<th>Rheumatology</th>
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<td>- Leflunomide therapy is a rare but potentially life-threatening cause of pneumonitis.</td>
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The authors have declared no conflicts of interest.

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