CASE REPORT

Tocilizumab for refractory organising pneumonia associated with Sjögren's disease

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SUMMARY

Lung involvement in primary Sjögren syndrome occurs in approximately 10–20% of patients. Tocilizumab, an anti-interleukin-6 receptor antibody, has demonstrated efficacy and safety in small series of systemic sclerosis, and systemic lupus erythematosus, but its effect on interstitial lung manifestations of connective tissue diseases is not well known. We report the use of tocilizumab in a refractory organising pneumonia associated with Sjögren's disease. Our observation suggests that tocilizumab could be an alternative therapeutic in refractory organising pneumonia.

BACKGROUND

Lung involvement in primary Sjögren's syndrome (pSS), as defined by symptoms and either pulmonary function testing or radiographic abnormalities, is seen in between 0% and 20% of patients.[1] Among the histopathological patterns described in pSS, organising pneumonia (OP) is infrequently observed.[2] The optimal treatment for patients with pSS-associated interstitial lung disease (ILD) is not known but likely depends on the specific underlying pathology. Prednisone therapy in the range of 0.5–1 mg/kg/day is favoured as the initial treatment for OP. Although OP is considered to have a good prognosis and to be corticosteroid responsive, some patients with OP treated with corticosteroids relapse, especially those patients with connective tissue disease (CTD).[3] Tocilizumab, an anti-interleukin 6 (IL-6) receptor antibody, has demonstrated efficacy and safety in a small series of rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus,[4] but its effect on interstitial lung manifestations of these CTDs is not well known. We report the first case of steroid refractory pSS-associated OP successfully treated by tocilizumab.

CASE PRESENTATION

A 55-year-old Caucasian non-smoking man was referred for an acute bilateral pneumonia (figure 1A). He also had associated diffuse bilateral arthritis of the hands and knees for 1 month and fever persisting after several antibiotic treatments. His medical history was unremarkable. He denied recent travel or relevant exposures. He never had any gastroesophageal reflux disease symptoms or a proton pump inhibitor. The patient described Raynaud phenomenon: persistent troublesome dry eyes and feeling of dry mouth. Schirmer's test was positive. Labial salivary gland biopsy showed a focal sialadenitis with a focus score of 3/4 mm^2. Laboratory evaluations showed elevated C reactive protein levels (296 mg/L) and positive antinuclear antibodies (1:320). No Sjögren's syndrome type A antigen (SSA)/Ro or SSB/La antibodies were detected. Serum protein electrophoresis revealed a polyclonal hypergammaglobulinemia with a γ-globulin level of 33 g/dL. X-rays and CT scans showed diffuse, migrating, bilateral subpleural alveolar consolidations (figure 2). Bronchoalveolar lavage analysis revealed a mildly elevated lymphocyte count (20%, CD4/CD8 0.25). Microbial cultures for bacteria, fungus and mycobacteria were all negative. [18F]-Fluorodeoxyglucose positron emission tomography revealed a mild uptake in the area of consolidation. According to the consensus of classification criteria,[5] pSS-associated OP was diagnosed.

TREATMENT

Oral prednisone (1 mg/kg/day) was started. Respiratory symptoms and arthritis rapidly improved, and the alveolar infiltrates diminished on the CT scan (figure 1B). Steroids were tapered, however, 8 months after treatment initiation, the first relapse of OP and arthritis was observed at a dose of 12.5 mg/day (figure 1C). Methotrexate was added (25 mg/week), but was ineffective in controlling the arthritic and pulmonary symptoms after 6 months of treatment (figure 1D). The patient received two injections of rituximab (1000 mg each). The prednisone dose was kept above 25 mg/day after treatment initiation, because of persistent arthritic and OP activity (figure 1E). Nearly 2 years after the diagnosis was made, we decided to give tocilizumab (8 mg/kg, ie, 785 mg/month), in combination with prednisone and methotrexate (25 mg/week).

OUTCOME AND FOLLOW-UP

After two infusions, the patient significantly improved (figure 1F). Prednisone was progressively tapered to 5 mg/day. Eight months after initiating tocilizumab, the EULAR Sjögrens Syndrome Disease Activity Index was stable at 4. CT scan and pulmonary function tests were normalised (figure 3). To this point, the treatment was well tolerated.

DISCUSSION

The pathophysiology of OP is unclear and the role of IL-6 in the disease has never been investigated. However, in a murine model of virus-induced OP, high IL-6 messenger RNA levels in the lungs have been observed.[6] Lymphocytes and neutrophils, regulated by IL-6, are increased in alveolar spaces and bronchiolar lumens, especially during early stages of the process.[7] These data could be the

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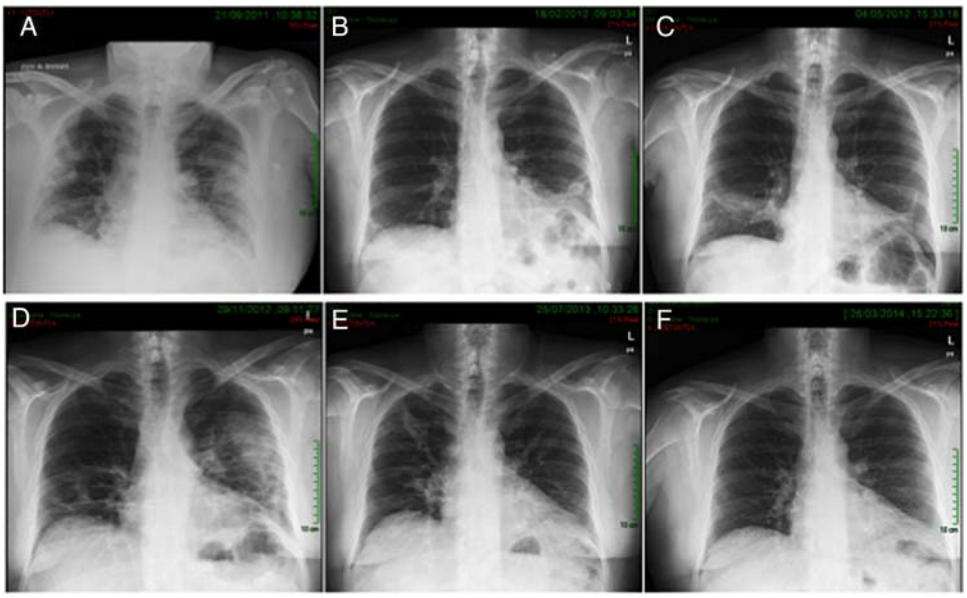

Figure 1 Evolution of chest X-rays: (A) at diagnosis, (B) improvement after receiving prednisone 30 mg/day, (C) first relapse, with a daily dose of 12.5 mg/day of prednisone, (D) after 6 months of treatment with methotrexate (25 mg/week) and prednisone 25 mg/day, (E) after two rituximab infusions, methotrexate and prednisone 25 mg/day and (F) after two infusions of tocilizumab plus methotrexate, prednisone can be tapered to 5 mg/day without any relapse of organising pneumonia or arthritis.

beginning of an explanation for the effect of IL-6 blockade observed in our case.

Oral prednisone is the recommended treatment regardless of the aetiology. However, responsiveness seems to be poorer in OP in patients with CTD.[2 5] In a small series of 18 pSS-associated ILD, OP was observed in 4 of 18 patients, and all improved after steroid therapy.[8] One case of steroid refractory fatal OP has been reported.[9] For refractory cases, immunosuppressive agents such as cyclophosphamide, azathioprine, cyclosporine[10] and recently, infliximab and rituximab, have been used.[10]

The effect of tocilizumab on pSS has not been investigated except in one short report.[11] The treatment effect on CTD ILD has not been well established; concerning systemic sclerosis, no effect has been observed on lung fibrosis,[12] but some cases of ILD improved after tocilizumab in rheumatoid arthritis (RA),[13] and no effects on undifferentiated autoinflammatory disorder have been reported.[14] However, concerns have been raised about pulmonary toxicity of tocilizumab in RA, since there have been several cases of exacerbation of ILD,[15 16] and the appearance of ILD,[17] including a case of OP,[18] after this treatment. Further investigations are required to assess the role of tocilizumab as an alternative therapeutic in refractory OP.

Learning points

- Lung involvement in primary Sjögren's syndrome (pSS), as defined by symptoms and either pulmonary function testing or radiographic abnormalities, is seen in between 0% and 20% of patients.[1]
- To the best of our knowledge, this is the first reported case of successful use of tocilizumab in refractory organising pneumonia (OP) associated with pSS.
- Further investigations are required to assess the role of tocilizumab as an alternative therapeutic in refractory OP.

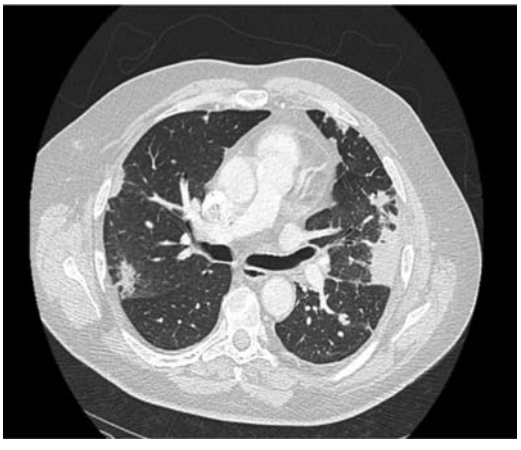

Figure 2 Chest CT scan at admission: diffuse bilateral migrating subpleural consolidations are observed.

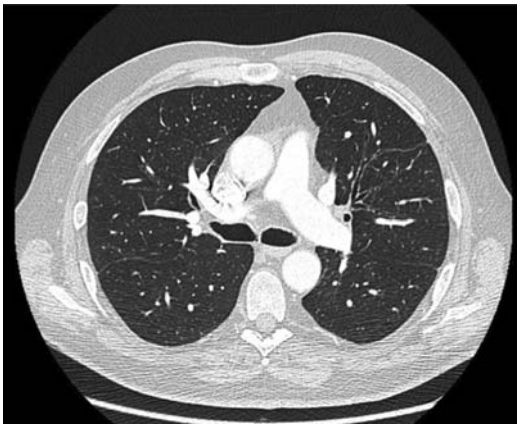

Figure 3 CT scan after two perfusion of tocilizumab: dramatic improvement is observed. No relapse was observed when prednisone was tapered to 5 mg/day.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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