Sarcoidosis and tocilizumab: is there a link?

Sirs.

Tumour necrosis factor (TNF) blocker has been reported to induce sarcoidosis, but with tocilizumab (TCZ) one case only has been described in rheumatoid arthritis (RA) (1). We report a second case occurring in a RA patient on TCZ. A female patient, 54-year-old, of North African descent with a 22-year-history of seropositive (RF and ACPA) and erosive RA according to the 2010 ACR/EULAR classification criteria. She was refractory to etanercept and adalimumab. Infliximab was introduced in June 2010 but stopped in 2012 because of disabling paradoxical psoriasis.

In August 2013, after one year on TCZ and methotrexate she suffered from dyspnea. A chest computed tomography (CT) revealed micronodular infiltration of both lung apices. Pulmonary function test showed decreased diffusing capacity of the lung for carbon monoxide. Bronchoscopy with bronchoalveolar lavage showed lymphocytosis (35%) and an increase in the CD4+/CD8+ ratio. Histologic examination showed non-caseating epithelioid granulomas. The angiotensin-converting enzyme level was mildly elevated at 79 IU/L (n=0-68 IU/L) and the 1.25 dihydroxyvitamin D level rose to 111ng/L. QuantiFERON and HIV serology were negative and articular symptoms controlled. She did not develop dry cough, cutaneous nodules, eye problems or cardiac lesions. As a result, stage 1 pulmonary sarcoidosis was diagnosed.

In February, chest CT revealed an accentuated parenchymal infiltration of both lung apices. In January 2015, 4 months after TCZ was reintroduced and although corticoids had been stopped, the chest CT showed parenchymal damage and lymphadenopathy regression and carbon monoxide diffusing capacity normalisation. This case shows that the relationship between biological treatments and possible paradoxical effects is not so clear.

Pulmonary sarcoidosis was diagnosed and worsened when treated with TCZ. This would suggest a causal link.

However, a further examination of a previous chest CT revealed discrete parenchymal micronodules predominant on the lung apices, consistent with sarcoidosis. Since the patient had been treated with TNF blockers from 2000 to 2012, we hypothesised that a TNF-blocker-induced sarcoidosis was already present in 2011 before TCZ was introduced to fight the RA severity. When corticoids were stopped, sarcoidosis lesions decreased despite the TCZ treatment, which suggested that contrary to expectation TCZ could have a beneficial effect on sarcoidosis.

The aetiology of sarcoidosis is characterised by non-caseating epithelioid cell granulomas in the organs affected. The precise formation of granulomas is unclear but we know that several cytokines are involved in their development such as interleukin (IL) 1b and TNF-α (2, 3). IL-6, which is produced by T cells, monocytes, fibroblasts and other cells, has been reported to be involved in the development of sarcoidosis by different mechanisms (4-6).

Lung alveolitis – essentially composed of activated alveolar macrophages (AMs) and T cells – precedes granuloma formation and there is a significant correlation between IL-6 levels in the cultured AMs supernatants and the CD4+/CD8+ ratio of the bronchoalveolar lavage fluid (4, 7, 8). Thus, due to the possible involvement of IL-6 in the initiation and maintenance of alveolitis, IL-6 blocking agents could have a beneficial protective effect on sarcoidosis. However, further study is still necessary to understand the mechanism of IL-6 blockers in this disease.

References