Letters to the Editors

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 was 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 accentuation of parenchymal damage and mediastinal lymphadenopathy so TCZ was stopped in March 2014.

Corticoids 30 mg/day were introduced in May 2014 allowing the parenchymal infiltrates stabilisation and mediastinal lymphadenopathy decrease.

However RA flared (DAS28 = 4.83). Erythrocyte sedimentation rate rose to 104 mm/h. Methotrexate was increased to 15 mg/week but did not prove efficient enough. Consequently, in September 2014 TCZ was reintroduced with corticoids 20 mg/day. In October 2014 the patient discontinued prednisone.

In January 2015, 4 months after TCZ was reintroduced and although corticoids had been stopped, 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 expectations 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 involvment 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.

L. BUSTAMENTE[1]
M. BUSCOT[2]
C.-H. MARQUETTE[3]
C. ROUX[1]

[1]Rheumatology Department, LAHMESS laboratory, University of Nice Sophia-Antipolis, Hôpital Pasteur 2, Nice, France;
[2]UMR E-4320 TIRO-MATOs CEA/iBEB, University of Nice Sophia-Antipolis, Faculté de Médecine Nice, France;
[3]Pneumology Department, University of Nice Sophia-Antipolis, Hôpital Pasteur 1, Nice, France.

Address correspondence to:
Dr Cristian Roux,
Rheumatology Department,
LAHMESS laboratory, University of Nice Sophia-Antipolis, Hôpital Pasteur 2,
06000 Nice, France.
E-mail: roux.c2@chu-nice.fr

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