Reply

Sirs,

In their correspondence, Shin J *et al*. comment on our paper reporting 2 cases of sarcoidosis occurring during anti TNF-α treatment given for inflammatory rheumatic disease, rheumatoid arthritis in one case and ankylosing spondylitis for the second. Similar saroidosis or sarcoid-like granulomatous diseases have been reported in the literature, asking the question of the relationship between the development of these granulomatous reactions and the exposition to the TNF-α blocking agent. Different mechanisms have been suggested and most authors highlighted the distinct immunological properties of the 2 of classes of TNF-α blockers (p75 soluble receptor *vs*. monoclonal anti- TNF-α antibodies).

Shin *et al*. suggested that the cytokine balance and the signaling pathway NFκB may also be involved in these granulomatous-induced reactions. They proposed that IFN-γ may play a role since it inhibits apoptosis in macrophages. Etanercept administration may lead to granuloma development because this agent has no influence on IFN-γ. Conversely, infliximab and adalimumab, which inhibits IFN-γ production, can limit NFκB pathway activation which, in turn, reduces apoptosis. Thus, the 2 classes of TNF-α blockers may favour granuloma formation by influencing apoptotic events. TGF-β is another relevant cytokine which may influence the development of sarcoidosis. As suggested by Shin *et al*., suppressing the production of TGF-β by anti- TNF-α agents may increase IFN-γ which can promotes granuloma formation.

We agree with Shin *et al*. regarding these cytokine and molecular mechanisms. However, we think that paradoxical reactions such as the development of sarcoidosis or sarcoid-like diseases in patients receiving TNF-α blockers cannot be explained by a single mechanism: indeed, the biological properties of etanercept *vs*. those of the monoclonal anti- TNF-α antibodies could support the predominance of these granulomatous diseases with this agent. This is also reflected by the lack of efficacy of etanercept in treating granulomatous inflammatory disease such as Crohn's disease and the greater risk of tuberculosis with the monoclonal anti-TNF antibodies. Finally, the role of infectious agents must be also highlighted. It is well known that TNF-α blocking agents are associated with increased susceptibility to infection and an infectious cause has been suspected in sarcoidosis pathophysiology. Thus, several distinct mechanisms (changes in cytokine balance, apoptosis and cellular events, modification of the environment with increased susceptibility to infection) are relevant for explaining the development of sarcoidosis during anti-TNF-α treatment.

Another remark is that these cases of sarcoidosis were reported in patients with ankylosing spondyltis or rheumatoid arthritis, two conditions which may be associated with sarcoidosis, an association which is certainly not fortuitous. Thus, another relevant question is what are the predisposing factors for this association and, in the same way, what could the predisposing factors be for the development of sarcoidosis under TNF-α blocking agents.

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