Letters to the Editor

Development of sarcoidosis during anti-TNF-α treatment: what is the mechanism?

Sirs,

We read with interest the article by Toussirot *et al*. (1). They reported two patients who developed sarcoidosis after anti-TNF-α agents (one infliximab and the other etanercept) which had been tried in cases of refractory sarcoidosis (1). They wondered why these paradoxical reactions had occurred, but could not explain possible mechanisms (1).

Firstly, they reported that these reactions occurred mainly with etanercept (7 patients etanercept, 3 infliximab, and one adalimumab) and speculated that these granulomatous syndromes might result from the different biological properties of etanercept and infliximab (infliximab inhibits interferon (IFN)-γ expression, while etanercept does not) (1). We somewhat agree with this opinion, because IFN-γ participates in granuloma formation. It has been reported that apoptotic events are reduced in sarcoid granulomas, which explains their characteristic long-lasting inflammation (2). Xaus *et al*. (2) described that IFN-γ inhibits apoptosis in macrophages through the expression of p21(Wafl). Therefore, reduced apoptosis may be an important factor in the pathogenesis of sarcoidosis development. However, it cannot be explained with this theory why such reactions can occur after infliximab therapy.

Lawrence *et al*. (3) reported the two faces of nuclear factor (NF)-κB which is potently activated by tumour necrosis factor (TNF)-α (4). They showed that NF-κB activation in leukocytes recruited during the onset of inflammation is associated with pro-inflammatory gene expression, whereas such activation during the resolution of inflammation is associated with the expression of anti-inflammatory genes and the induction of apoptosis. Conversely, NF-κB inhibition reduced leukocyte apoptosis (3). Given these results, reduced apoptosis by infliximab might have influenced the development of sarcoidosis regardless of IFN-γ in Toussirot *et al*.'s patient (1).

Secondly, the possible role of TNF-α-transforming growth factor (TGF)- β axis should also be considered. It has been reported that granulomatous inflammation of sarcoidosis is characterised by dominant expression of T helper 1 cytokines such as IFN-γ and interleukin (IL)-12, which are inhibited by TGF-β (5). Moller reported that TGF-β is produced at higher levels by lung cells from those patients who undergo disease remission (5), suggesting that increased TGF-β might be important in downregulating granulomatous inflammation in sarcoidosis by inhibition of IFN-γ and IL-12 production. With this mechanism, anti-TNF-α agents may have a beneficial effect on the treatment of refractory sarcoidosis, because TNF-α inhibits TGF-β (6).

However, Salez *et al*. showed that overproduction of TGF-beta1 is associated with functional impairment in patients with pulmonary sarcoidosis (7). These contrasting results may also be due to the two faces of NF-κB (3). Lawrence *et al*. also demonstrated that inhibition of NF-κB reduced TGF-β1 expression *in vivo* (3). Therefore, there is a possibility that anti-TNF-α agents might paradoxically suppress the production of TGF-β1, leading to increase the IFN-γ and IL-12 production, causing sarcoidosis.

Therefore, careful clinical monitoring would be necessary in patients receiving anti-TNF-α and further studies should be performed to elucidate the pathogenesis of sarcoidosis and to evaluate the relationships among TNF-α, TGF-β, IL-12 and IFN-γ at the various stages of sarcoidosis.

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