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# Side effects of anticytokine strategies

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## ABSTRACT

Anticytokine strategies probably represent the most important breakthrough in the treatment of inflammatory diseases in the last decade. However, blocking the bio-activity of proinflammatory cytokines, crucial activators of host defence, has proved to be accompanied by an increased susceptibility to infections, especially with *Mycobacteria*, *Salmonellae* and fungal pathogens. Multiple mechanisms for these side effects have been proposed, such as inhibition of gamma-interferon production, decreased expression of pattern-recognition receptors, and leucocyte apoptosis. Caution is therefore warranted when these treatments are given to patients with an increased risk for infections. A range of side effects other than infection have been reported.

Treatment strategies interfering with proinflammatory cytokines such as tumour necrosis factor (TNF)  $\alpha$  and interleukin-1 (IL-1) constitute a breakthrough in the treatment of rheumatoid arthritis (RA) and other inflammatory disorders. However, some 10 to 15 years ago it was demonstrated in experimental animals that treatment with antibodies against TNF was deleterious in mycobacterial infections, fungal infections and abscesses. The exact mechanisms by which interference with TNF produced these results were not entirely clear, but it was concluded that containment of micro-organisms within granulomas and abscesses was not achieved or maintained.<sup>1,3</sup>

Based on these observations, it was easy to predict that large-scale and prolonged anti-TNF treatment in humans would lead to infections, especially by organisms that

induce a granulomatous response. Indeed, such complications (especially mycobacterial and *Salmonella* infections) were readily encountered, but still seemed to come as a surprise to the medical community.

In this issue of the journal, Efde and colleagues report a case of tonsillar tuberculosis, a rare manifestation of this infectious disease, occurring during anti-TNF treatment.<sup>4</sup> The occurrence of these infections has important implications for pretreatment assessment of patients, and guidelines for this purpose are appearing, also in the Netherlands.<sup>5</sup> Two years ago, the Netherlands Journal of Medicine published a state-of-the-art review by Arend *et al.* on this topic with a detailed account of the literature and a proposal for the management of patients at risk.<sup>6</sup> The patient reported in this issue of the journal received a six-month course of isoniazid for latent tuberculosis. As noted in the review<sup>6</sup> and by the authors of the case report,<sup>4</sup> a period of six months of isoniazid is not optimal. It also implies that the risk of reactivation of tuberculosis during anti-TNF treatment in patients harbouring dormant bacilli should not be underestimated.

It is interesting that the risk for infection is greater with the monoclonal antibodies against TNF (infliximab and adalimumab) than with the TNF receptor construct etanercept: during infliximab therapy the risk is estimated to be 200 per 100,000 treatments, with etanercept it is 9 per 100,000.<sup>7</sup> Theoretically, one would expect differences between the various types of anti-TNF drugs, as they differ in their capacity to interact with TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin), and with membrane-bound TNF. Another

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interesting, not well-explained observation is that treatment with the recombinant interleukin-1 receptor antagonist, IL-1Ra (anakinra), does not seem to lead to excess infection.

How inhibition of TNF impairs host defence in patients is still enigmatic, but several mechanisms have been suggested. Firstly, blockade of TNF itself can impair host defence, as TNF is known to activate the microbicidal properties of neutrophils and macrophages.<sup>8</sup> Secondly, TNF blockade can inhibit secondary activation of the cytokine cascade. We have demonstrated in patients with a serious *Salmonella* infection that interferon- $\gamma$  production was strongly inhibited.<sup>9</sup> The role of the latter cytokine in host defence against micro-organisms is much better understood: a deficient response to this cytokine has been shown to lead to serious infections.<sup>10-12</sup> Important questions that remain are whether all patients who receive anti-TNF treatment respond with a down-regulation of the interferon- $\gamma$  response, and whether we can predict the risk for infection by assessing the production of this cytokine. It is also tempting to speculate that the capacity to down-regulate the interferon- $\gamma$  response explains the difference in occurrence of infection between IL-1 inhibition and TNF inhibition, but more research is needed to answer this question. Other mechanisms of anti-TNF treatment include down-modulation of pattern recognition receptors such as TLR4,<sup>9</sup> and leucocyte apoptosis.<sup>13</sup> One may also ask the question whether anticytokine treatment, for example in patients with rheumatoid arthritis, has more effects that are not intended. A range of side effects other than infection have been reported, albeit with a lower incidence.<sup>14</sup>

Treatment with TNF inhibitory agents has been associated with rare cases of onset or exacerbation of demyelinating disorders, which met with a partial or complete response when treatment was stopped. In addition, despite the elevated TNF concentrations in the cerebrospinal fluid and in the circulation of multiple sclerosis (MS) patients, blocking this cytokine resulted in a worsening of the disease.<sup>15</sup> The mechanisms underlying this side effect are still unknown.

Development of autoantibodies including antinuclear antibody (ANA) and anti-double-stranded DNA have been reported during therapy with anti-TNF agents. The clinical relevance of this is uncertain, although post-marketing surveillance reports mention cases of autoimmune diseases, especially leucocytoclastic vasculitis and lupus-like syndrome, improving after therapy was discontinued.

Concerns have been raised about haematological disorders, especially non-Hodgkin's lymphoma, and cytopenia during anti-TNF therapy. Very few cases have been reported in patients with long-lasting RA receiving multiple drugs.

The role of anti-TNF drugs is therefore unknown. Congestive heart failure proved to worsen by TNF blockade, despite earlier studies predicting the opposite: chronic heart failure (CHF) was associated with elevated production of TNF. Trials intended to show the benefit of suppressing TNF in CHF patients met with increased mortality in the anti-TNF group compared with placebo.<sup>16</sup> However, one should be prudent when interpreting the onset of CHF in patients with RA receiving anti-TNF therapy, as cardiovascular diseases are a leading cause of death among these patients.

Perhaps more interestingly, therapy of RA patients with TNF blockers might also have beneficial consequences, other than those related to the inflamed joints.

An increased mortality due to cardiovascular and cerebrovascular diseases is seen in RA patients when compared with the general population. The contribution of inflammation to the development of atherosclerosis and insulin resistance is now regarded to be more and more important, and TNF has emerged as playing a key role in these processes. In addition, markers of inflammation, such as C-reactive protein (CRP), are now considered to be important predictors of future acute cardiovascular events. In that respect, we recently investigated whether the profile of cardiovascular risk factors in such patients ameliorates during anti-TNF treatment.<sup>17</sup> This would not be unexpected, since TNF is known to increase interleukin-6 (IL-6) and CRP and induce proatherogenic changes in lipid profile.

We found that anti-TNF treatment with adalimumab enhanced the concentrations of HDL cholesterol and decreased the concentrations of CRP and IL-6 within 14 days. To what extent these changes remain during prolonged observation and translate into a lower cardiovascular risk is the subject of future studies.

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