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 bioactivity of proinflammatory cytokines, crucial activators of host defence, has proved to be accompanied by an increased susceptibility to infections, especially with Mycobacteria, Salmonella 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.

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. The occurrence of these infections has important implications for pretreatment assessment of patients, and guidelines for this purpose are appearing, also in the Netherlands. 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. The patient reported in this issue of the journal received a six-month course of isoniazid for latent tuberculosis. As noted in the review and by the authors of the case report, 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. Theoretically, one would expect differences between the various types of anti-TNF drugs, as they differ in their capacity to interact with TNF-α and TNF-β (lymphotoxin), and with membrane-bound TNF. Another
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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.\textsuperscript{16} 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.\textsuperscript{17} 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.

### References


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