EDITORIAL

IL-6 inhibition and infection: treating patients with tocilizumab

Is there a greater risk of infections?


Understanding a new therapy starts with a process of weighing risks and benefits. This process can be difficult, as most available information will come from the highly selected environment of randomized controlled trials (RCTs). At this stage, clinical experience from real life is lacking and studies of more general use are important. Over time post-marketing surveillance, case series and personal experiences can all be helpful. For biologic therapies, the development of large national databases to record efficacy and side effects has been vital. A specific concern about treatments that block immune function is that they may increase the likelihood of infections. Thankfully, TNF blockers have generally been associated with fairly low levels of infectious risk. A report from the British Society for Rheumatology Biologics Register (BSRBR) described an increased risk of serious infection associated with the use of adalimumab, etanercept and infliximab with an adjusted hazard ratio of 1.2 (95% CI 1.1, 1.5) [1].

A study published in this issue of the Journal analyses the use of the IL-6 receptor blocker tocilizumab in 112 patients with RA in Germany and suggests a higher level of infections than those seen in clinical trials [2]. In this study, Lang et al. observed RA patients attending routine outpatient clinics who had started tocilizumab therapy between 2008 and 2010 (n = 112). During treatment, 23.2% of these patients developed an infection (58/100 patient-years), which is much higher than the levels reported for tocilizumab in RCTs and summarized in the recent Cochrane reviews [3, 4]. Eighteen patients had mild infections, while eight had serious infections. All serious infections were bacterial, with four occurring in the gut, one had pneumonia and one had osteomyelitis. In the logistic regression models used, the predictors of infection were long disease duration, higher number of previous DMARDs, previous use of rituximab, concurrent use of LEF and the use of proton-pump inhibitors.

A major strength of this study is that it observes the outcomes of patients who received tocilizumab in the unfiltered setting of rheumatology outpatient clinics. Information from this source can help predict the effects of a therapy on a range of different individuals attending clinics rather than the group included in RCTs. However, the study may suffer from a selection bias often associated with the early use of a new therapy. Initially, new treatments are prescribed to patients with the most severe, longstanding RA that is resistant to standard treatment. This group of patients may have a particularly increased likelihood of developing serious infections. RA is associated with an increased risk of infection regardless of treatment, which rises with increasing disease activity [5]. The patients described by Lang et al. were in many ways typical of RA populations from other studies, with 79.5% being women and having a mean age of 55 years. However, patients had a longer disease duration (mean 11.5 years) and had received a greater number of different DMARDs (mean 4.5) than the population seen in the RCTs with tocilizumab [3].

Despite possible bias, the study shows a significantly increased likelihood of developing infections during treatment with tocilizumab. So, could inhibition of IL-6 be associated with a greater risk of developing infectious complications than other biologic therapies? IL-6 is a key driver of the acute-phase response and has an important role to play in the production of CRP in the liver. IL-6 knockout mice models show an impaired acute-phase response and are vulnerable to bacterial and fungal infections [6]. In addition, CRP binds to phosphocholine, which is a common component of the cell membranes of fungi and bacteria. Once bound, CRP activates the classical complement pathway and can opsonise, allowing increased phagocytosis.

The RCTs of tocilizumab have reported several serious infections with common bacterial and viral pathogens, although none stand out as unusual. A recent Cochrane review did not show a significant increase in the risk of serious infections in individuals who were receiving tocilizumab as compared with those who were given placebo [3, 4]. Tocilizumab has been associated with neutropenia, but this occurrence is rarely a major problem and does not seem to be associated with an increased infectious risk [7, 8]. Infections occurring while receiving tocilizumab may be detected late because of the masking effect of a suppressed CRP response. Interestingly, in the study by Lang et al., CRP levels rose significantly in six of the eight patients with serious infection.

So should this study worry us? There are plausible biological explanations to suggest that suppressing IL-6 may increase infectious risk. After all, IL-6 and CRP play
important roles in the acute-phase response and in the fight against infectious organisms. However, the experience from the tocilizumab clinical trial programme is mostly reassuring, and in general, risk of infections has been manageable with other comparable cytokine blockers such as TNF inhibitors. This study emphasizes the importance of obtaining safety information from as many different sources as possible. In particular, national registries are a vital way of looking at long-term safety in a real-life setting and should be available for all new biologic therapies. As a result of this study, it seems reasonable to exercise caution when giving tocilizumab to patients who take LEF or rituximab. A suppressed CRP in some individuals could lead to a delay in the detection of a serious infection, although this is not a new phenomenon and may be encountered in patients taking CSs or other immunosuppressants.

The possibility of serious infectious complications occurring as a result of biological therapy should serve as a reminder for the need to assess infectious risk and consider appropriate immunization in all patients. It might also make us question whether it is safe to monitor and perform infusions of biologic therapies in the community. Finally, it should encourage us to address the importance of educating general practitioners and acute physicians about the risks and benefits of new therapies for RA.

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