

# Autoimmune Hepatitis and Allergic Reactions During Anti-TNF $\alpha$ Treatment

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In this issue of *IMAJ*, Petříková et al. [1] describe the interesting case of a 33 year old woman affected by primary Sjögren's syndrome (SS) since 2005 and who developed seropositive rheumatoid arthritis (RA) in 2008. Based on the 2013 European League Against Rheumatism (EULAR) guidelines [2], she was treated with disease-modifying anti-rheumatic drugs (DMARDs) combined with glucocorticosteroids. She was treated first with methotrexate (MTX) which was stopped due to inefficacy and adverse events, and then with anti-malarial agents which were discontinued because of lack of efficacy.

Rheumatoid arthritis is characterized by joint inflammation and destruction and leads to functional limitations, working disability and a poor quality of life [3]. It is more frequent in females and has an estimated adult prevalence of 0.8% worldwide. Synovial inflammation can cause erosive changes that are generally irreversible and often occur early in the disease process [3]. Given these data, the EULAR recommended that DMARD treatment be started as soon as possible after RA has been diagnosed, with the primary therapeutic aim of obtaining remission (especially in the case of early RA) or, especially in patients with long-standing RA, to achieve a low level of disease activity [3]. The treatment target should preferably be reached within 6 months. MTX is con-

sidered the cornerstone of RA treatment, but an inadequate response to the optimal or maximally tolerated dose of a first-line DMARD may be followed by a switch to an alternative DMARD (such as sulfasalazine or leflunomide) or a combination of DMARDs [2]. If the treatment target is not achieved using the first DMARD strategy, combined treatment with a tumor necrosis factor (TNF) inhibitor – such as adalimumab (ADA), certolizumab pegol (CTZ-pegol), etanercept (ETN), golimumab and infliximab, or biosimilars such as abatacept, tocilizumab or, under certain circumstances, rituximab – is considered similarly efficacious and safe [2].

The patient mentioned above [1] was treated with ADA, but after three subcutaneous doses she developed signs and symptoms compatible with a diagnosis of autoimmune hepatitis (AIH) – i.e., malaise, increased liver enzyme levels, positivity to antinuclear antibody (ANA), anti-smooth muscle antibodies (ASMA) and anti-mitochondrial antibodies (anti-AMA), and altered liver biopsy findings – and was therefore treated with prednisolone 40 mg/day (0.75 mg/kg/day, the standard starting dose for AIH for 2 weeks, with the dose reduced by 10 mg every 2 weeks. The maintenance dose was set at 10 mg/day and proved to be beneficial. Four months after stopping ADA due to disease activity, ETN was administered for 1 month before being stopped because of a serious allergic skin reaction at the injection site. Finally, CTZ-pegol was initiated but also failed because of an allergic reaction.

Although there are no published guidelines suggesting the best strategy to adopt after a first anti-TNF failure, switching from one TNF inhibitor to another has

become common practice in the case of patients who fail to respond or are unable to tolerate their initial treatment [4]. The most frequent reason for discontinuing both first- and second-line treatments is lack of efficacy; nonetheless, regardless of the reason or the sequence of administered drugs, disease activity is reduced after switching [4]. Discontinuation of the second drug because of adverse events is usual in patients who discontinued the first for the same reason. Survival on a second biological treatment is longer than on the first, but shorter than observed in non-switchers. RA patients can be successfully treated with a second TNF antagonist, especially those who experienced secondary failure or adverse events with the first. In the case of primary failure, it is possible that other biological agents with different mechanisms of action may be more successful [4].

The 2013 EULAR recommendations suggest that if the first biological DMARD strategy fails, any other biological DMARD may be used. They also refer to tofacitinib as a targeted synthetic DMARD (tsDMARD), which is recommended after the use of at least one biological DMARD, and biosimilars [2].

The safety issues relating to all current TNF antagonists are infections (including *Mycobacterium tuberculosis* and other opportunistic infections), demyelinating disorders, autoimmune syndromes (such as systemic lupus erythematosus), congestive heart failure, and administration reactions [5]. The BIOGEAS project (a Spanish registry that collects data on the use of biological agents in adults with systemic autoimmune diseases) has reported more than 800 cases of autoimmune diseases secondary to

anti-TNF drugs, mainly lupus, vasculitis and optic neuritis [6]. Injection site reactions (ISRs), which usually appear during the first month of treatment and become less frequent as the treatment progresses, are typically experienced by 10–20% of the patients receiving ADA and ETN [7]; ISRs are less frequent and mild or moderate in patients treated with CTZ-pegol.

The rare cases of AIH represent fewer than 2% of all the autoimmune processes associated with anti-TNF agents: the BIOGEAS registry has reported its occurrence in 19 patients, most of whom responded completely to the withdrawal of anti-TNF treatment [6]. The majority were treated with corticosteroids (azathioprine was added in five cases and mycophenolate in one) and, as is usually the case with drug-induced AIH, liver enzyme levels normalized within 2 months of the discontinuation of anti-TNF treatment [6].

However, although anti-TNF-induced AIH is rare and responds well to treatment, the increasing number of reported cases over the last few years render it a serious problem that needs to be considered and carefully monitored. Approximately 9% of the cases of AIH are triggered by drugs [8], but it may be difficult to distinguish drug-induced AIH from de novo AIH or other drug-induced liver conditions since their clinical, biochemical, serological and histological patterns may be similar [9]. ANA positivity can develop after the use of anti-TNF drugs in patients with systemic rheumatic diseases such as RA [5] but, alone, is insufficient to support a diagnosis of AIH which, as in the case described here, is more likely to require

the presence of more specific antibodies such as ASMA, soluble liver antigen, or a combination of two antibodies. The pathogenesis of the AIH triggered by anti-TNF therapy remains unspecified [10], but one of the causes may be reactive metabolites of anti-TNF drugs which, like those of other drugs, may be recognized by the immune system as neo-antigens [10].

The patient described by Petříková et al. [1] responded well to anakinra, a recombinant non-glycosylated form of human IL-1RA (rhIL-1RA) produced in *Escherichia coli* and approved for the treatment of RA patients who do not respond to DMARDs [11]. Its efficacy and safety (alone or in combination with DMARDs) have been demonstrated in a number of randomized clinical trials [11] but has proved less effective in clinical practice and is currently rarely used to treat RA. A recent meta-analysis confirmed that its effect on pain, global health assessment and Health Assessment Questionnaire scores is much less than that of other biological agents [12], but we have found it useful in the subset of RA patients with diabetes.

In conclusion, on the basis of this case report, we suggest that liver enzyme levels be monitored in patients with systemic rheumatic diseases treated with anti-TNF agents, even though many receive multiple infusions and only a handful develop AIH.

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