Tumor Necrosis Factor-Alpha at the Crossroad between Rheumatoid Arthritis and Autoimmune Cholangitis

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KEY WORDS: autoimmune cholangitis, inflammatory arhritis, anti-tumor necrosis factor-alpha (anti-TNFα), biologic agents

IMAJ 2015; 17: 112–113

We have been largely convinced by data presented in recent years that common factors outnumber differences between autoimmune diseases, particularly when pathogenetic mechanisms are evaluated [1,2], as in the case of B or CD8+ T cells [3], with obvious therapeutic implications [4,5]. Nonetheless, in some cases this may be a double-edged sword, as represented by liver autoimmunity induced by biologic drugs [6], while in others the frequent coexistence of multiple autoimmune conditions allows evaluation of new treatments in unsuspected diseases [7]. In this issue of *IMAJ* Kovacs and colleagues [8] describe a case in which two paradigmatic organ-specific and systemic autoimmune diseases, i.e., primary biliary cirrhosis (PBC) and rheumatoid arthritis (RA), were successfully treated by targeting tumor necrosis factor-alpha (TNFα) with etanercept.

RA and PBC are both autoimmune diseases of largely unknown etiology sharing some similarities, such as the presence of specific serum autoantibodies (namely rheumatoid factor, anti-citrullinated peptides for RA, and anti-mitochondrial antibodies for PBC), the possibility of seronegative patients, and the striking predominance of female patients [9]. RA is a chronic systemic inflammatory disease affecting approximately 0.5–1% of the general population, where genetics, environmental risk factors (such as smoking) and autoimmunity contribute to disease onset. RA is characterized by symmetric articular involvement, chronic synovitis and systemic inflammation with significant cardiovascular morbidity [10,11]. The pathogenesis of RA is based on chronic inflammation that initiates when a T cell is activated by an endogenous trigger, which in turn activates macrophages and fibroblasts to produce TNFα, interleukin (IL)-6, IL-17, IL-1 and IL-23. Also B cells are involved in RA pathogenesis, as the presence of specific autoantibodies demonstrates, and once started, inflammation is chronically maintained by the continued afflux of new inflammatory cells in the area. In contrast, PBC is a rare chronic autoimmune cholestatic liver disease, affecting about 20/1,000,000 men and 20/100,000 women, mostly perimenopausal, in the general population [12]. Serum anti-mitochondrial antibody (AMA) is found in 95% of patient sera, usually at high titers, and the disease is largely asymptomatic [2].

Similar to RA, PBC etiology remains enigmatic, and apparently both genetics and environmental agents have a role in the development of the disease [13-15], as is well demonstrated by monozygotic twins [16]. Both innate immunity and adaptive immunity are involved in the development of PBC [17], but the role of TNFα in PBC has not been clarified. Its expression appears to be enhanced in biliary epithelial cells, possibly leading to PBC cholestasis and inflammation, while some studies have shown opposite findings. Its expression, nonetheless, decreases after ursodeoxycholic acid (UDCA) therapy, which is currently the only approved therapy for PBC. TNFα genetic polymorphisms have been evaluated to assess whether they are associated with a higher risk of PBC developing compared to the general population, but different results have been reported, particularly in genome-wide studies.

Despite the similarities between these two diseases, the therapeutic approaches are very different. In fact, in RA, there is a broad armamentarium of drugs, such as disease modifying anti-rheumatic drugs (DMARDs) and biologic agents, especially directed at blocking TNFα as well as other cytokines such as IL-6 and, most recently, intracellular signaling inhibitors. In contrast, the PBC therapeutic cornerstone remains UDCA, and the only ultimate cure is liver transplantation [2]. In recent years however, different therapeutic approaches are being evaluated in this rare disease, mainly because of unsatisfactory responses to the standard therapy. Methotrexate (MTX) and other immunosuppressant drugs, as well as biologic agents such as rituximab, have been evaluated, while the newest promising data have been provided for obeticholic acid. In the case of PBC, one should be aware that liver tests in general and alkaline phosphatase levels in particular are the only outcome measures to be used in clinical trials because changes in liver histology occur over several years.

Etanercept is a soluble recombinant TNFα receptor used in the treatment of different rheumatic and dermatologic diseases

(i.e., RA, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psorisias). It is administered subcutaneously at a dosage of 50 mg/week, but its use is hampered by adverse events including latent infection reactivation, recurrent infections, and by injection site reactions; apart from that the treatment is generally well tolerated. It has been used off-label for vasculitis, especially Wegener's granulomatosis, but it did not show efficacy.

When two different autoimmune conditions are approached, the treatment options are sometimes limited, especially when putative drugs for one disease, e.g., MTX, may potentially cause a worsening of the other condition. Cases of PBC associated with rheumatic conditions treated with anti-TNFα agents have been reported previously, with conflicting outcomes. The first, by Spadaro et al. in 2008 [18], was a report on anti-TNFα treatment for a patient with both PBC and RA. However, since infliximab treatment did not yield a satisfactory clinical response and there was no amelioration of liver test abnormalities, etanercept was started and led to a prompt clinical response and liver test normalization. Second, Ogata et al. [19] also reported the case of a woman with PBC and RA treated with etanercept that resulted in improvement in both clinical symptoms and liver test abnormalities. A third case of PBC associated with RA treated with etanercept was reported by Kubo et al. [20], and in this case, as well, etanercept improved the results of liver tests.

The response to etanercept in the previous cases and in the case reported in this issue of *IMAJ* suggests that TNFα is important in PBC pathogenesis. Thanks to our better understanding of disease pathogenesis, novel biological treatments targeting not only TNFα will likely develop in the next few years and data from comorbidities will be crucial. As examples, tocilizumab may ameliorate RA, and limit systemic sclerosis overlap, PBC, and generalized lymphadenopathy. Beyond the therapeutic implications, the present case report [8] illustrates the possibility that liver test abnormalities observed in rheumatic diseases may be unrelated to DMARDs but may represent the coexistence of PBC with its common manifestations. Furthermore, novel treatment targets are being developed as the pathogenesis of these diseases becomes more clear; this will lead hopefully to more specific treatments with less serious adverse events and to tackling more than one pebble in the mosaic of autoimmunity.

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"Don't tell me the moon is shining; show me the glint of light on broken glass"

Anton Chekhov (1860-1904), Russian dramatist, author and physician. Apart from his must-esteemed short stories, he is most known for his plays: *The Seagull*, *Uncle Vanya*, *Three Sisters* and *The Cherry Orchard*. "Medicine is my lawful wife," he once said, "and literature is my mistress"

"Fear prophets and those prepared to die for the truth, for as a rule they make many others die with them, often before them, at times instead of them"

Umberto Eco (b. 1932), Italian philosopher, literary critic and novelist. He is best known for his groundbreaking 1980 historical mystery novel *Il nome della rosa* (*The Name of the Rose*)