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**20<sup>th</sup> anniversary of TNF inhibitors in rheumatoid arthritis**

**Key words: Biologic, rheumatoid arthritis, tumor necrosis factor, TNF, TNF inhibitors**

## **Introduction**

The past quarter century has witnessed unprecedented advances in our understanding of the pathophysiology of rheumatoid arthritis (RA). Fortunately, for the majority of patients with this disease, the current outlook is significantly improved when compared with a generation earlier [1]. Even so, RA continues to have a substantial impact on the quality of life of many patients [2]. Several factors have contributed to the dramatic changes in the management of RA over this time period, but arguably most notable was the approval two decades ago and subsequent clinical availability of biologic inhibitors of tumor necrosis factor (TNF).

## **The role of tumor necrosis factor in rheumatoid arthritis**

TNF itself is pleiotropic, with multiple functions including immune regulation and pro-inflammatory roles. Biological effects of TNF on responder cells are mediated via binding to one of two different receptors, TNF receptor (TNFR) I, or TNFRII, with subsequent activation of different signal transduction pathways and consequently distinct effects. In the context of the rheumatoid joint, where TNF is overexpressed and dysregulated, these effects include synovial proliferation and angiogenesis as well as regulation of other proinflammatory mediators, which include various cytokines, prostaglandins and matrix metalloproteinases [3]. Consequently, TNF plays an important role in articular tissue destruction as well as contributing to periarticular osteoporosis, which is an early characteristic of RA.

## **Development of the first biologic therapies for rheumatoid arthritis**

Two concurrent advances in the 1980s are considered responsible for the evolution of biologic treatments in the management of RA. First, the development of new methodologies, allowing cataloging of cytokines in rheumatoid joint tissue, brought about the identification of TNF as a dominant pro-inflammatory molecule and potential therapeutic target. Second, a breakthrough in protein engineering resulted in production of clinical grade antibodies, or engineered derivatives, necessary to validate the hypothesis that TNF was a cytokine of relevance to the pathology of RA.

## *Preclinical data*

The identification of TNF as a key cytokine and potential therapeutic target in RA came about as a result of studying synovial tissue donated by RA patients with active disease. At this time, fewer effective drugs were available, and therefore synovial tissue tended to be more floridly inflamed in these patients. Further supporting evidence consistent with these findings emerged from studies of preclinical murine models [4].

### *Clinical data*

Confirmatory evidence of the pathogenic role of TNF came when proof of concept clinical trials demonstrated an unequivocal amelioration of signs and symptoms in a majority of patients treated with TNF inhibitors [5]. And perhaps most strikingly, when used in combination with concomitant methotrexate, biologic TNF inhibition was found to abrogate radiographic progression; previously considered an inexorably progressive feature of RA [6]. The most impressive benefits of biologic TNF inhibitors have been demonstrated when therapy is initiated in the earliest stages of RA [7–9]. This is perhaps not surprising, given that preservation of function is dependent on both reduction in disease activity and prevention of joint damage. Once damage is established as RA progresses, this component is generally not reversible.

### **Risk of adverse effects**

#### *Infection*

While TNF inhibitors have proven to be highly effective, target-related toxicity remains an ever-present concern. Risk of infectious complications, with a particular concern regarding intracellular pathogens, was predictable given knowledge of TNF biology. During early use of TNF inhibitors, cases of tuberculosis were reported in approximately 1 in 1000 patients, however routine screening prior to initiation of biologic has significantly reduced this rate [10].

#### *Lymphoma*

Other theoretical concerns included the role of TNF in tumor surveillance, and potential toxicities associated with long-term TNF inhibition. However, after two decades of clinical experience with biologic TNF inhibitors, no evidence has been found to suggest that this class of biologics increases risk of lymphoma [11,12]. Although there is an increased risk of lymphoma in patients with RA treated with TNF inhibitors, as compared with healthy controls, current thinking suggests that it is the total inflammatory burden over time that predisposes these patients to increased risk of lymphoma, rather than the treatment intervention [13]. This is consistent with the observed early data to emerge from various national registries which were largely comprised of RA patients with persistently high levels of disease activity prior to starting treatment with a TNF inhibitor.

### **Development of new biologic therapies**

The early, positive experience in the use of biologic TNF inhibitors in RA led to a rapid expansion in this class of drugs, and a subsequent extension of therapeutic indications into a wide range of

chronic inflammatory disorders with concomitant, unprecedented commercial success. This paved the way for a broader revolution in development of biologic therapies targeting other cytokines and immune cells, and consequently, a greatly expanded therapeutic armamentarium for the treatment of RA. In monotherapy, interleukin-6 receptor (IL-6R) blockade has been shown to have superior efficacy for symptoms and signs [14,15]. However, when used in combination with methotrexate, no biologic of different mechanism of action has proved more efficacious than TNF inhibitors.

### *Biosimilars*

Prohibitively high drug costs of biologic TNF inhibitors have been to the considerable detriment of healthcare economies, and disincentivized earlier and more optimally effective use of TNF inhibitors. However, as the first generation of biologic anti-TNF 'originators' have come off patent, biosimilars of infliximab, etanercept, and adalimumab have emerged, with a corresponding improvement in cost-effectiveness. Strict regulatory definitions of 'biosimilarity' have been designed to ensure that any post-translational modifications of the primary amino acid sequence, which is identical to that of the originator, still give rise to highly similar efficacy outcomes without the penalty of newly arising adverse events. To date, clinical experience with biosimilars, particularly in Europe [16], has been very favorable, and has resulted in significant savings for the healthcare economies adopting them.

### **Conclusion**

Two decades of clinical experience with biologic TNF inhibitors in the management of RA have confirmed a favorable benefit:risk profile. While not without associated adverse effects, particularly infection, these biologic therapies have a remarkable overall safety record [17]. In spite of all of these welcome advances, many unmet needs remain for people living with RA [2]. These include primary non-response in a significant minority of patients and a high rate of secondary loss of response over time. This may in part be related to a fundamental challenge associated with biologic drugs, namely immunogenicity of administered protein. Furthermore, in established, csDMARD-refractory RA, where TNF inhibitors are most widely used, the desirable treatment target of remission remains aspirational for the majority of patients [18]. And although a new generation of efficacious small molecular, orally available therapies is now impacting on RA management [19], it looks likely that TNF inhibitors will continue to play a major role in the therapeutic armamentarium for the foreseeable future.

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