Editorial - Long-term safety and efficacy of sarilumab over 5 years in patients with rheumatoid arthritis refractory to TNF inhibitors.

Title: rheumatologists at a crossroads: blocking TNF or IL-6 in DMARD-IR patients

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In this issue of *Rheumatology*, Fleischmann and colleagues (1) published the 5-years follow-up results of the EXTEND trial, in which longstanding rheumatoid arthritis (RA) patients with an inadequate response or intolerance (IR) to TNF inhibitors (TNFi) received sarilumab 200 mg every 2 weeks plus conventional synthetic DMARDs (csDMARDs). This is the Open-Label Extension (OLE) of the TARGET trial, in which sarilumab 150 or 200 mg every 2 weeks (q2w), plus conventional synthetic DMARDs (csDMARDs) was compared to placebo plus csDMARDs in the same population. Most patients discontinued prior anti-TNF therapy because of an inadequate response (92.3%); thus, TARGET was primarily composed of a population of TNFi inadequate responders (2). Importantly, the OLE focused on safety through descriptive statistics.

The cumulative observation yielded 1654.8 patient-years (PY; n = 521), with 51% showing ≥4 years exposure. Interestingly, the incidence rates per 100 PY of adverse events (AEs) leading to discontinuation or serious infection were 8.1 and 3.9, respectively. Neutropenia was the most common AE (15.3 per 100 PY), with neutrophil count <1000 cells/mm3 observed in 74 patients (14.2%), and normalized without any intervention in 65%. Notably, there was no temporal association between either infection or serious infection and neutropenia. The rate of Herpes zoster infections (0.7 per 100 PY, all localized) was not higher than expected. Similarly, thromboembolic events occurred at the expected rate for RA patients (0.54 per 100 PY), and were all resolved. From a clinical perspective, it is important to note that the incidence rate of AEs was greater for patients with >1 TNFi failure than 1 TNFi failure (290.6 and 197.9 per 100 PY, respectively), although discontinuation rates were similar.

Concerning efficacy, patients who either remained on 200 mg or reduced to 150 mg of sarilumab showed a sustained response over 5 years, without difference for patients with 1 or >1 TNFi failure (about the 25% of the entire population). Therefore, taken together, these results reinforce the concept that TNF inhibition and IL-6 inhibition are definitely alternative treatment strategies in RA. In fact, patients showing baseline low levels of IL-6 did not respond differently to adalimumab or sarilumab, while patients with high levels of IL-6 appeared to have a greater chance to reach remission with sarilumab than with adalimumab (3).

The most recent EULAR recommendations for RA management advised bDMARDs or targeted synthetic DMARDs (tsDMARDs) in csDMARD-IR population without specifying preference for any treatment class apart for monotherapy in patients who cannot tolerate methotrexate (4). The urgent question to be addressed is how to make the choice of the first bDMARD or tsDMARD in each patient. Importantly, the pooled data of five Nordic biologics registers on patients who started treatment with a non-TNFi as first ever bDMARD and then switched to a second bDMARD, found that the survival-on-drug and primary response of a second bDMARD in RA patients is modest, while some patients may benefit from TNFi when used after failure of a non-TNFi as first bDMARD (5). Even if the selection bias can affect that result (6), it is clear that the first question to be answered by the clinician is whether to treat RA targeting TNF or targeting IL-6 first.

Among the numerous proinflammatory cytokines which are involved in the pathogenesis of RA and can be therapeutically targeted, TNFα and IL-6 have clearly shown their major role over the others such as IL-1.

However, although they are closely related in the inflammatory cascade, in the pathogenesis of RA, it seems that they promote distinct inflammatory pathways (7). In fact, TNFα activates

macrophages, T-cells, fibroblasts, and endothelial cells inducing the release of other proinflammatory cytokines, migration of leucocytes into the synovial joint and neoangiogenesis, leading to joint destruction by increasing proliferation of fibroblast-like synoviocytes and formation of osteoclasts, while IL-6 causes B-cell proliferation and antibody production and it also induces differentiation of T-cells into IL-17-secreting T-helper cells, therefore decreasing regulatory T-cell differentiation. IL-6 has also been shown to stimulate angiogenesis and osteoclastogenesis. Recent integrated histopathological and clinical observations support the notion that different patterns of rheumatoid synovitis exist, TNFα and IL-6 being the main drivers of the two most common types of rheumatoid synovitis (i.e., myeloid and lymphoid synovitis, respectively) (8). Thus, TNFα and IL-6 are the two cytokines that most likely contribute to many pathogenic signaling events that lead to RA, and they can condition the histotype of synovitis and thereby the response to treatment.

While TNFα inhibitors heralded a new era of biologic treatments for RA, the validation of other biological targets, including IL-6, opens up the option of selecting the best treatment for an individual patient to address specific unmet needs, such as pain, fatigue, morning stiffness, mood disorders, sleep disturbances, over the sole objective of inhibiting synovial inflammation and radiographic progression. In this context, IL-6 as a soluble mediator with pleiotropic effects not only on inflammation and immune response, but also on hematopoiesis, pain signal, metabolism and on the cardiovascular system, appeared a good target for covering these new unmet needs for RA patients (9). The history of the therapeutic indications for the drugs targeting TNF or IL-6 has elucidated the difference between these two targets in different chronic inflammatory diseases (figure 1).

Overall, the clinician can choose four treatment strategies as first-line therapy in DMARD-IR RA patients focusing on TNF or IL-6 as the main pathogenic targets: targeting TNF

directly or indirectly by blocking T-cell activation, or targeting IL-6 directly or by JAK inhibitors, which add the interferon pathway and innate immunity downregulation. This decision is now driven by comorbidity and patient's preference, since no biomarker has been validated up to now (10).

As more treatment options are becoming available, the need for tools of precision medicine that can aid physicians and patients in choosing the right treatment, both for efficacy and tolerability, is the major challenge for future research. Tantalazingly, since the technology is becoming cheaper and more reliable, and artificial intelligence is being applied to better understand complex cross-platform biology and Big Data, the recently published R4RA trial suggests this may be feasible (11,12).

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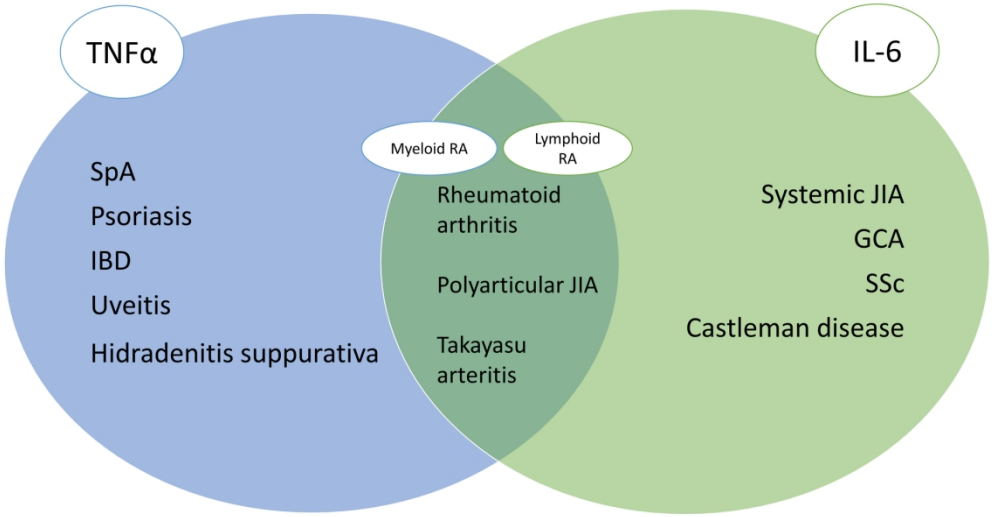
Legend to the figure

Figure 1. Main registered indications and off-label uses of the TNF or IL-6 inhibitors in chronic inflammatory disorders. RA, rheumatoid arthritis; SpA, seronegative spondyloarthritis; JIA, juvenile idiopathic arthritis; IBD, inflammatory bowel diseases; GCA, giant cell arteritis; SSc, systemic sclerosis.



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