Achieving drug-free remission: elucidating the role of TNF in rheumatoid arthritis

"The fact that biologics targeting TNF greatly reduce protein levels in the body can teach us about the novel pleiotropic bioactivity of TNF, as shown in TNF gene-targeting models."

KEYWORDS: biologics ■ remission ■ rheumatoid arthritis ■ TNF ■ treatment

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Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality. RA patients should be started with disease-modifying antirheumatic drugs such as methotrexate (MTX) as early as possible. However, the use of MTX often fails to control disease activity and prevent structural damage, and more effective treatment strategies are needed. TNF plays a pivotal role in the pathological processes of RA through the accumulation of inflammatory cells and the self-perpetuation of inflammation, leading to joint destruction. The combinational use of MTX and biologics targeting TNF, including infliximab, etanercept and adalimumab, has revolutionized the treatment of RA, producing significant improvements in clinical, radiographic and functional outcomes that were not previously observed, as well as producing the emerging outcome and upcoming end point for treatment [1–5]:

- Clinical remission
- Sustained reduction of progress in joint destruction (structural remission)
- Improvement and maintenance of physical functions (functional remission)

We recently reported that discontinuation of infliximab is possible in RA patients, after a reduction in disease activity has been obtained by the use of infliximab and MTX, implying that biologic-free remission is possible [6]. Based on the clinical findings, the need for clinical and basic approaches to the process-driven disease of RA will be described.

Biologic-free remission using TNF inhibitors

Our next goal is biologic-free remission and subsequent drug-free remission. Although global evidence of the efficacy and safety of TNF inhibitors (e.g., infliximab) has accumulated, including our RECONFIRM studies and many others [1–5], there is no well-established evidence regarding biologic-free remission. We conducted a study, remission induction by Remicade in RA patients (RRR), of RA patients from 26 centers and reported that 55% of patients, who achieved low disease activity (Disease Activity Score [DAS] 28 < 3.2) for more than 24 weeks during treatment with infliximab, were able to discontinue infliximab for more than 1 year without flaring. In addition, 43% had scores below 2.6 after discontinuation, indicating that they were in remission. The study registered patients with established disease. Their mean age was 51.4 years, mean disease duration was 5.9 years, mean total Sharp score was 63 and baseline DAS28 was 5.5. Furthermore, yearly progression of total Sharp score was less than 0.5 points in 67% and the health assessment questionnaire score was only 0.174 in patients who maintained low disease activity for 1 year after discontinuation. Therefore, we concluded that more than half of the patients who maintained low disease state for more than 24 weeks on infliximab could discontinue the drug and keep low disease activity for a year without radiographic or functional disease progression. These results suggest that the biologic-free remission is possible using infliximab and that the treatment may change or modify the course of disease.

The potential for biologic-free remission in RA patients was initially reported by a British group (TNF20 study). The combination of infliximab and MTX in early RA patients who had less than 12 months of symptoms provided tight control of the disease activity and a significant reduction in MRI evidence of synovitis and erosions at 1 year. At 2 years, functional and quality-of-life benefits were sustained, despite withdrawal of infliximab therapy. On the other

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hand, the Behandelstrategieën (BeSt) study was conducted to observe clinical and radiological outcomes of patients with early RA treated with infliximab and MTX who discontinued infliximab after achieving sustained low disease activity (DAS44 < 2.4) [7,8]. At 5 years after receiving infliximab and MTX as initial treatment for RA, 58% of 120 patients discontinued infliximab and 19% of patients discontinued all antirheumatic drugs and remained in clinical remission, with minimal joint damage progression. The biggest difference of the enrolled patient population in the RRR and BeSt studies was disease duration (mean disease duration was 0.4 years in the BeSt study versus 5.9 years in the RRR study). This implies that biologic-free remission is possible not only in early RA patients, but also in long-established RA and that infliximab may alter the disease course of RA. In our institution, of 400 patients who were treated with infliximab, 50 patients reached biologic-free remission and five are currently in a drug-free remission without taking MTX [9]. Interestingly, rheumatoid factor converted from positive to negative in these five patients, suggesting its relevance to immunological remission. Thus, because treatment with TNF inhibitors may change or modify the course of disease, a clinical and basic approach to research of the process-driven disease of RA is warranted.

Experimental findings suggest the involvement of TNF in the disease process

Accumulated studies indicate the involvement of TNF in the disease process in animal arthritis models. TNF is generally a major mediator in the early stages of joint inflammation in every experimental arthritis model. Moreover, the introduction of TNF transgene into mouse results in chronic polyarthritis, showing hyperplasia of the synovium, inflammatory infiltrates in the joint space, pannus formation and cartilage and bone destruction. However, the polyarthritis and joint destruction are completely ameliorated by both the preventive and curative application of TNF inhibitors.

In other words, TNF deficiency reduced the incidence of autoimmune arthritis in most models. For instance, K/BxN is a novel model of arthritis, which expresses both T-cell receptor (TCR) transgene *KRN* and the MHC class II molecule. In the mouse, TCR recognizes a self-antigen glucose-6-phosphate isomerase (GPI) and produces anti-GPI-antibody, and arthritis is induced by the injection of the serum to naive mice. Although TNF is highly expressed in K/BxN mice, the deficiency of TNF markedly reduced both incidence and the severity of the autoimmune arthritis. SKG is another inflammatory arthritis model with a point mutation of ZAP-70, a signaling kinase associated with TCR. A knockout mutation of TNF gene in SKG mice ameliorates both the incidence and severity of the arthritis. Also, multiple immune complex-mediated arthritis models (including collage-induced arthritis) can be attenuated in TNF and/or TNF-receptor deficiency.

> *"... polyarthritis and joint destruction are completely ameliorated by both the preventive and curative application of TNF inhibitors..."*

These accumulated studies of TNF deficiency in multiple arthritis models indicate that TNF is pivotally involved in the process of the disease. TNF is indispensable not only in inflammation formation but also in the expression of autoimmunity. In other words, if animal data suggest efficacy of TNF inhibitors in patients with RA, this implies that TNF inhibitors may change or modify the process-driven disease course by intercepting the pathological processes, which may cure the disease without approaching the cause of the disease.

TNF in the process of bone resorption

On the other hand, clinical studies regarding the efficacy of TNF inhibitors on structural changes of RA help us to understand its pathological mechanism. Although the rate of clinical remission by TNF inhibitor with MTX is approximately 30–40% of RA patients, the rate of structural remission is about 80–90%. Thus, contrary to expectations, the control of joint destruction appears to be easier than regulating synovitis, and structural damage can be reduced even when disease activity-related control is insufficient.

Bone resorption by the osteoclasts (which originated from their precursor monocytes in periphery) results in bone destruction. In general, the precursors differentiate to multinucleated osteoclasts after being stimulated by RANKL expressed on osteoblasts. In RA synovitis, osteoclasts accumulate at the border of synovium and bone, where they resorb bone. Because osteoblasts do not exist there, it is osteoblast-independent bone resorption by osteoclasts that is characteristic for RA. TNF both directly

and indirectly stimulates osteoclast maturation by inducing RANKL on synovial fibroblasts and T-cells in synovium. In TNF-transgenic mice, joint inflammation, maturation of osteoclast and bone erosion are observed. Furthermore, urinary levels of NTx, a bone resorption marker, are elevated in patients with RA, compared with age- and sex-matched health volunteers, whereas the bone mineral density of spines is comparable between RA and controls. Therefore, it can be postulated that osteoclast maturation is deviated from the bone metabolic turnover by direct and/or indirect stimulation with TNF, which results in characteristic bone destruction in the absence of osteoblasts in RA.

Furthermore, TNF inhibitor reduces the levels of bone resorption markers and regulates joint damage independently of the improvement of disease activity, although bone mineral density does not change by the treatment. It was also reported that the expression of RANKL deteriorates and osteoprotegerin is upregulated in synovium, and thus bone destruction is restrained accordingly. Therefore, TNF inhibitors may restore the osteoclasts deviated from bone turnover, which results in efficient regulation of joint damage in RA.

Conclusion & future perspective

The mortality and incidence of cerebrovascular events and myocardial infarction is known to be reduced in RA patients treated with TNF inhibitors, compared with other RA patients. We also observed that serum levels of high-molecular-weight adiponectin and HDL-cholesterol are increased in RA patients treated with infliximab, independently of any improvement in disease activity [10].

The fact that biologics targeting TNF greatly reduce protein levels in the body can teach us about the novel pleiotropic bioactivity of TNF, as shown in TNF gene-targeting models. Taken together with the effects of TNF inhibitors on joint damage, it can be assumed that TNF plays an important role in the process of metabolic disorders observed in bone, lipid and glucose systems beyond the inflammatory immune system. Thus, both clinical and basic approaches to the process-driven disease of RA and metabolic disorders involving bone should elucidate pathological mechanisms and treatment strategies.

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