Tumor necrosis factor (TNF) becomes a well-known name largely owing to the success of its antagonists in therapy of inflammatory diseases. In 1975, in searching for cancer therapeutic agent, Lloyd Old and colleagues found a substance in the serum of mice received endotoxin and bacillus Calmette-Guérin infection, which can cause tumor necrosis in experimental tumor models. The substance was named TNF. The gene of TNF was later cloned and proved to be identical to a molecule called cachectin which was referred to as TNF-related molecule with tumor necrosis activity. For a while TNF was called TNF-β. However, this was short-lived. The name change for TNF was protested as inappropriate confusion in the literature, I urge authors to use the original name, TNF for this cytokine, as has been done by many other authors in their publications.

TNF is the first cytokine to be successfully targeted for treatment of rheumatoid arthritis (RA) and Crohn disease (CD). TNF inhibitors (TNFi) have been medications prescribed by physicians in daily practice for treating various inflammatory diseases. The success of TNF blockade in chronic inflammatory disease was built on the failure of treatment of sepsis and septic shock. The first two TNF inhibitors, infliximab and etanercept were initially produced for clinical trials for patients with septic shock. Unfortunately, blocking TNF activities did not achieve the expected therapeutic effect in those patients with sepsis. It was fortunate for patients with RA and those with CD where TNF was identified to be a therapeutic target as it is highly expressed in the synovial tissue in RA and in the submucosal tissue in CD.

Five TNFi, namely infliximab, golimumab, adalimumab, certolizumab pegol and etanercept, and their biosimilars are in the market for management of patients with RA. The pivotal role of TNF in the pathogenesis of RA has been proved by the high efficacy of TNFi not only in clinical trials but also in real world patient care. The efficacy of other potent biological agents has been compared with that of TNFi to inform recommendations for management of RA in guidelines. A similar efficacy rate of TNFi has been achieved in inflammatory bowel diseases (IBD) to improve the health outcome and reduce the need for surgical intervention. TNFi are also effective to treat extra-intestinal manifestations of IBD.

TNFi include therapeutic monoclonal antibodies and a fusion protein consisting of extracellular domains of type 2 TNF receptor and human IgG1 Fc fragment. In general,
these TNFi have similar therapeutic and adverse effect profiles, but difference exists between these TNFi. The most notable one is etanercept which is ineffective in treating IBD or non-infective uveitis. All of these TNFi are able to neutralize activity of soluble TNF and transmembrane TNF to exert their inhibition effect. Etanercept, but not other TNFi, also binds LTα and LTβ and block their activities. For cells bearing transmembrane TNF, antibody mediated cytotoxicity and complement mediated cytotoxicity may take place in vivo in TNFi treatment. In addition, reverse signaling via transmembrane TNF may also involve in killing of TNF producing cells. The subtle difference in mechanism of action of these TNFi has reflected in management of patients with inflammatory diseases. It is not uncommon that a patient might fail to respond to one but will respond to another TNFi.

TNF was also highly expressed in the site of inflammatory tissue, sacroiliac joints in patients with ankylosing spondylitis (AS), suggesting involvement of TNF in the pathogenesis of AS. Inspired by the success in RA and CD, the first randomized control single-centered study with infliximab in spondyloarthritis (SpA) patients was conducted in 2000 after promising results were achieved from two open labeled trials. Significant clinical improvement was observed as soon as two weeks after the first dose of infliximab infusion, along with significant reduction of C-reactive protein. The magnitude of therapeutic effect of infliximab in these initial trials of patients with AS or SpA is comparable to that seen in RA patients. Numerous subsequent clinical trials confirmed the therapeutic effects of infliximab and other TNFi and demonstrated a high efficacy in treating AS and SpA as measured by various clinical disease activity assessments. Moreover, treatment of TNFi for AS and SpA has become a disease modifying therapy for those patients. TNFi can slow down the progression of spondylitis and protect patients from neo-ossification in patients on long-term treatment. It must be noted that the long-term structural protection effect is demonstrated only in those patients who have been on continuation of TNFi for more than 4 years. The benefit has translated in patients in real-world observational studies.

As seen in RA patients, TNFi have demonstrated benefit in reducing disability and cardiovascular complications in SpA patients.

The success of TNF blockade in treating inflammatory diseases has become a model for developing targeted therapy and set a high bar for subsequent development of targeted therapy in inflammatory diseases. For instance, clinical improvement by blocking interleukin-17 (IL-17) therapy for RA did not reach the magnitude of TNF blockade, thereby was considered to be a failure. However, IL-17 blockade has become a second class of highly efficacious biological therapies for patients with SpA. Despite the inferior therapeutic effect to TNF in RA, IL-17 inhibition has been extremely potent in treating psoriasis and has been effective in SpA. Antibodies to IL-17A or a dual specific antibody (bimekizumab) to IL-17A and IL-17F have clearly shown the superiority over placebo in SpA patients in both TNFi-naive and TNFi-experienced cohorts. The clinical efficacy of TNFi and IL-17 inhibitors (IL-17i) appear to be similar for treating SpA patients, but it is not possible to state which is superior since there are no head-to-head comparative data available. Interestingly, observational studies showed in axial spondylitis (axSpA) patients who failed prior TNFi had comparable responsiveness to secukinumab versus an alternative TNFi. Since syndesmophyte formation is a slow process, whether IL-17i have significant suppressive effect on new bone formation will need long-term observations to determine. Enthesitis is an important comorbidity in SpA patients but is only recently recognized. Therapeutic effect of enthesitis by IL-17i have been assessed (mainly in patients with psoriatic arthritis).

TNF blockade has become the gold standard in treating many inflammatory diseases in assessing the efficacy of novel targeted therapeutic agents as in the case of IL-17i and Janus kinase (JAK) inhibitors. Furthermore, TNFi have also been a reference for safety assessment for JAK inhibitors.

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