

Invited Speaker Abstract

IS21

Treatment of rheumatoid arthritis

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A defining feature of rheumatoid arthritis (RA) is its propensity to produce bone and cartilage destruction in the context of persistent synovial inflammation. The synovium generates large amounts of TNF- α and RANKL, which together are responsible for osteoclastogenesis. The TNF- α also increases Dkk-1 expression, which blocks canonical Wnt-signaling while reducing OPG expression. These signaling events inhibit osteoblasts while promoting osteoclastogenesis, resulting in focal bone erosion. In pre-clinical arthritis models, the downregulation of osteoclasts either via RANKL antagonism, genetic manipulations or TNF-blockade similarly and potently stop focal bone erosion with variable effects on cartilage. The relative contributions of bone or cartilage damage to functional disability in RA are not defined however functional loss in early arthritis is tightly linked to the intensity of joint inflammation while damage is correlated to the inflammatory burden over time.

Methotrexate (MTX) is the 'anchor drug' for long term RA management and results in significant symptom improvement and slowing of structural joint damage. Targeted anti-TNF therapy was developed because conventional therapy is still associated with measurable joint destruction. In contrast, TNF- α inhibition more reliably arrests damage, acts rapidly and shows greater efficacy in reducing symptoms and signs of arthritis. TNF- α inhibition is most effective when combined with MTX and remission rates of ~50% are possible. Thus, anti-TNF has a preferentially greater effect on structural damage compared with conventional therapy. Based on the known effects of gp-130 signaling and IL-17 on bone cell biology, the IL-6R and IL-17 anti-cytokine strategies that are currently in development will likely yield similar structural protection.

Targeted RANKL inhibition has been pursued to address all aspects of bone disease in RA. Denosumab is a high-affinity, high-specificity fully human IgG₂ monoclonal antibody which binds human RANKL so interfering with all steps of osteoclastogenesis. The emerging data from a continuing Phase II clinical trial show that denosumab (added to MTX) significantly reduced radiographic bone erosion, periarticular and systemic bone loss. However, in line with data in the animal models, selective RANKL inhibition in RA exerted no effect on synovial inflammation or cartilage despite bone protection. The utility of targeted RANKL inhibition compared to the existing anti-TNF- α strategies will require additional studies.