Introduction TNF and IL-17A are proinflammatory cytokines critically involved in the pathogenesis of psoriatic arthritis (PsA). Currently, targeting TNF is the first choice of a biologic disease-modifying antirheumatic drug (bDMARD) in PsA. However, up to 30% of patients receiving anti-TNF mono-therapy fail to respond and require switching to a second TNF-inhibitor or bDMARD with different modes of action. Strategies targeted at neutralising IL-17A have shown beneficial effects on skin, enthesis, dactylitis and joint inflammation.

Objectives We explore the effect of neutralising IL-17A versus anti-TNF on the expression of proinflammatory cytokines and metalloproteinases (MMPs) and whether dual-therapy targeting TNF and IL-17A may have superior activity than treatment with either agent alone.

Methods An allogeneic co-culture system was used comprising synovial fluid T helper (Tb) memory cells and synovial fibroblasts (SF), derived from patients with active PsA. Anti-CD3 and CD28 stimulation was used during culture, and anti-IL-17A antibody (Secukinumab), anti-TNFα antibody (Adalimumab), or the combination were added. PsA unstimulated synovial Tb memory cells co-cultured with PsA SF were included as a control group as well as an isotype antibody control group. After 72 hours, supernatants were harvested for ELISA and cells were lysed for qPCR analysis.

Results Anti-TNF Ab treatment had no effect on IL-17A levels and neutralisation of IL-17A did not influence the TNF production in co-culture system. Both anti-TNF and anti-IL-17A single treatment significantly inhibited the production of IL-8 and reduced the mRNA expression of IL-1β. Interestingly, neutralisation of IL-17A resulted in a significant suppression of IL-6 level which was not reduced by anti-TNF. Anti-TNF inhibited the production of MMP-3 and only the combination of anti-TNF and anti-IL-17A resulted in a significant suppression of MMP-1 levels and MMP-9 mRNA expression. MMP-13 mRNA expression was significantly suppressed by anti-TNF but not by anti-IL-17A. However, neutralising both showed a significant improvement in downregulating MMP-13 mRNA expression compared to single treatment. Moreover, anti-IL-17A reduced RANK mRNA expression significantly compared to anti-TNF, but no additive effect was noted for combination blocking. Interestingly, only neutralising both IL-17A and TNF significantly reduced the mRNA expression of RANKL. OPG mRNA expression was not influenced by either treatment or both.

Conclusions Neutralising IL-17A or TNF in the PsA synovial T cell–SF co-culture system resulted in overlapping but also distinct effects on proinflammatory cytokine expression. TNF inhibition markedly suppress different MMPs with mostly an additional effect upon neutralisation of IL17A. Neutralisation both IL-17A and TNF is needed to downregulate RANKL expression which changes the RANKL/OPG balance. Together, these data suggest that dual therapy targeting IL-17A and TNF may be superior in their activity to protect against erosive arthropathy in PsA than treatment with either agent alone.

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