A47 ANTI-INTERLEUKIN 17A THERAPY INHIBITS TUMOUR NECROSIS FACTOR-MEDIATED BONE LOSS BY MODULATION OF T CELL BALANCE

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Objective Immune activation is the major driver of local and systemic bone loss. Pro-inflammatory cytokines, in particular

tumour necrosis factor (TNF), link immune activation with bone loss. Recently, T cells have been implicated as regulators of bone turnover. Th1 and Th2 associated lymphokines such as interleukin 12 (IL12), interferon γ and IL4 are strong inhibitors of osteoclastogenesis, whereas IL17A produced by Th17 cells increases osteoclast differentiation. In this study we blocked IL17A in a murine TNF-mediated arthritis model.

Methods Human TNF transgenic (hTNFtg) mice were treated with an anti-IL17A antibody for 4 weeks. Mice were clinically and histologically assessed for signs of inflammation, cartilage damage and bone damage. T cell balance was evaluated with quantitative mRNA analysis of T cell-associated genes and measurement of serum cytokines. Moreover, we analysed the effects of IL17A blockade in hTNFtg mice devoid of IL1 signalling.

Results Despite only minor effects on inflammation, IL17A blockade effectively reduced local and systemic bone loss based on reduced osteoclast differentiation in vivo. These effects were due to a shift to bone-protective T cell responses including Th2 differentiation, induced IL4 and IL12 expression and an increase in foxp3-expressing lymphocytes. When blocking IL17A in IL1-/-TNFtg mice, arthritis was virtually abrogated and no osteoclasts and bone erosions formed. Moreover, no shift in T cell lineages was observed in IL1-/-TNFtg mice treated with IL17A and no additional benefit of IL17A blockade on bone mass was found.

Conclusion We conclude that IL17A regulates bone mass in conjunction with IL1 through suppression of bone regulatory pathways of T cell-mediated adaptive immunity.