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O015 IL-17 BLOCKADE WITH SECUKINUMAB IN PERIPHERAL SPONDYLOARTHRITIS IMPACTS SYNOVIAL IMMUNOPATHOLOGY WITHOUT COMPROMISING SYSTEMIC IMMUNE RESPONSES

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Introduction Secukinumab (anti-IL-17A) is an effective therapy for ankylosing spondylitis(AS) and psoriatic arthritis (PsA), the prototypical forms of spondyloarthritis (SpA).

Objectives This study assessed if secukinumab modulates the immunopathology of target lesions without blunting systemic immune responses, using peripheral SpA (pSpA) as model.

Methods 20 active peripheral SpA patients were included in a 12 week open-label trial with secukinumab (300 mg weekly for 4 weeks followed by every 4 weeks). Outcomes included clinical response, cytokine production by peripheral blood cells using TruCulture technology, and histological and qPCR analysis of synovial biopsies before and after treatment.

Results All patients completed the 12 week study, without SAEs or severe treatment-related AEs. The primary efficacy endpoint, EULAR DAS 28 response at wk 12, was achieved by 18/20 patients (10 good and 8 moderate responders), with rapid and significant improvements in all clinical disease activity measurements. Clinical improvement in joint counts was associated with histological decrease in synovial sublining macrophages ($p=0.028$) and neutrophils ($p=0.004$), sensitive synovial biomarkers of response in pSpA, as well as with decreased synovial expression of IL-17A ($p=0.010$) but not TNF. Systemically, secukinumab treatment decreased CRP ($p<0.01$) and ESR ($p<0.01$), as well as MMP-3 production in the truculture system ($p<0.01$). With exception of IL-17A itself, however, the capacity of peripheral blood cells to produce a broad panel of cytokines and chemokines upon stimulation with microbial antigens was not affected.

Conclusions This mechanism-of-action study in pSpA indicates that clinical improvement upon secukinumab treatment is paralleled by immunomodulation of the inflamed target tissues without compromising systemic immune responses.

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O016 SYNOVIAL IL-17+ CD8+ T CELLS ARE A PRO-INFLAMMATORY TISSUE RESIDENT POPULATION ENRICHED IN SPONDYLOARTHRITIS

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Introduction Spondyloarthritis (SpA) describes a group of inflammatory joint diseases affecting ~1% of the population. SpA has strong genetic associations with *HLA-B/RUNX3* implying a role for CD8 +T cells. Furthermore, genetic associations with *IL23R/TRAF3IP2* and the clinical efficacy of IL-17 blockade in SpA, indicate a role for IL-17 in these diseases.

Objectives This provides a strong rationale to investigate the presence, phenotype and functional capacity of IL-17 +CD8 +T cells in the joints of patients with SpA.

Methods Mononuclear cells were isolated from peripheral blood (PB) and synovial fluid (SF) from patients with PsA, other peripheral-SpA types (including ankylosing spondylitis/non-radiographic axial SpA/reactive arthritis/enteropathic arthritis/undifferentiated SpA) and rheumatoid arthritis (RA). Cells were stimulated *ex-vivo* before analysis of surface marker/cytotoxic molecule/cytokine expression by flow cytometry or cytokine secretion assay (CSA). Sorting was performed on unstimulated SFMC and gene expression analysis performed by RT-PCR.

Results Frequencies of IL-17 +CD8+T cells were increased in the SF of PsA ($p<0.0001$) and SpA ($p=0.0009$), but not RA patients ($p=0.3$) vs. paired PB, with IL-17 secretion confirmed by CSA. Phenotypically, SF IL-17 +CD8+T cells were largely composed of TCRab +T cells (~95%), with small proportions of MAIT/NK/gd-T-cells (all <5%). Considerable proportions of SF IL-17 +CD8+T cells expressed markers typical of skin/gut tissue residency including β7 integrin (median-66%), CD49a (57%), and cutaneous lymphocyte antigen (27%), as well as Th17-associated markers (CCR6/CD161 expression). Interestingly, SF IL-17 +CD8+T cells expressed hallmarks of tissue resident memory T cells (T_{RM}; CD45RA-CCR7-CD103+) whilst sorted CD8 +CD69+CD103+T_{RM} cells from the PsA joint were enriched for IL-17, and expressed *RORC* transcript. Functionally, a high frequency of SF IL-17 +CD8+T cells co-expressed granzyme B and the pro-inflammatory cytokines IFN-γ, GM-CSF, TNF-α, some IL-21 and IL-22, but very little anti-inflammatory IL-10.

Conclusions These novel findings show an enrichment of IL-17 +CD8+T cells in the joints of patients across multiple SpA types and identify a phenotypic signature for IL-17 +CD8+T cells, consisting of type 17 and tissue-associated markers. Our data demonstrate, to our best knowledge for the first time, the presence of T_{RM} cells in the PsA joint. Functionally, IL-17 +CD8+T cells exhibit cytotoxic potential and co-express pro-inflammatory cytokines, suggesting these cells are important contributors to the pathogenesis of PsA and other SpA.

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