## A167 ADMINISTRATION OF IL-18BP BY GENE THERAPY REDUCES INFLAMMATION AND PREVENTS JOINT DESTRUCTION BY DOWNREGULATION OF MMP9 IN RAT AIA: ROLE OF MMP9 IN BONE AND JOINT DESTRUCTION IN ARTHRITIS

Hubert Marotte,[1,2] Salahuddin Ahmed,[1] M Asif Amin,[1] Jeffrey H Ruth,[1] Phillip L Campbell,[1] Bradley J Rabquer,[1] Charles Lesch,[1] Benjamin P Lewis,[1] Jean Dudler,[3] Alisa E Koch[1,4] *[1]Department of Internal Medicine/Division of Rheumatology, University of Michigan Medical School, Ann Arbor, Michigan, USA; [2]INSERM U890, Rheumatology Department, University Hospital of St-Etienne, St-Etienne, France; [3]Service de Rhumatologie, Médecine Physique et Rééducation, CHUV, Lausanne, Switzerland; [4]Department of Veterans Affairs, VA Medical Service, Ann Arbor, Michigan, USA*

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**Background and objectives** Interleukin 18 (IL-18) is a pleiotropic cytokine involved in rheumatoid arthritis (RA) pathogenesis. This study was carried out to evaluate the efficacy of IL-18 binding protein (IL-18BP) gene therapy in the rat adjuvant-induced arthritis (AIA) model and to decipher the mechanisms by which IL-18BP delivery lessens bone destruction.

**Materials and methods** Arthritis was induced in female Lewis rat by *Mycobacterium butyricum* and the mRNA expression of IL-18 and IL-18BP was determined in the joints. In a preventive study, rats were divided into an adenovirus producing IL-18BP-Fc (AdmIL-18BP-Fc) group (n=8) and an adenovirus producing green fluorescent protein (AdGFP) group (n=7). On day 8 after AIA induction, adenoviruses were injected. Clinical parameters were assessed. At day 18, during maximal arthritis, the rats were euthanized, ankles were collected and x-rays were performed. mRNA and protein were extracted from joints for analysis by quantitative reverse transcriptase-PCR, multiplex, Western blot and zymography.

**Results** The authors observed a decrease in the (IL-18BP/IL-18) ratio from day 7 to 45. Administration of AdmIL-

18BPd-Fc decreased clinical parameters and prevented bone and joint destruction compared to AdGFP administration. IL-18BP delivery reduced the (receptor activator of nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG)) ratio by 70%, the matrix metalloproteinase 9 (MMP9) level by 33% and the tartrate-resistant acid phosphatase (TRAP) level by 44% in the joint homogenates from AdmIL-18BPd-Fc compared to AdGFP treated rats.

**Conclusions** In rat AIA, a decrease in the (IL-18BP/IL-18) ratio was observed. IL-18BP delivery prevented joint and bone destruction by downregulating MMP9, (RANKL/OPG) and TRAP, suggesting a potential benefit of a similar therapy in RA.

**Abstract topics** Towards novel therapeutic strategies.