A90 A TLR 9 ANTAGONIST DIMINISHES ARTHRITIS SEVERITY IN A RAT MODEL OF RHEUMATOID ARTHRITIS

S Herman,[1] A Fischer,[1] J Pfatschbacher,[1] M Hoffmann,[2] G Steiner[1] *[1]Department of Rheumatology, Medical University of Vienna, Vienna, Austria; [2]Division of Medical Inflammation Research, Karolinska Institutet, Stockholm, Sweden*

10.1136/ard.2010.148973.8

Background There is evidence that release of endogenous nucleic acids may trigger autoimmune reactions crucially involved in the induction of systemic autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis (RA). In recent years, endosomal toll-like receptors (TLRs – TLR3, TLR7, TLR8 and TLR9) have been implicated in autoimmune processes due to their ability to recognise these nucleic acids.

Objective To study the role of TLR7 and TLR9 in the pathogenesis of erosive arthritis by antagonising them in the pristane-induced arthritis (PIA) model in DA rats.

Methods Different immunoregulatory sequences (IRS) known to inhibit TLR7 and/or TLR9 activity were investigated in cultured rat splenocytes. Using the PIA model, these IRS were also tested for their efficiency in inhibiting arthritis development compared to placebo animals. The IRS' were applied twice a week subcutaneously at the base of the tail. Weight changes were measured during the experiment and arthritis was assessed using an established scoring system. Expression of TLRs was analysed in paws, lymph nodes and spleen by Western blotting, reverse transcription-PCR and immunohistochemistry.

Results IRS specific for TLR7, TLR9 or TLR7/9 inhibited in a dose-dependent manner production of pro-inflammatory cytokines in rat splenocytes preactivated by TLR specific stimulators. However, neither the TLR7 specific inhibitor nor the inhibitor targeting TLR7 and TLR9 showed an effect on incidence and severity of PIA. Remarkably however, antagonising TLR9 alone led to delayed disease onset and reduced arthritis severity, which was accompanied by diminished TLR9 protein expression levels in paws and lymph nodes compared to the phosphate-buffered saline treated control animals.

Conclusion The authors' first in vitro and in vivo results indicate a potential involvement of TLR9 in the initiation of inflammatory arthritis pointing to a possible new therapeutic option in the treatment of RA.