18 ANTI HMGB1 TREATMENT REDUCES INFLAMMATION IN MODELS OF EXPERIMENTAL AUTOIMMUNITY

P Lundbäck,[1] L Klevenvall,[2] L Ottosson,[2] H Schierbeck,[2] K Palmblad,[2]U Andersson,[2] H Erlandsson Harris[1] *[1]Department of Medicine, Karolinska Institutet, Solna, Sweden; [2]Women's and Children's Health, Karolinska Institutet, Solna, Sweden*

10.1136/annrheumdis-2011-201238.18

Background and objectives High mobility group box protein 1 (HMGB1) is a nuclear protein present in all cells. HMGB1 is passively released extracellularly during cell death and, similarly, HMGB1 can be actively secreted from activated cells. Extracellular HMGB1 mediates multiple inflammatory processes. High levels of extracellular HMGB1 have been demonstrated in synovial joints of arthritis patients, intraarticular injection of HMGB1 causes synovitis in mice and neutralisation of HMGB1 by peptide inhibitors or polyclonal antibodies ameliorates experimental arthritis.

In this study, we investigated and compared the effects of an HMGB1 peptide inhibitor and a mouse monoclonal antibody

(mAb) targeting HMGB1 in an experimental model of arthritis and in acute autoimmune hepatitis. Defining a mAb or peptide inhibitor with ameliorative effects will forward the development of HMGB1 blockade suitable for clinical trials.

Methods Collagen induced arthritis (CIA) was induced in DBA/1 mice. Arthritis severity was evaluated by clinical grading of inflammation. Mice with established arthritis were treated every other day with mAb 2G7 or irrIgG and monitored for 7 days. Autoimmune hepatitis was induced by ConcavalinA injection in C57/bl6 mice pretreated with Abox, mAb 2G7 or PBS. After 8 h, sera and liver biopsies were collected. Serum ALT levels, along with HTX staining of liver biopsies were assessed. Liver myeloid peroxidase (MPO) were measured as an indication of neutrophil infiltration. Pro-inflammatory mediator levels were quantified by ELISA. HMGB1 levels were evaluated by ELISA and immunohistochemistry.

Results mAb 2G7 treatment significantly ameliorated inflammation in CIA mice and also reduced destruction, as assessed by histological analysis. In mice with autoimmune hepatitis, we recorded an upregulated HMGB1 expression damaged liver lobules. Abox treatment minimised liver damage and mAb 2G7 reduced neutrophil infiltration. Reduced interferon γ and CXCL1 levels were demonstrated in both Abox and mAb 2G7 treated mice.

Conclusion By these studies, we have for the first time defined a mAb targeting HMGB1 that effectively reduces inflammation and destruction during CIA. Beneficial effects of this mAb were also demonstrated in a model of autoimmune hepatitis. Furthermore, we could confirm the inhibitory effects of the peptide inhibitor A box, previously demonstrated in CIA, in experimental autoimmune hepatitis. Hence, our current work with humanisation of mAb 2G7 and assessements of its therapeutic effects can be performed in the autoimmune hepatitis model. This allows us to rapidly screen multiple humanised mAb clones and also avoids xenoreactivity effects. Hence, we have facilitated the development of HMGB1 blockade for clinical use.