therapeutic protocol (after disease onset). The effect on disease severity (visual scores) as well as parameters of cartilage and bone destruction were evaluated.

Results Clinical scores were significantly reduced after IL-18 blockade (rhIL-18BP 1 mg/kg, $p < 0.001$, $n = 13$; anti-IL18 IgG, 2 mg, $p < 0.05$, $n = 9$, Mann Whitney test, treated versus placebo groups). Histological examination showed cartilage protection (decrease erosion scores, $p < 0.05$) that was accompanied by significantly reduced levels of serum cartilage oligomeric matrix protein (an indicator of cartilage turnover) and VDIPEN expression (a neoepitope present after digestion by matrix metalloproteinases). X-ray analysis of joints provided evidence of reduced bone erosion.

Conclusion These results clearly demonstrate that neutralising endogenous IL-18 is therapeutically efficacious in the CIA model and support the use of IL-18 neutralisation as a novel cartilage and bone sparing therapy for the treatment of destructive arthritis. Recombinant hIL-18BP could therefore represent a new disease-modifying anti-rheumatic drug that warrants testing in clinical trials in patients with rheumatoid arthritis.

OP0018 EARLY TREATMENT OF RECENT-ONSET RHEUMATOID ARTHRITIS PATIENTS IMPAIRS THE EFFECT OF HLA CLASS II ANTIGENS ON THE PROGRESSION OF JOINT DESTRUCTION

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Background HLA class II antigens influence disease progression as measured by extend of joint destruction in RA. This effect is supposed to be caused by formation of auto reactive T-cells after presentation of (auto) antigens in the context of HLA class II.

Objectives To investigate whether in patients with recent-onset RA early DMARD treatment could prevent the involvement of autoreactive T cells, we analysed the association of HLA class II and joint damage in 110 patients with early RA that were treated according to the pyramid strategy with DMARDs and 98 patients with early RA that were promptly treated with DMARDs at two weeks after the first visit.

Methods DNA isolation, DRB1 typing and subtyping and DQB1 typing were performed. Extend of joint damage was measured by the modified Sharp score of the radiographs of hand and feet.

Results In the early treatment group the increase in the median Sharp score in the SE+ group was 1.0 to 5.0 in contrast to 1.0 to 3.0 in the SE- group ($P > 0.5$). However, in the pyramid group the increase in joint damage was 0.0 to 16.0 in the SE+ group in contrast to 0.0 to 5.0 in the SE- group ($p < 0.005$). On the other hand, in the RF+ group of the early treatment group the increase in joint damage was 1.0 to 6.5 in contrast to 1.0 to 1.0 in the RF- group ($p < 0.005$). In the pyramid group the increase in joint damage was 0.5 to 17.0 in the RF+ in contrast to 0.0 to 3.0 in the RF- group ($p < 0.005$).

Conclusion This study shows that early anti-rheumatic drug treatment abolishes the effect of HLA class II alleles on extend of joint damage in early RA patients.

OP0019 ENDOGENOUS DNA AND ARTHRITIS

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Background Recent studies have shown that DNA, in addition to functioning as hereditary material, is able to activate the immune system. In particular, bacterial DNA displays *in vivo* and *in vitro* immunostimulatory properties. These properties have been attributed to certain unique properties of bacterial DNA including high content of unmethylated cytosines in CpG dinucleotides. Although eukaryotic nuclear DNA is not immunostimulatory, we have found that mitochondrial DNA (mtDNA), like bacterial DNA, can activate inflammation.

Objectives The aims of our studies were to assess the arthritogenicity in mice of endogenous mtDNA sequences and to assess a potential role in human inflammatory disease.

Methods Highly purified mtDNA as well as synthetically produced oligonucleotides were injected intra-articularly into murine knee joints. The development of arthritis was evaluated histopathologically. In addition, we analysed by PCR the synovial fluids (SF) of rheumatoid arthritis (RA) patients for the presence of free mtDNA.

Results Intra-articular injection of mtDNA and fragments of the mitochondrial genome containing unmethylated CpG sequences gave rise to arthritis in mice. This inflammation was mediated by macrophages and their products, such as TNF-alpha. In contrast, T/B lymphocytes or granulocytes did not participate in the onset or progression of the disease. The SF of 40/54 RA patients tested contained extracellular, PCR-amplifiable mtDNA.

Conclusion Our results indicate that endogenous mtDNA is pro-inflammatory and may participate in the induction and/or propagation of arthritis in man.

OP0020 TUMOUR NECROSIS FACTOR ALPHA ACTS DIRECTLY ON OSTEOCLAST FORMATION BY SYNOVIAL MACROPHAGES AND MONOCYTES IN RHEUMATOID ARTHRITIS

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Background Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology that results in progressive destruction of bone and cartilage in affected joints. It has been reported that in mouse bone marrow cell cultures TNF-alpha directly induces osteoclast formation and IL-1alpha stimulates osteoclast activation, and that this osteoclast formation and activation is independent of osteoprotegerin ligand (OPGL) signalling system.^{1,2}

Objectives TNF-alpha and IL-1alpha considered master cytokines in the process of RA but little is known about the direct effects of these cytokines on development of human osteoclasts. This study aims to determine the role of TNF-alpha and IL-1alpha, on synovial macrophage- and monocyte-osteoclast differentiation in RA.

Methods Macrophages and monocytes isolated from RA patients were cultured with TNF-alpha and/or IL-1alpha on glass coverslips and dentine slices in the presence of M-CSF. Anti-TNF-alpha, anti-IL-1alpha and osteoprotegerin (OPG) was added to this cultures. Cultures were assessed for cytochemical and functional evidence of osteoclast differentiation.