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IMMO-LDRT01 TRIAL: IMMUNOMODULATORY EFFECTS OF LOW DOSE RADIATION THERAPY OF CHRONIC DEGENERATIVE AND INFLAMMATORY DISEASES

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Career situation of first and presenting author Student for a master or a PhD.

Introduction The treatment of chronic inflammatory and/or degenerative diseases by low dose radiation therapy (LDRT) is a successful alternative treatment option, especially for patients who were refractory for treatment with drugs. Generally, LDRT aims to reduce pain of patients and to increase their mobility. Although LDRT has successfully been applied since the late 19th century, the underlying immunological mechanisms are only fragmentarily analyzed.

Objectives Therefore we have aimed to analyze the impact of locally delivered LDRT on systemic immune changes.

Methods For this the IMMO-LDRT01 study (NCT02653079) was initiated in 2016. The study will include 150 patients suffering from chronic inflammatory and/or degenerative diseases, such as arthritis, arthrosis or benign calcaneodinia. The patients are treated with six local irradiations (single dose per fraction of 0.5Gy) in three weeks. If necessary, the serial irradiation can be repeated after 8–12 weeks, in order to achieve a further reduction of the pain. Blood samples are taken before and after every serial irradiation, as well as during follow-up appointments of the patients. For detailed immunophenotyping of whole blood, we established a multicolor flow cytometry assay, which allows the monitoring of seven main immune cell types, 26 immune cell subtypes, and the activation status of the immune cells.

Results To date 80 patients have been included in the study. First evaluations showed a significant reduction of B cells and cytotoxic T cells in the peripheral blood of patients. In particular, LDRT impacted on activation markers of immune cells. One has to stress that the immunological effects of LDRT were dependent on the particular type of disease of the patients. Currently, the data of the immunophenotyping are correlated to pain perception and quality of life of the patients.

Conclusions These analyses will be helpful to optimize LDRT. A better patient stratification based on pain- and immune-related biomarkers is envisaged for the future, alongside with initiation of deliberated randomized clinical trials.

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Disclosure of Interest None declared.

P156/008

SYSTEMIC INFLAMMATION ORIGINATING FROM THE SKIN OR THE INTESTINE COMBINED WITH BIOMECHANICAL STRESS HAS DIFFERENT EFFECTS ON THE JOINTS IN AN IN VIVO MOUSE MODEL

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Introduction Psoriasis (PsO) and inflammatory bowel disease (IBD) share a wide range of comorbidities, including psoriatic arthritis (PsA). Enteses, the attachment sites of tendons and ligaments into the bones, spread the mechanical forces generated by movement onto the bone and are considered as a primary disease localization in PsA. Increasing evidence supports the hypothesis that biomechanical stress, together with inflammatory triggers from distant sites, such as the skin or the intestine, can contribute to the onset of PsA by inducing microdamage in the enteses.

Objectives In this study, we aimed to investigate the role of biomechanical stress together with cutaneous or intestinal inflammation in initiating joint disease.

Methods Eight-week-old male C57/Bl6 mice were treated with imiquimod cream (IMQ) on a shaved area of the back skin or with dextran sodium sulphate (DSS) dissolved in the drinking water to induce PsO-like skin or IBD-like gut inflammation. Control mice were left untreated. Afterwards, half of the mice were subject to a forced treadmill running protocol to increase biomechanical stress. Control mice with or without IMQ or DSS treatment did not run. Severity of cutaneous or intestinal inflammation was assessed clinically and by histology; knees and paws were analyzed by microCT, histology and immunohistochemistry.

Results Local induction of cutaneous or intestinal inflammation led to a systemic response, as detected by splenomegaly, trabecular subchondral bone loss and bone marrow hypercellularity.

On a background of PsO- but not of IBD-like inflammation, discrete signs of synovitis determined by the presence of CD45 + cells and overexpression of IL-17 were detected, with no significant impact of the running protocol. The CD45+ cells in the IMQ non-running condition were identified as F4/80+cells, in contrast to the running condition where the CD45+ cells could not be further identified, showing negative results for F4/80, CD3, MPO and MCSF-R stainings.

Furthermore, forced exercise and PsO-like inflammation both induced overexpression of IL-17 at the enteses and acted synergistically when combined.

Conclusions Local induction of PsO- or IBD-like inflammation triggers a systemic response with inflammation-associated bone loss and discrete signs of joint disease. PsO-like inflammation in combination with biomechanical stress increased the degree of synovitis and enthesitis, showing that systemic inflammation combined with biomechanical stress may contribute to disease manifestations in PsA.

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RADIORESISTANT AND RADIOSENSITIVE CELLS CONTRIBUTE TO IL-18BP PRODUCTION IN A MODEL OF MACROPHAGE ACTIVATION SYNDROME

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Introduction Interleukin (IL)-18 is a pro-inflammatory cytokine, the activity of which is regulated by its natural inhibitor IL-18 binding protein (IL-18BP). If the balance between IL-18 and IL-18BP is dysregulated, abnormal levels of free bioactive IL-18 (fIL-18) are detected, such as in the sera of patients with macrophage activation syndrome (MAS). We showed that endogenous IL-18BP exerts a protective role in a murine model of MAS induced by repeated injections of the TLR9 agonist CpG. IL-18BP production is strongly increased in liver, lung, and spleen in this model, but its cellular origin is unknown.

Objectives To study the relative contribution of radioresistant and radiosensitive cells to IL-18BP production using bone marrow (BM) transfer experiments.

Methods Following whole-body irradiation, WT or *Il18bp*^{-/-} recipient mice were reconstituted with WT or *Il18bp*^{-/-} BM to create 4 groups of mice: WT recipient mice transferred with WT BM (WT/WT), WT/*Il18bp*^{-/-}, *Il18bp*^{-/-}/WT, and *Il18bp*^{-/-}/*Il18bp*^{-/-}. BM chimeric mice were challenged with CpG injections on days 0, 2 and 4 and sacrificed on day 7. We assessed body weight during the course of the experiment, blood cell counts before and after CpG injections and spleen weight after sacrifice. Liver, lung and spleen mRNA levels of *Il18*, *Il18bp*, *Ifng*, and IFN- γ signature genes *Cxcl9* and *Ciita* were determined by RT-qPCR. Circulating levels of IL-18BP, fIL-18, and CXCL9 were measured by ELISA.

Results The severity of CpG-induced MAS, as assessed by body weight changes, spleen weight and blood cell counts, was increased in *Il18bp*^{-/-}/*Il18bp*^{-/-} mice, but not significantly different between the three other groups. As reflected by a higher disease severity in *Il18bp*^{-/-}/*Il18bp*^{-/-} mice, an enhanced IFN- γ signature and elevated levels of circulating fIL-18 were observed in these mice. In the other groups, IL-18BP levels were still sufficient to inhibit IL-18 activity. Indeed, circulating IL-18BP levels dropped drastically only in the *Il18bp*^{-/-}/*Il18bp*^{-/-} group. Despite this, *Il18bp* mRNA levels, as assessed by RT-qPCR, varied in the different organs, consistent with the relative contribution of radioresistant versus radiosensitive cells. Indeed, following CpG stimulation radioresistant cells were the main contributors in liver (65%) and lung (90%), whereas radiosensitive cells were the primary source of IL-18BP in spleen (80%).

Conclusions Our results demonstrate that IL-18BP is produced by both radioresistant and radiosensitive cells and is present at high levels in the circulation to prevent the deleterious systemic effects of IL-18 in MAS.

Disclosure of Interest None declared.

P158/O07 PATHOLOGICAL INFLAMMATION IN EXPERIMENTAL SPONDYLOARTHRITIS IS CHARACTERIZED BY HIGH ENDOTHELIAL VENULES AND ECTOPIC LYMPHOID STRUCTURES IN THE BONE MARROW

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Introduction Tumour necrosis factor (TNF) is important in immune-mediated inflammatory diseases such as spondyloarthritis (SpA). Transmembrane (tm)TNF-transgenic (tg) mice¹ that overexpress tmTNF develop SpA symptoms, including inflammation, ectopic lymphoid structures (ELS) in bone marrow (BM), bone destruction and bone formation. SpA patients have extensive angiogenesis in inflammatory and bone forming regions.

Objectives To investigate whether there is a link between pathological angiogenesis and ELS in tmTNF tg mice in the BM.

Methods Ankles, femora, tibiae, vertebrae and spleens from 6 and 12 weeks and 8 months old tmTNF tg mice and wild-type (WT) littermates (n=5 per age per group) were dissected and analyzed with confocal microscopy and analyzed 12 week old tmTNF tg and WT mice (n=4) with flow cytometry. To study the importance of TNF-R signaling, tmTNF tg mice lacking TNF-RI (tmTNF tgxTNF-RI^{-/-}) or TNF-RII (tmTNF tgxTNF-RII^{-/-}) (n=4 per group) were used.

Results Immunofluorescent evaluation demonstrated that BM of tmTNF tg mice contained significantly more and extensive ELS. These ELS are limited to BM of the vertebrae and ankles, and are in close proximity of MECA79⁺ high endothelial venules (HEVs). ELS predominantly consisted of B220⁺ B cells, of which most are IgD⁺ naive B cells. Preliminary flow cytometric analysis revealed a trend towards an increase in IgD-CD95⁺ germinal center B cells and CXCR5⁺PD-1⁺FoxP3⁻CTLA4⁻ T follicular helper cells and CXCR5⁺PD-1⁺FoxP3⁺CTLA4⁺ in the vertebrae of tmTNF tg mice compared to WT littermates. Meanwhile, B cell lineages in the BM of tmTNF tg hind limbs were not altered. Furthermore, preliminary data indicates that BM and spleen from tmTNF tg mice contain more IgA⁺ plasma cells compared to WT littermates. tmTNF tgxTNF-RI^{-/-} mice did not display lymphoid aggregates or HEVs in the BM, while tmTNF tgxTNF-RII^{-/-} mice did, although to a lesser extent than tmTNF tg mice.

Conclusions tmTNF overexpression in mice results in extensive ELS associated with HEVs in the BM, which is likely to be mediated through TNF-RI signaling. HEV formation may lead to persistence of inflammation in the BM which contributes to pathology.

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Disclosure of Interest None declared

P159/O30 OLT1177™, AN ORAL NLRP3 INFLAMMASOME INHIBITOR, INHIBITS ACUTE JOINT INFLAMMATION AND CIRCULATING IL 1 β DURING GOUT FLARES IN HUMANS

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