Conclusions: BMSCs were restricted to the joint injury or inflammatory site,differentiated into chondrocytes, and then participated in the cartilage repairing.

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AB0096 EFFICACY AND SAFETY OF ORAL ADMINISTRATION OF PURE CELASTROL IN AIA RATS

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Background: Celastrol, a pentacyclic-triterpene isolated from *Tripterigium wilfordii* roots, has shown great therapeutic potential for the treatment of several inflammatory diseases, including rheumatoid arthritis (RA). We have previously demonstrated that celastrol has significant anti-inflammatory and bone protective effects in the adjuvant-induced rat model of arthritis (AIA), when administered via intraperitoneal route. For further preclinical evaluation of celastrol as a candidate compound for RA treatment, an effective and safe oral administration is crucial.

Objectives: In this work we aimed to study the dose range for both therapeutic and toxic effects for oral administration of pure celastrol using the AIA rat model.

Methods: Celastrol (1, 2.5, 5, 7.5, 12.5 and 25μg/g/day, N=5/group) was administrated orally in female AIA rats after 8 days of disease induction (therapeutic model) for a period of 14-days. A group of healthy (N=8) and untreated arthritic (vehicle, N=15) gender and age-matched Wistar rats were used as control. During the period of treatment, the inflammatory score, ankle perimeter and body weight were measured. At the end of the treatment, animals were sacrificed, blood was collected for clinical pathology, and necropsy was performed, with collection of internal organs for histopathological analysis and of paw samples for disease scoring.

Results: Oral administration of pure celastrol at 2.5, 5 and 7.5μ g/g/day reduced the inflammatory score and ankle swelling, preserved articular joint structure with a reduction in synovial inflammatory infiltrates and proliferation, halted articular bone destruction, and diminished the number of synovial CD68+ macrophages (a biomarker of response to anti-arthritic treatment). This compound also reduced the number of osteoclasts and osteoblasts present in joints. Bone resorption and turnover was also reduced at both 5 and 7.5μg/g/day, with a significant decrease in serum levels of TRACP-5b, P1NP and CTX-I. Of note, no significant variation in body weight, evidence of nephro-, hepato- or cardiotoxic effects, nor alterations in blood cell counts were observed at these concentrations. However, the dose of 7.5μ g/g/day was already associated with thymic and hepatotoxic changes, and higher doses showed toxicity signs. The lethal dose (LD) and LD_{50} were defined as 25μg/g/day and 12.5μg/g/day, respectively. Of note, oral celastrol at 1μg/g/day had no effect in arthritis progression.

Conclusions: Our results clearly show that 2.5μg/g/day is the lowest and 5μg/g/day is the highest effective and safe oral doses of celastrol in the setting of AIA rat model. These findings suggest that while celastrol is potentially very effective to treat RA, it has a narrow therapeutic window.

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AB0097 METHOTREXATE AND LOW DOSE PREDNISOLONE DOWNREGULATE OSTEOCLAST FUNCTION IN MONOCYTES FROM EARLY RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid arthritis (RA) is a systemic, immune mediated inflammatory disease that is associated with bone erosions and joint destruction. Methotrexate (MTX) slows bone damage but the mechanism by which it acts is still unknown.

Objectives: In this study we aimed to assess the effect of MTX and low dose prednisolone (MTX+PDN) on circulating osteoclast (OC) precursors and OC differentiation in RA patients.

Methods: RA patients before and at least 6 months after MTX therapy were analyzed and compared with healthy donors. A blood sample was collected in order to assess receptor activator of NF-κB (RANK) ligand (RANKL) surface expression on circulating leukocytes and frequency and phenotype of monocyte subpopulations. Serum quantification of bone turnover markers and cytokines and *in vitro* OC differentiation assays were performed.

Results: The number or $RANKL^+$ neutrophils increased in RA patients when compared to healthy donors (p=0.006) and after treatment with MTX+PDN their count was reduced to healthy control numbers (p=0.0155). Classical activation markers of monocytes such as HLA-DR, CD86, CCR2 and CD11b, and also RANK were increased in RA patients at baseline, comparing to control healthy donors. After MTX+PDN exposure, expression decreased to healthy control levels. Serum RANKL levels were increased at baseline comparing to healthy donors (p=0.0164) and normalized after therapy.

Although the number of OC was not different between groups, resorbed area and resorbed area/pit were elevated when compared to controls (p=0.0436 and 0.0249, respectively) and reduced after treatment ($p<0.0001$).

Conclusions: Our results suggest that MTX+PDN play an important role in downregulating OC function, which we believe occurs through a decrease in RANK surface expression in monocytes.

Disclosure of Interest: None declared

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AB0098 EFFECTS OF TOFACITINIB IN EARLY ARTHRITIS BONE LOSS

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Background: Rheumatoid arthritis (RA) causes immune mediated local and systemic bone damage.

Objectives: The main goal of this work was to analyze, how treatment intervention with tofacitinib prevents the early disturbances on bone structure and mechanics in adjuvant induced arthritis rat model. This is the first study to access the impact of tofacitinib on the systemic bone effects of inflammation.

Methods: Fifty Wistar adjuvant-induced arthritis (AIA) rats were randomly housed in experimental groups, as follows: non-arthritic healthy group (N=20), arthritic non-treated (N=20) and 10 animals under tofacitinib treatment. Rats were monitored during 22 days after disease induction for the inflammatory score, ankle perimeter and body weight. Healthy non-arthritic rats were used as controls for comparison. After 22 days of disease progression rats were sacrificed and bone samples were collected for histology, micro-CT, 3-point bending and nanoindentation analysis. Blood samples were also collected for bone turnover markers and systemic cytokine quantification.

Results: At tissue level, measured by nanoindentation, tofacitinib increased bone cortical and trabecular hardness. However, micro-CT and 3-point bending tests revealed that tofacitinib did not revert the effects of arthritis on cortical and trabecular bone structure and on mechanical properties.

Conclusions: Possible reasons for these observations might be related with the mechanism of action of tofacitinib, which leads to direct interactions with bone metabolism, and/or with kinetics of its bone effects that might need longer exposure.

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