Conclusion: This study showed the apoptosis of lining cells derived from macrophages resulted in the formation of the discoid fibrosis. These findings indicated TNFi might induce apoptosis of macrophage leading to the suppression of RA synovitis.

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Fig.1 a Discoid fibrosis in sublining layers. **b** TUNEL stain positive cells are around Discoid fibrosis

Acknowledgments : This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.1644

SAT0020

MOMELOTINIB, A JANUS KINASE 1/2 AND ACTIVIN RECEPTOR 1 INHIBITOR, AMELIORATES JOINT INFLAMMATION, SYSTEMIC TH17 DIFFERENTIATION AND ARTHRITIS-LINKED ANEMIA IN PRE-CLINICAL AUTOIMMUNE RA

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Background: Janus kinases (JAKs) serve as signaling hubs orchestrating inflammation, innate and adaptive immunity and erythropoiesis. Unfortunately, some of these agents cause suppression of JAK-dependent erythropoiesis, thereby exacerbating inflammation-associated anemia, leading to potential under-dosing and reduced therapeutic benefit. We previously showed that the JAKi momelotinib (MMB) can correct anemia in a rat model of RA, an effect that has been clinically reproduced in myelofibrosis patients treated with MMB. Subsequently, the molecular basis for MMB's anemia benefit was determined to be a consequence of its potent inhibition of Activin Receptor Type 1 (ACVR1), resulting in decreased hepcidin and, as a consequence, increased systemic iron availability and improved erythropoiesis.

Objectives: The goal of the current study was to investigate the effects of MMB on arthritis in pre-clinical RA models.

Methods: The anti-arthritis activity of daily administration of MMB was assessed in Streptococcus cell wall-induced arthritis in Lewis rats (PG-PS model) and in collagen antibody-induced arthritis (CAIA) in DBA/1 mice. Consecutive assessment of arthritis was performed by joint thickness measurements and paw scoring. Following 3 weeks of treatment, synovial immune cell infiltration and T cell subset differentiation was quantified. Cytokine gene expression was profiled by quantitative rt-PCR. Anemia was assessed by determination of blood hemoglobin and serum, spleen and liver iron levels.

Results: MMB reduced inflammatory granulocyte and macrophage infiltration in synovial tissue by more than 60% at all tested doses as compared to vehicle treatment in PG-PS animals. Importantly, MMB treatment effectively decreased arthritogenic Th17 cell differentiation and overall CD4+ T cells in the synovia beginning at the lowest tested dose and coincided with complete remission of joint swelling at 25 mg/kg. Anti-arthritis activity of MMB was confirmed with significant reductions in arthritis scoring, which demonstrated non-inferiority versus the TNF- α inhibitor, etanercept, in the CAIA model. Consistent with its inhibitory

activity on the ACVR1-hepcidin axis, MMB reduced circulating hepcidin levels and mobilized systemic iron, resulting in substantial improvement of the RA-associated anemia in rats.

Conclusion: MMB is a highly efficacious anti-arthritis agent that ameliorates local joint inflammation and reduces the systemic differentiation of major arthritogenic effector cell population, Th17 lymphocytes. In accord with our previous report, MMB is distinct from other JAKi due to its ability to inhibit ACVR1 signaling leading to decreased plasma hepcidin, improved iron homeostasis and increased erythropoiesis. The dual anti-inflammatory and anemia-improving pharmacologic activities of MMB position it as a promising and differentiated therapeutic agent for the treatment of RA and other inflammatory diseases with an anemia component.

Disclosure of Interests: Piotr Tymoszek: None declared, Verena Petzer: None declared, Malte Asshoff: None declared, Andrea Schroll: None declared, Markus Seifert: None declared, Ryan Hansen Employee of: I'm a former employee of Sierra Oncology, Snezana Milutinovic Employee of: I'm a former employee of Sierra Oncology, Bryan Strouse Employee of: I'm an employee of Sierra Oncology, Christian Hassig Employee of: I am a former employee of Sierra Oncology, Guenter Weiss: None declared, Igor Theurl Grant/research support from: I have received research support from Sierra Oncology, Consultant of: I have consulted for Kymba Ltd.

DOI: 10.1136/annrheumdis-2020-eular.1844

SAT0021

STRUCTURAL EFFECTS OF LOCAL CRYOTHERAPY IN RHEUMATOID ARTHRITIS: A STUDY IN ADJUVANT-INDUCED ARTHRITIS

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Background: The control of joint destruction caused by rheumatoid arthritis (RA) is a key issue in the treatment of this disease. Recent evidence showed that radiographic progression of joint damage occur despite a sharp decrease in disease activity and the use of aggressive Disease Modifying Anti-Rheumatic Drug (DMARD) therapies [1]. Whether alternative treatments such as cryotherapy may have beneficial effects on joint destruction at the early stages of the disease remains to be demonstrated, but such strategy would be of interest as it would not interfere with DMARDs treatment.

Objectives: The aim of this study was to evaluate the effect of a 14-days-treatment of local cryotherapy on radiological outcomes in rat adjuvant induced arthritis.

Methods: Adjuvant-induced arthritis (AIA) was induced in 6-weeks old male Lewis rats by injection of *Mycobacterium butyricum* in Freund's incomplete adjuvant at the basis of the tail. A control group received saline. At the onset of arthritis, AIA rats were treated or not by application of cryotherapy on paws using either a cold spray or ice, twice a day for 14 days. Arthritis score and paws skin temperature was daily monitored. At the end of treatment, radiological exam of hind paws was performed and a score taking into account (swelling, osteoporosis, cartilage destruction, bone erosion, bone destruction and new bone formation) was assigned, according to Ackerman *et al* [2]. Circulating levels of cytokines (IL-6, IL-1 β , TNF- α) was measured by Magpix Luminex kit.

Results: Compared to untreated AIA, local cryotherapy significantly reduced the progression of arthritis score, whatever the modality ($p < 0.05$), and to the same extent (reduction of arthritis score at day 24 post-immunization: -38% with cold spray, $p < 0.01$, -37% with ice, $p < 0.01$). Radiological score was significantly reduced by both treatments with no difference between the two treatments (-33% with cold spray, $p < 0.01$, -44% with ice, $p < 0.01$). All the items of the radiological score were equally reduced by ice and cold spray except swelling that was significantly reduced only by ice. Interestingly, the use of the cold spray induced a greater decrease in the skin temperature than the ice treatment (18.32 ± 0.07 °C vs 20.46 ± 0.08 °C, $p < 0.001$). Conversely, cryotherapy did not significantly change the level of cytokines. No correlation was found between radiological score and arthritis score or cytokine levels.

Conclusion: These data demonstrated that local cryotherapy had positive effects on structural damage in adjuvant-induced arthritis. The mechanisms involved remain now to be determined. These results suggest that local cryotherapy would be an interesting complement to conventional DMARDs in early RA.

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