spondyloarthritis, a prototype chronic inflammatory disease. Furthermore, it attenuated inflammation and improved disease activity, function, and quality of life.

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Disclosure of Interest None declared.

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PEFICITINIB TARGETS SYNOVIAL FIBROBLASTS IN RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Post-doctoral fellow.

Introduction Tofacitinib and baricitinib are the first approved Janus kinase inhibitors (JAKi) in Europe for treatment of rheumatoid arthritis (RA). Other JAKi differing in the inhibition profile of the four isoforms JAK1, JAK2, JAK3 and TYK2 are currently examined in clinical trials. Especially filgotinib, inhibiting mainly JAK1/2, and the panJAKi peficitinib are well tolerated up to doses causing C_{max} values higher than 1 μ M. However, less is known about the effect of JAKi in RA on synovial fibroblasts (RASf) activated by IL-1 β . RASf contribute to the growing pannus and develop an aggressive cartilage-destructive phenotype.

Objectives The aim of the study was to examine the effect of JAKi on activated RASf and further characterize the most effective inhibitor.

Methods Isolated human RASf were pretreated with JAKi for 2 hour and then stimulated with IL-1 β and JAKi with/without soluble IL-6 receptor (sIL-6R). IL-6 and MMP-3 were measured in supernatants by ELISA. Stimulation with oncostatin M served as control. The proliferation of RASf was detected using a BrdU-incorporation assay. The effect of peficitinib on RASf migration was investigated by cell culture inserts using a FCS gradient. For adhesion assays, RASf were treated with JAKi, detached and seeded in culture plates. Then, plates were extensively shaken and adherent RASf quantified by counting crystal violet stained cells. Cell viability, cytotoxicity and apoptosis were measured using commercially available assays.

Results Addition of the sIL-6R caused an additional release of IL-6 in RASf treated with IL-1 β compared to IL-1 β alone. This release was fully blocked by tofacitinib at 0.5 and 1 μ M (both $p < 0.01$). However, tofacitinib was not able to reduce the IL-6 release of IL-1 β activated RASf without sIL-6R. In contrast, peficitinib attenuated the IL-6 levels by 62% at 5 μ M ($p < 0.001$, $n = 7$) and by 24% at 1 μ M. Filgotinib resulted in a reduction of 30% at 5 μ M only ($p < 0.05$). The MMP-3 release was reduced by peficitinib (88%, $p < 0.001$) at 5 μ M. Peficitinib was the only JAKi able to reduce the proliferation of activated RASf by 23% at 1 μ M ($p < 0.05$).

Furthermore, peficitinib at 1 and 5 μ M decreased the migration of RASf by 38% and 92% ($p < 0.001$, $n = 4$). Peficitinib up to 5 μ M did not act cytotoxic on RASf even after 48 hour.

Conclusions JAKi suppress the inflammatory response induced by transsignaling of IL-6 in RASf. Peficitinib appears to be superior to other JAKi in suppressing the IL-1 β induced response and the proliferation of activated RASf. Thus, patients suffering specifically from severe synovial proliferation could benefit from treatment with peficitinib.

Disclosure of Interest None declared.

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TARGETING ACTIVATED SYNOVIAL FIBROBLASTS USING PHOTODYNAMIC THERAPY IN HUMAN RHEUMATOID ARTHRITIS SYNOVIAL TISSUE

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Introduction Activated synovial fibroblasts (ASF) play an important role in the pathogenesis of rheumatoid arthritis (RA). They contribute to the pro-inflammatory environment in the joint and degradation of cartilage and bone. Depleting ASF could ameliorate both these hallmarks of RA. ASF are characterized by the expression of fibroblast activation protein (FAP).

Objectives Here, we investigated the potential of FAP-targeted photodynamic therapy (tPDT) using the photosensitizer IRDye700DX conjugated to the anti-FAP antibody 28 H1 (28H1-700DX) to selectively kill these cells.

Methods To demonstrate the proof-of-concept of FAP-based tPDT in *ex vivo* human tissue, RA synovial tissue obtained during joint replacement surgery was trypsin digested and fibroblasts were cultured for at least 5 passages. Cells were incubated with or without 1 μ g/well 28H1-700DX for 4 hour, washed with PBS and either exposed to 690 nm light or not exposed. A luminescent cell viability assay (CellTiter-Glo) was used to measure cell viability. In parallel, 6 mm biopsies of synovial tissue were taken and used for FAP-based tPDT ($n = 8$ patients). They were subjected to tPDT as described above and formalin fixed after 1 hour. To measure cell death, 5 μ m paraffin slices were stained for FAP, gamma-H2AX and caspase-3 expression for activated fibroblasts, DNA double-strand breaks and early apoptosis, respectively.

Results FAP-tPDT performed on the cultured fibroblasts showed a light dose dependent increase in cell death when incubated with 28H1-700DX for 4 hour. Cell viability was not affected when cells were incubated with 28H1-700DX without illumination ($101.37\% \pm 3.9\%$ remaining compared to $100\% \pm 5.07\%$ in the normalized control). Radiant exposure of 17.6 J/cm² did not significantly decrease cell viability ($6.4\% \pm 9.8\%$ decrease, ns). Radiant exposures of 52.8, 105.6 and 158.4 J/cm² significantly decreased cell viability ($38.6\% \pm 6.9\%$, $67.5\% \pm 10.9\%$ and $80.6\% \pm 5.8\%$ respectively, $p < 0.001$ for all). After FAP-tPDT, the human synovial biopsies showed a significantly increased staining of the caspase-3 marker, but not of gamma-H2AX (Friedman's ANOVA, $p = 0.007$ and $p = 0.810$ respectively). Pairwise comparison