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Novel insights in inflammatory mediators

OP0089 COMBINATION THERAPY OF SELECTIVE MMP9 AND TNF INHIBITORS ARE EFFICACIOUS IN THE MOUSE CIA MODEL OF RHEUMATOID ARTHRITIS

S. Kim, B. Carr, L. Tong, D. Jin, R. Wang, D. Marshall, D. Gossage, V. Smith.
Gilead sciences, Inc., Foster city, United States

Background: Matrix metalloproteinase-9 (MMP9) is highly expressed by infiltrating inflammatory cells, pannus tissue, and multinucleated cells in the synovium and subchondral bone tissue, including osteoclasts. MMP9 is implicated in rheumatoid arthritis (RA) by its involvement in joint destruction, activation of cytokines and chemokines, and promotion of tissue destruction by degrading the basement membrane of epithelia and vasculature. MMP9 knockout mice are protected from collagen-induced arthritis (CIA) disease progression. A potent, allosteric antibody inhibitor of MMP9 is currently being investigated in clinical trials. The ability of a functional murine analog of this antibody to reduce disease signs and symptoms in established, chronic mouse CIA model both as a single agent and in combination with anti-TNF, was investigated.
Objectives: We evaluated the efficacy and safety of selective MMP9 inhibition both alone and in combination with anti-TNF (etanercept), in CIA models of RA.
Methods: CIA was induced in male DBA/1J mice (n=15/group) and treatments were administered after disease establishment. Efficacy was assessed via metrics of joint injury including clinical score (erythema/ paw swelling, score 0–4) in addition to histopathological assessment of destructive joint remodeling (soft tissue changes: edema, necrosis, inflammatory cell infiltration, and fibroplasia, sum score 0–16; bone changes: cartilage damage, bone erosion, periosteal bone formation, synovitis, pannus formation, and joint destruction, sum score 0–24).
Results: All animals were included in the evaluation. In all endpoints assessed, treatment with each therapeutic agent, on its own or in combination, resulted in improvement with respect to body weight change, clinical score, and histopathological measures. The combination group provided the best overall trend for therapeutic benefit, although statistical significance as compared to each single agent alone was not met in most parameters. Body weight recovery was superior in combination as compared to single agent therapies (52% vs. 12–34%, relative to sham; $p<0.05$ combination vs. single agents). Clinical score and histopathology measures in soft tissue and bone changes were most improved in the combination therapy group, although it did not achieve statistical significance as compared to each single agent (26% vs. 17–21%; 1.5 vs. 1.5–1.8; and 7 vs. 7–9, respectively). Importantly, combination therapy resulted in a significant number of limbs with zero or mild disease as compared to single agents (no disease sign: 256% vs. 172–223%; mild disease sign: 178% vs. 138–141%). Analysis of complete blood count at the end of study revealed no abnormalities in any treatment group.
Conclusions: Selective inhibition of MMP9 was active in reducing disease severity in CIA models of RA. The combination of anti-MMP9 with anti-TNF was well tolerated and increased the number of limbs with no or mild disease compared to anti-TNF alone. Further studies are required to examine combination therapy of selective anti-MMP9 and anti-TNF therapies in a clinical setting.
Disclosure of Interest: S. Kim Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, B. Carr Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, L. Tong Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, D. Jin Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, R. Wang Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, D. Marshall Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, D. Gossage Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc, V. Smith Shareholder of: Gilead sciences, Inc, Employee of: Gilead sciences, Inc
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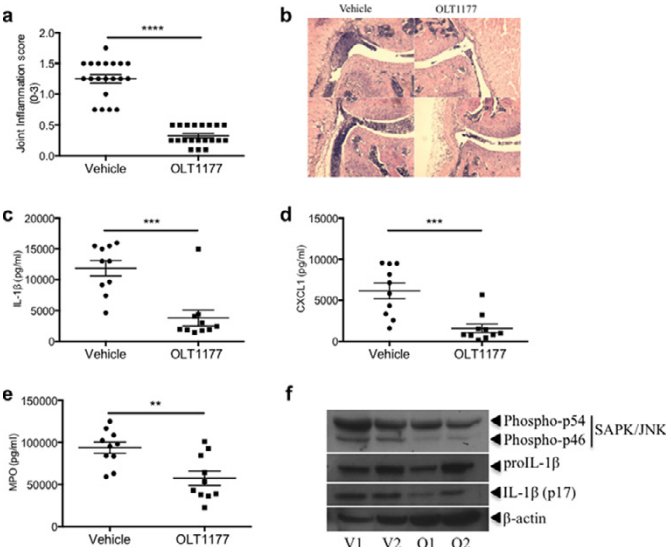
OP0090 THE HUMAN SAFE NLRP3 INFLAMMASOME INHIBITOR OLT1177 SUPPRESSES JOINT INFLAMMATION IN MURINE MODELS OF EXPERIMENTAL ARTHRITIS

C. Marchetti[1], B. Swartzwelter[1], M.I. Koenders[2], C.A. Dinarello[1], L.A. Joosten[3].
[1]Department of Medicine, University of Colorado, Aurora, United States; [2]Department of Rheumatology; [3]Department of Medicine, Radboud University Medical Center, Nijmegen, Netherlands

Background: NLRP3 is an essential component of the inflammasome, an intracellular macromolecular complex, which activates caspase-1 for the processing and release of active IL-1β and IL-18. Activation of the NLRP3 inflammasome takes place in inflammatory joint diseases, including gout. Although inhibition of IL-1β with either the IL-1 receptor antagonist anakinra or canakinumab, a neutralizing monoclonal antibody for IL-1β is highly effective for reducing the gout flares, a clinical need remains for a safe, oral treatment of recurrent gout flares refractory to standard of care. The small orally active and safe β-sulfonyl nitrile molecule OLT1177 is a specific inhibitor of the NLRP3 inflammasome, and currently being evaluated in a Phase 2 study for the treatment of acute gout flares.
Objectives: To investigate the anti-inflammatory effect of NLRP3 inflammasome inhibitor OLT1177 in mouse models of acute joint inflammation.
Methods: Two models of experimental arthritis were used in mice: zymosan- and monosodium urate (MSU)-induced arthritis. Knee joints of male C57BL/6 mice were injected intraarticularly with 180 μg heat-killed Zymosan or 300 μg of monosodium urate (MSU) crystals mixed with 200 μM C16.0 fatty acid and bovine serum albumin. Joints were assessed 24 and 4 hours after the zymosan or MSU/C16.0 injection, respectively, for clinical, histological and cytokine analyses.
Results: Intraarticular Zymosan induced a severe joint swelling with neutrophil infiltration, high levels of synovial IL-1β, IL-6 and the neutrophil chemokine CXCL1. Treatment with OLT1177 induced reduction of joint swelling and neutrophil infiltration ($P<0.0001$ and $P=0.006$ respectively) and suppression of IL-1β and IL-6 by 55% and CXCL1 by 30% compared to mice treated with the vehicle. Four hours following intra-articular injection of MSU crystals, an elevated clinical score for knee joint inflammation was observed in vehicle-treated mice (Fig. 1). Oral treatment with OLT1177 showed reduction in joint inflammation as depicted in Fig. 1a when compared to the vehicle group ($P<0.0001$). Histological analysis of the knee revealed suppression of the influx of inflammatory cells in the articular space with OLT1177 treatment ($P<0.05$; Fig. 1b). Treatment with OLT1177 showed significant reduction in synovial tissue extracts for IL-1β (69%; $P<0.001$; Fig. 1c); IL-6 (70%; $P<0.001$); CXCL1 (75%; $P<0.001$; Fig.1d) and MPO (39%; $P=0.006$; Fig. 1e). Mice were also treated with a single dose of OLT1177 1 hour after of intraarticular MSU and reduced joint swelling and IL-1β levels ($P<0.05$) were observed. OLT1177 treatment suppressed activation of the mitogen-activated protein kinases (MAPK) family, c-jun N-terminal kinase (JNK), which is implicated in the pathophysiology of rheumatoid arthritis and gout (Fig. 1f).



Conclusions: The orally active molecule OLT1177 is a potent inhibitor of IL-1β-driven inflammatory arthritis, particularly in a model of acute gout. Considering the outstanding safety profile in humans, OLT1177 is a potential therapeutic strategy to target NLRP3-driven IL-1β-mediated disorders.
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OP0091 S100A8 TRIGGERS A NOVEL IMMUNE-REGULATORY MECHANISM IN DEVELOPING DENDRITIC CELLS

D. Popp[1], F. Rühle[2], W. de Jager[3], T. Vogl[1], J. Roth[1]. *[1]Institute of Immunology; [2]Institute of Human Genetics, Münster, Germany; [3]Multiplex Core Facility, Wilhelmina Children's Hospital (UMC Utrecht), Utrecht, Netherlands*

Background: S100A8/A9 heterodimers are well-known alarmins that, upon release from activated or necrotic phagocytes, promote inflammation by binding to Toll-like receptor 4 (TLR4). These proteins are highly expressed in synovial phagocytes during arthritis and proved to be reliable biomarkers for monitoring disease activity in RA. Interestingly, we now identify a novel immune-regulatory mechanism of S100A8 in human monocyte-derived dendritic cells (moDCs).
Objectives: This study aims to analyze immune-regulatory functions of S100 proteins in human DCs.
Methods: MoDCs are differentiated with or without exposure to S100A8 prior to maturation with LPS. After characterization of the activation status using flow cytometry, the ability of these cells to induce autologous $CD4^+$, $CD8^+$, and γδ T-cell proliferation is investigated. Cytokines, secreted during development are analyzed by Luminex cytokine arrays. The metabolic state of DCs is examined by using Seahorse XFp Analyzer assays. Finally, to identify molecular mechanisms leading to an immune-regulatory phenotype, the mRNA expression of moDCs is analyzed by genome-wide gene expression arrays.