Background: MSC are a potential therapeutic approach for the treatment of inflammatory diseases. Their anti-inflammatory role in both local and systemic diseases has been demonstrated in different experimental models and human diseases. Gouty arthritis is a systemic disease characterised by deposition of monosodium urate (MSU) crystals in soft tissues and joints. Frustrated phagocytosis of MSU crystals by resident leukocytes leads to NLRP3 inflammasome activation and subsequent release of IL-1β and IL-18 and ROS production. The latter is central to the pathogenesis of gouty arthritis. The present study demonstrated that JAK inhibitors affect innate immunity in humans. They can fine-tune various immune networks through a variety of mechanisms and seem suitable potential therapeutic agents for the treatment of diverse autoimmune diseases.

Methods: Acute gout flare was induced in 15 NZ rats by intra-articular injection of MSU crystals in both knees. 7 of these rats received a single dose of 2.5 × 10^6 hAD-MSC/kg, administered through the right femoral artery. 1 hour after MSU injection (MSU-MSC group), while 8 animals were not treated (MSU group). This route of administration allowed the study of the effect of a direct MSC administration in the right knee synovial membrane (SM) in comparison to the contralateral knee, which received the cells after their vascular distribution through the organism. Inflammation was followed up measuring knee swelling and serum CRP. 4 healthy rats were simultaneously followed (Ctrl group). Animals were sacrificed 72 hour after MSU injections and SM were collected for further studies.

Results: hAD-MSCs were able to attenuate joint swelling in both knees 24 hour after MSU injections, inducing a decrease in knee perimeter. Additionally, a significant decrease in serum CRP after 24 hour was observed in the treated group (Ctrl 73±1; MSU 1818±238; MSU+MSC 270±241 mg/mL; #p<0.05 vs. Ctrl). Histopathological analysis showed that hAD-MSCs were able to significantly diminish SM inflammation after 72 hours of MSU injection (Kienoc Score: Ctrl 0.2±0.8; MSU 5.6±5.9; MSU-MSC 3.4±3.3). SM vascularisation was reduced in treated animals (%CD31-staining: Ctrl 0.5±0.2; MSU 0.8±0.2; MSU+MSC 0.6±0.2%). hAD-MSC treatment also evoked a significant reduction of the inflammasome components in the SM: pro-IL-1β (Ctrl 0.9±0.2; MSU 1.5±0.5; MSU+MSC 1.2±0.2%), pro-caspase-1 (Ctrl 1±0.2; MSU 3.5±3.1%; MSU+MSC 1.4±0.5%), NALP3 (Ctrl 1±0.3; MSU 2.9±2.1%; MSU+MSC 1.4±0.7%). The synthesis of the pro-inflammatory cytokines COX-2 (Ctrl 0.9±0.1; MSU 4.2±3.3; MSU+MSC 3.4±3.3) and TNFa (Ctrl 0.9±0.3; MSU 1.3±0.3; MSU+MSC 0.5±0.2) were also reduced in the MSU+MSC animals, while TGFβ (Ctrl 0.9±0.2; MSU 0.7±0.2%; MSU+MSC 1.3±0.3) and IL10 (Ctrl 1.1±0.5; MSU 1.1±0.7; MSU+MSC 1.8±0.5) were increased in comparison to MSU group. There were no differences between the direct and the indirect treatment, since both right and left SMs were equally damaged.

Conclusions: Our data showed that a single dose of hAD-MSCs is able to modulate the inflammatory response in an acute gouty arthritis model in rabbit. Therefore, it is a promising therapeutic approach to attenuate gout flare, especially in patients with different comorbidities that complicate a conventional treatment.

Disclosure of Interest: None declared


Methods: The effects of baricitinib and tofacitinib were evaluated using human monocyte-derived dendritic cells (MoDCs), plasmacytid dendritic cells (pDCs), B cells and fibroblasts.

Results: The expression of costimulatory molecules CD80/86 on MoDCs were induced 48 hours after LPS stimulation. Baricitinib concentration-dependently suppressed the expression of CD80/CD86. Inhibition of CD80/CD86 expression by tofacitinib was comparable to that induced by baricitinib. pDCs stimulated for 5 hours with CpG produced both TNF-α and IFN-α. Baricitinib reduced the proportion of these IFN-α producing pDCs in a concentration-dependent manner. On the other hand, TNF-α production was not affected by baricitinib. Baricitinib also suppressed the differentiation of B cells into plasma blasts by B cell receptor (BCR) and type-I IFN stimuli, and inhibited the production of IL-6 from B cells. Tofacitinib also suppressed BCR- and IFN-α-induced plasmablast differentiation and IL-6 production. However, neither baricitinib nor tofacitinib altered IgG production by B cells. Human CD4+ T cells proliferated after T cell receptor stimulation with anti-CD3 and anti-CD28 antibody; however, such proliferation was suppressed by baricitinib in a concentration-dependent manner. In addition, baricitinib inhibited Th1 differentiation after IL-12 stimulation and Th17 differentiation by TGF-β1, IL-6, IL-17 and IL-23 stimulation. Tofacitinib showed similar effects in these experiments. In naïve CD4+ T cells, IFN-α and IFN-γ induced phosphorylation of STAT1, which was inhibited by baricitinib as well as tofacitinib. Furthermore, IL-6-induced phosphorylation of STAT1 and STAT3 was also inhibited by JAK inhibitors.

Conclusions: The present study demonstrated that JAK inhibitors affect innate and adaptive immunity in humans. They can fine-tune various immune networks through a variety of mechanisms and seem suitable potential therapeutic agents for the treatment of diverse autoimmune diseases.

Disclosure of Interest: S. Kubo: Speakers bureau: Biocytum, Pfizer, and Takeda, S. Nakayamada Grant/research support from: Mitsubishi-Tanabe, Novartis and MSD, Speakers bureau: Bristol-Myers, UCB, Astellas, Abbvie, Eisai, Pfizer, Takeda, X. Ma: None declared, S. Lee: None declared, K. Yamasita: None declared, K. Nakano Grant/research support from: Mitsubishi-Tanabe and Eisai, Speakers bureau: UCB, Astellas, Mitsubishi-Tanabe, S. lwata: None declared, K. Hanami: None declared, S. Fukuyo: None declared, I. Miyagawa: None declared, Y. Tamaki: None declared, Y. Tanaka Grant/research support from: Mitsubishi-Tanabe, Takeda, Chugai, Astellas, Eisai, Taisho-Toyama, Kyowa-Kirin, Abbvie, and Bristol-Myers. Speakers bureau: Abbvie, Daiichi-Sankyo, Chugai, Takeda, Mitsubishi-Tanabe, Bristol-Myers, Genos, Eisai, Jansen, Pfizer, Asahi-kasei, Eli Lilly, GlaxoSmithKline, UCB, Teijin, MSD, and Santen