MECHANICAL STRAIN DETERMINES THE SITE-SPECIFIC DIRECTION OF INFLAMMATION AND TISSUE DAMAGE IN ARTHRITIS

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Abstract THU0056 – Figure 1. 14–3–3ζ is a critical mediator of PGRN regulation of macrophage polarization and contributes to PGRN’s anti-inflammation action. (a, b) pQC analysis of Il6 and Nos2 (a), or Arg1 and M1g1 (b) mRNA expression in WT, or 14–3–3ζ−/− macrophages which are polarised to M1 (a) or M2 (b) in the absence or presence of PGRN (200 ng/mL). (c) Clinical arthritis score of WT or 14–3–3ζ−/− CIA mice treated with or without PGRN. n=8 (d, e) CD45+CD11b+ cells were analysed for MFI of INOS (d) and percentage of CD206+ cells (e). *p<0.05, **p<0.01, NS=no significance

Conclusions: Both in vitro and in vivo results indicate that 14–3–3ζ is a key molecule regulating macrophage polarization which plays an important role in inflammatory arthritis, and it is an essential component for PGRN/TNFR2 mediated protective effect against inflammatory arthritis.

Disclosure of Interest: None declared


THU0057

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Conclusions: Voluntary running of CIA in C57BL/6 mice markedly induced an early onset and increased progression whereas no disease onset could be observed in the hind paws from animals in unloaded conditions. CAIA in running RAG2−/− mice also induced early arthritic symptoms and severe progression. Intriguingly, running conditions were sufficient to induce arthritis without the need of LPS as an inflammatory trigger. Mechanical strain did not alter however IgG autoantibody titres on September 21, 2023 by guest. Protected by copyright.http://ard.bmj.com/ Ann Rheum Dis: first published as 10.1136/annrheumdis-2018-eular.1865 on 12 June 2018. Downloaded from http://laid.bmj.com/ on 12 June 2018. Thursday, 14 June 2018 253

Disclosure of Interest: None declared


THU0058

TAS8274, A HIGHLY SELECTIVE JANUS KINASE 3 INHIBITOR, SHOWS POTENT EFFICACY, BUT DOES NOT AFFECT HOST DEFENSE, IN PRECLINICAL MOUSE MODELS


Background: The family of Janus kinases (JAKs) plays important roles in signaling pathways mediated by various cytokine receptors. An aberrant activation of JAK-STAT signaling has been reported to be involved in the pathogenesis of autoimmune diseases1. Pan-JAK inhibitors have shown a good efficacy in patient with rheumatoid arthritis (RA)2. However, their use is limited due to safety concerns, including severe herpes zoster infection, by inhibiting JAK1-mediated interferon signaling3. Therefore, a selective JAK3 inhibitor would provide a better balance between efficacy and safety than pan-JAK inhibitors.

Objectives: We identified the characteristics of TAS8274, a novel highly selective inhibitor of JAK3, using in vitro assays, a mouse model of collagen-induced arthritis (CIA), and a mouse model of herpes simplex virus (HSV)-1 infection.

Methods: In vitro biochemical assay was performed using available kinase assay panels. The effects on anti-inflammatory responses were assessed by examining cytokine productions. IL-2, IL-3, and IFN-γ-induced phosphorylation of STAT proteins in peripheral blood mononuclear cells (PBMCs) were analysed by a flow cytometry method. NK cell cytotoxicity in the presence of IFN-γ was evaluated by Cr51 release assay. In a mouse model of HSV-1 infection, TAS8274 and tacrolimus were administered for 7 days before inoculation of the virus on the back skin, and then were administered for another ten consecutive days. At the end of this experiment, the number of papules on the back was counted. To evaluate the therapeutic efficacy using mouse CIA model, TAS8274 was orally administered to CIA mice after the disease onset. Disease severity was evaluated by clinical score of paw swelling, and the scores of inflammation, pannus, cartilage, and bone damage were performed using a modified Mankin score system.

Results: TAS8274 inhibited the enzymatic activity of JAK3 (IC50=0.16 nM), and showed more than 1000-fold selectivity against other JAK kinases. In the cell-based assays, TAS8274 strongly inhibited IL-17 production from differentiated Th17 cells. TAS8274 also suppressed the IL-2-induced STAT5 phosphorylation in PBMCs, but had much lower inhibitory effects on the IFN-γ-induced STAT1 phosphorylation. In contrast, Tofacitinib and Baricitinib had robust inhibitory effects on the IFN-γ-induced STAT1 phosphorylation. Furthermore, Tofacitinib and Baricitinib dose-dependently reduced the NK cell cytotoxicity, while TAS8274 had little effect on that. Tacrolimus-treated group significantly increased the number of papules compared with vehicle-treated group in a mouse HSV-1 infection model, but TAS8274-treated group did not increase the number of papules. In an established mouse CIA model, TAS8274 dose-dependently reduced the severity of arthritis and histopathological scores compared with vehicle-treated mice.

Conclusions: TAS8274 did not inhibit the JAK3-independent STAT signalling pathway in vitro and showed potent efficacy at dose range without exacerbation of the risk of HSV-1 infection. Our study demonstrates that TAS8274 would be an attractive therapeutic agent with excellent balance between efficacy and safety.

REFERENCES:


Disclosure of Interest: None declared