Therapeutic Effect of ICAM-1 Mimic on Experimental Axial Spondyloarthritis

Melissa Lim[1], Shagheyegh Foroozon[1], Michael Tang[1], Zoya Qaiyum[1], Enoch Yau[1], Robert D. Inman[1,2,3]

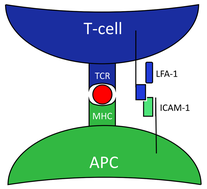
[1]Schroeder Arthritis Institute, University Health Network and University of Toronto, Toronto, Canada

[2]Department of Immunology, University of Toronto, Toronto, Ontario, Canada. [3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

Introduction

Axial Spondyloarthritis (AxSpA) is a chronic inflammatory arthritis primarily affecting the axial skeleton, with the possible presence of extra-articular manifestations such as gut and skin inflammation. Currently, patients with axSpA require lifelong treatment. Current approved biologics (TNFi, IL-17i, JAKi) for axSpA patients improve symptoms but are not curative and cannot prevent disease progression.

AI technologies enabled the discovery of several unique small molecules with potential efficacy in axSpA treatment. Our collaborator, Aria Pharmaceuticals, identified a small molecule that acts on the binding site of lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1). The LFA-1/ICAM-1 interaction is known to enable both T-cell activation and pro-inflammatory cytokine release. Administration of this ICAM-1 – mimic small molecule improved arthritis scores and decreased paw thickness in our collaborator's murine preclinical DBA/1 collagen induced arthritis model.



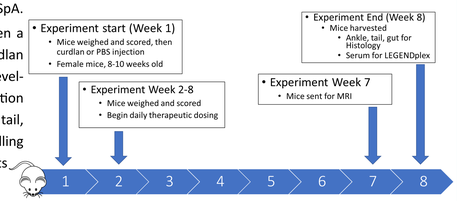
Objective/Hypothesis

This study investigates whether this ICAM-1-mimicking small molecule has therapeutic effects on an axSpA murine model. We hypothesize that the ICAM-1 mimic will ameliorate disease and reduce inflammation in the SKG model.

Methods

We employed the use of the SKG mouse, an IL-23 and IL17-dependent model leading to disease resembling human axSpA.

Female SKG mice given a single dose 3mg curdlan (intraperitoneal) developed skin inflammation in ears and tail, blepharitis, and swelling of ankles and wrists and digits.



Group	Treatment	Dose (mg/kg)
Group 1 (G1)	Healthy, no disease	0
Group 2 (G2)	Disease + vehicle	0
Group 3 (G3)	Disease + ICAM-1 mimic (low dose)	3
Group 4 (G4)	Disease + ICAM-1 mimic (mid dose)	10
Group 5 (G5)	Disease + ICAM-1 mimic (high dose)	20
Group 9 (G9)	Health + ICAM-1 mimic (high dose)	20
Group 11 (G11)	Disease + dexamethasone	10

Therapeutic treatment began one week post-curdlan disease induction for a total of 8 weeks. These mice were treated with either the vehicle, the ICAM-1 mimic (at varying doses), or dexamethasone (drug control group) via daily intraperitoneal (IP) injections and monitored for 8 weeks. At Week 7, the mice were sent for MRI scans. At Week 8, the mice were harvested for serum, ankle, tail, and small intestine.

Results - SpA Clinical Scores

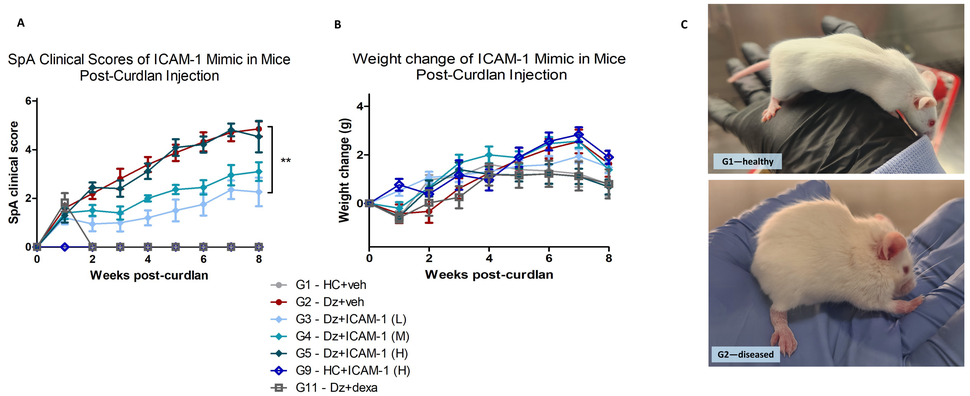


Figure 1. Mice treated with the low dose ICAM-1 mimic (G3) had better clinical scores compared to the disease group (G2). (A) Mice were scored weekly on the SpA scores for a total of 8 weeks. (B) Weight changes were recorded weekly for all groups. (C) Representative mouse images of healthy (G1) and diseased (G2) mice to constitute the extremes of the SKG mouse model. * p<0.05, ** p<0.001, *** p<0.0001, one-way ANOVA Tukey's test.

Results - Histology

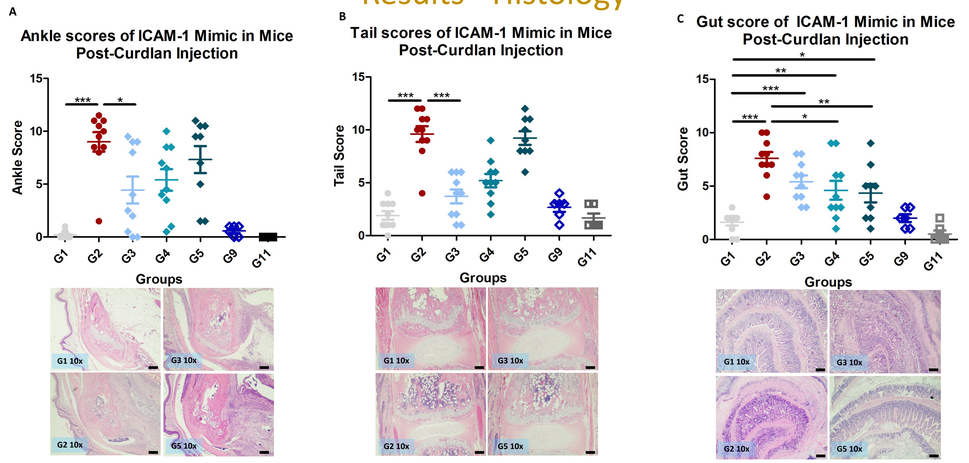


Figure 2. Mice treated with the low dose ICAM-1 mimic (G3) had better ankle and tail scores than the disease group (G2), but not better gut scores. (A) Ankle scores with significance seen between the disease (G2) and low dose (G3) groups. (B) Tail scores with significance seen between the same two groups. (C) Small Intestine (Gut) scores with no significance seen between G2 and G3 but a dose-wise response to the drug is trending (G3-G5). (A-C) Representative images of G1, G2, G3 and G5 are shown for each scored area. Scale bar: 200μM * p<0.05, ** p<0.001, *** p<0.0001, one-way ANOVA Tukey's test.

Results - MRI

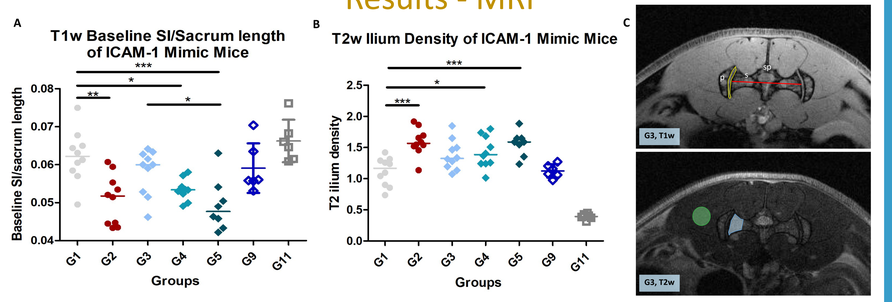


Figure 3. There is a dose-wise response seen in the ICAM-1 groups (G3-G5) that trend towards a joint space narrowing in the T1-weighted MRI images, and a subtle dose-wise response in these same groups that trend towards an increased edema in the T2-weighted MRI images. (A) T1w images compare the difference between sacrum length and SI area to measure the joint space narrowing. The smaller the ratio, the more narrow the space, indicating potential arthritic conditions (less cartilage, etc). B) T2w images look at ilium density and bone marrow edema (inflammation). (C) Representative MRI images of the mice showing the T1w and T2w images of the low dose group (G3). The red line represents the sacrum (s) width under the spinal cord (sp), the yellow shape represents the SI joint area by the ilium of pelvis (p). The blue shape represents the sacrum area that was compared to the control area (green shape). These shapes and points were used for the analysis conducted in MIPAV. * p<0.05, ** p<0.001, *** p<0.0001, one-way ANOVA Tukey's test.

Results - LEGENDplex

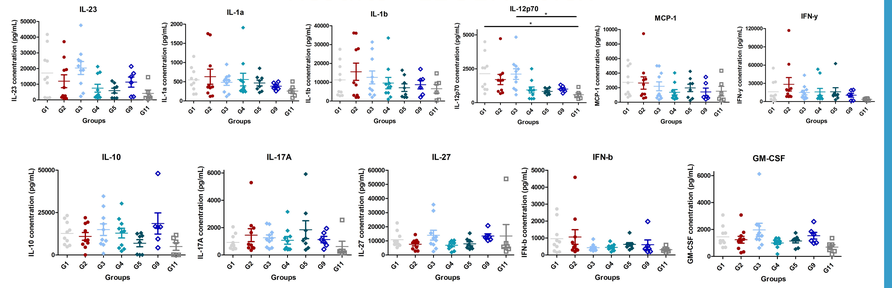


Figure 4. LEGENDplex results show the cytokine concentration levels of these 10 cytokines from the blood serum of the experimental mice. Overall, there was no significant difference except for IL-12p70 in G4 and G5 against the healthy group (G1). There seemed to be indications of dose-wise responses in IL-1b and IL-10. * p<0.05, ** p<0.001, *** p<0.0001, one-way ANOVA Tukey's test.

Conclusions

- There were significant differences seen in the low dose of the ICAM-1 mimic (G3) in both clinical scores and peripheral bone histology, but not in the gut.
- There was a trend towards a lower baseline SI/sacrum length ratio in the T1w images with the ICAM-1 mimic groups (G3-5) but no significance seen, and a trend towards increased density (more inflammation) in the T2w images, but with no significance.
- There were no significant differences seen in the LEGENDplex serum analysis, though this could have been due to sensitivity issues
- Future work would include flow cytometry in order to quantify cytokines and cell types that could not be analyzed in this study