Treatment of Established Rheumatoid Arthritis in a Collagen-Induced Arthritis Mouse Model using Intra-articular Injection of AAV6-delivered sIL17RA

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Rheumatoid arthritis (RA), a chronic autoimmune disorder affecting approximately 1% of individuals worldwide, is characterized primarily by inflammation of the joint tissues.[1] A significant barrier for current treatments is the difficulty of maintaining therapeutic concentrations in the joint.[2,3] This study investigated the ability of adeno-associated virus serotype 6 (AAV6) to deliver and maintain expression of a soluble, extracellular portion of human Interleukin-17 Receptor A (referred to as sIL17RA) in the joint as an inhibitor of interleukin-17A (IL17A), a key pro-inflammatory cytokine in RA pathophysiology.[4] After confirming the secretion ability of sIL17RA and assessing its capacity to inhibit IL17A function *in vitro*, a collagen-induced arthritis (CIA) mouse model was used to evaluate sIL17RA efficacy *in vivo*. CIA mice were injected intraarticularly with AAV6-sIL17RA (treatment group) or AAV6-Luciferase (vehicle group) in the left knee joint and PBS in the right on day 42, after the establishment of arthritis. We found that differences in histopathological scores between the right and left joints of individual mice in the treatment group compared to those of the vehicle and naive groups, while not statistically significant, demonstrated a trend towards improvement (0.389±0.175 vs -0.086±0.352 vs 0.012±0.219, 1-way ANOVA p = 0.439). Locally injected AAV6-sIL17RA did not leak appreciably into systemic circulation, as his-tagged sIL17RA was undetectable in sera; anti-collagen II antibody titers in sera were similarly unaffected, indicating no changes in systemic arthritis conditions between the treatment and vehicle groups post-local injection (5.88E4±3.80E4 vs 1.25E5±6.61E4, Welch's t-test p = 0.295). Our results suggest the potential of a novel approach to RA treatment– local, AAV6-mediated expression of sIL17RA– to improve arthritic conditions in a CIA mouse model, and highlights the role of this cytokine in late RA pathophysiology.

REFERENCES:

1. Lwin, M. N., Serhal, L., Holroyd, C., & Edwards, C. J. (2020). Rheumatoid Arthritis: The Impact of Mental Health on Disease: A Narrative Review. *Rheumatology and Therapy*, 7(3). https://doi.org/10.1007/s40744-020-00217-4
2. Curtis, J. R., & Singh, J. A. (2011). Use of Biologics in Rheumatoid Arthritis: Current and Emerging Paradigms of Care. *Clinical Therapeutics,* 33(6), 679–707. https://doi.org/10.1016/j.clinthera.2011.05.044
3. Goldberg, E. L., Dekoven, M., Schabert, V. F., & Coyle, A. (2009). Patient Medication Adherence: The Forgotten Aspect of Biologics. *Biotechnology Healthcare*, 6(2), 39–44. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799072/
4. Lubberts, E. (2008). IL-17/Th17 targeting: On the road to prevent chronic destructive arthritis? *Cytokine*, 41(2), 84–91. https://doi.org/10.1016/j.cyto.2007.09.014