Effects of Corticosteroid and Anti-TNF in Murine Collagen-Antibody Induced Arthritis

Dominic Poulin, Joe Cornicelli, Alan Young, Jean-François Lafond, Agathe Bédard, Rana Samadfam
Charles River Laboratories

1 INTRODUCTION

The purpose of this study was to compare the efficacy of the TNF alpha blockers (Etanercept and Humira) with a corticosteroid (dexamethasone) in a murine model of collagen-antibody induced arthritis (CAIA). Etanercept is derived by introducing human DNA into Chinese hamster ovary cells, creating a genetically engineered protein. On the other hand, Humira uses fully human proteins and phage display technology to produce monoclonal antibodies. Both Etanercept and Humira are directed against TNF-α, a key player in rheumatoid arthritis.

2 MATERIALS AND METHODS

Female BALB/C mice were assigned to non-disease or to CAIA groups. CAIA animals were further assigned to control, dexamethasone or anti-TNF treatments. Dexamethasone was given orally, daily after disease onset at 0.3mg/kg, Etanercept was given subcutaneously, twice weekly at 10 mg/kg and Humira was given intraperitoneally, every 3 days at 3 mg/kg. Clinical score and paw inflammation were evaluated. At necropsy, serum and paw samples were collected for cytokine analysis, and/or histopathology. Histopathologic assessment of the sampled paws was performed on all animals. Cytokine analysis was performed only for the Etanercept.

3 RESULTS

Clinical Parameters

In the CAIA animals, clinical score and paw inflammation was observed starting on Day 5, peaked on Days 11 to 13 and then slowly decreased towards the end of the study (Days 21 to 22). Etanercept reduced clinical score and paw inflammation by 25 to 50%, while dexamethasone reduced the same parameters by 50 to 75%. Humira had a slight effect (16% reduction) on paw volume from Day 14 onwards.

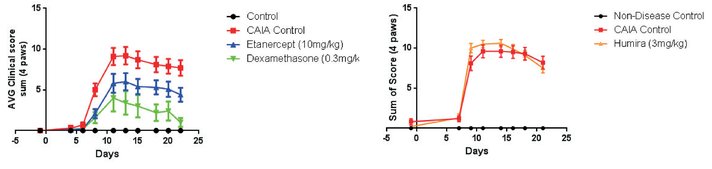


Figure 1: Clinical Score Following Treatment

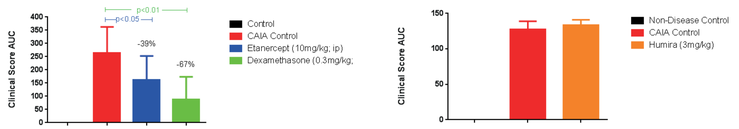


Figure 2: Clinical Score Overall Change Following Treatment

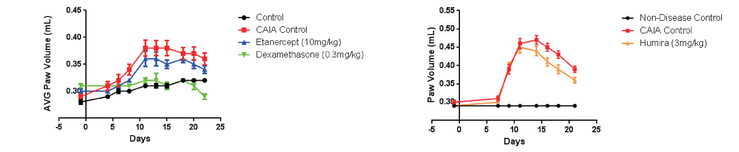


Figure 3: Clinical Score Following Treatment

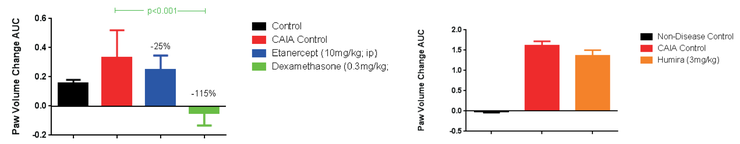


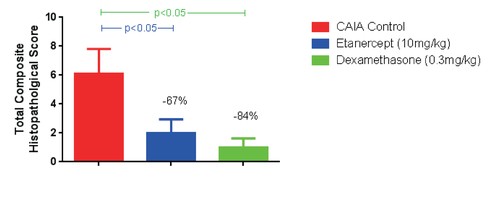
Figure 4: Clinical Score Overall Change Following Treatment

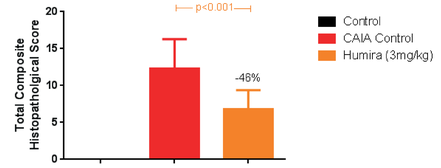
Cytokines

Increases in serum cytokines were limited to IFN-γ, IL-1β, IL-5 and TNF-α. All cytokines (as well as CRP) analyzed in the paw extract samples were increased from 34 to 450%. TNF-α and IL-1β, were especially elevated. Etanercept reduced all cytokines and CRP levels in the paw tissue, while the only serum cytokine affected by Etanercept was IL-1β. (Data not shown).

Anatomical Pathology

Histopathological changes associated with arthritis (inflammation, erosion, synovial hyperplasia, bone degeneration and periostal changes) were observed in CAIA control animals. Humira, Etanercept and dexamethasone also reduced the total composite histopathological score by 44, 67 and 84%, respectively.





4 CONCLUSION

We conclude that both corticosteroid and anti-TNF therapies are effective in ameliorating the arthritic response in the CAIA model, albeit to varying extents. The observed differences in efficacy of TNF blockers could be related to their differences in affinity at the murine target compared to their optimised human affinity.

5 ACKNOWLEDGMENT

The authors would like to thank the technical team in InVivo pharmacology, biomarkers and histopathology groups for their dedicated work.