A Naturally Occurring Novel Therapeutic and Oral Selective Inhibitor of TNF-α, *MYMD-1® (Isomyosamine),* Significantly Reduced the Inflammation and Disease Severity in Murine Model of Collagen Antibody Induced Arthritis

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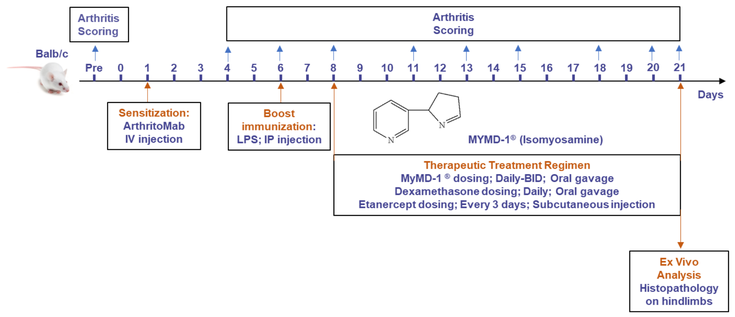
1 INTRODUCTION

Rheumatoid arthritis (RA) is the most prevalent chronic inflammatory disease and is characterized by inflammation of the synovium of the joints, resulting in joint destruction. It is associated with chronic pain, loss of function, and disability. The murine model of Collagen Antibody Induced Arthritis (CAIA) mimics many of the features of arthritis in humans and has been used successfully in addressing questions of disease pathogenesis and to screen candidate therapeutic agents. Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that plays a pivotal role in regulating the inflammatory response in chronic autoimmune diseases such as RA. The discovery of the role of TNF-α in the pathogenesis of RA has led to anti-TNF biological therapies as a breakthrough in the treatment of RA. The objective of this study was to investigate anti-inflammatory effects of MYMD-1®, a small molecule selective inhibitor of tumor necrosis factor-alpha (TNF-α) with easy access to the body including the brain, in the murine CAIA model.

2 EXPERIMENTAL PROCEDURES

The CAIA model was induced in female Balb/c mice by an intravenous injection of a monoclonal antibodies cocktail that are directed to collagen type II on Day 1 (sensitization), followed by an intraperitoneal injection of the endotoxin LPS on Day 6 (boost immunization). Three oral doses of MYMD-1® (50, 250 and 450 mg/kg/day) given BID (two times a day) were tested starting at the onset of the disease (Day 8 in this study). In addition, Dexamethasone was given daily by oral gavage at 0.3mg/kg and Etanercept was administered subcutaneously twice weekly at 10 mg/kg, both as positive controls. The therapeutic effect of MYMD-1® on inflammation was assessed by measuring the clinical score and paw inflammation (volume). At termination, the histopathological features such as infiltration of polymorphonuclear and mononuclear cells, pannus formation, cartilage degradation and bone resorption of the affected joints were analyzed.

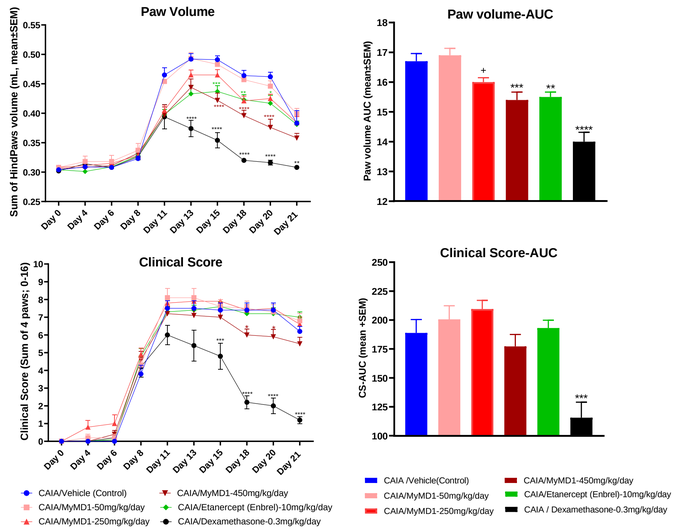
Statistical analysis were performed using Unpaired student t-test, One-Way or Two-way ANOVA in comparison to the CAIA/vehicle control. *;+p<0.05; **;++p<0.01; ***;+++p<0.001; ****;++++p<0.0001.



3 IN-LIFE RESULTS

Following arthritis induction, paw inflammation was observed starting from Day 8, peaked on Days 11 to 13 and then slowly decreased towards the end of the study (Days 20 to 21). Treatment with MYMD-1® 450 mg/kg/day significantly reduced the clinical score and the paw volume in BALB/c arthritic mice when compared to CAIA disease control (Figure 1). A similar observation was noted with MYMD-1® at 250 mg/kg/day but at lesser extent. There was no clinical signs and no effect on body weights associated with MYMD-1® treatment.

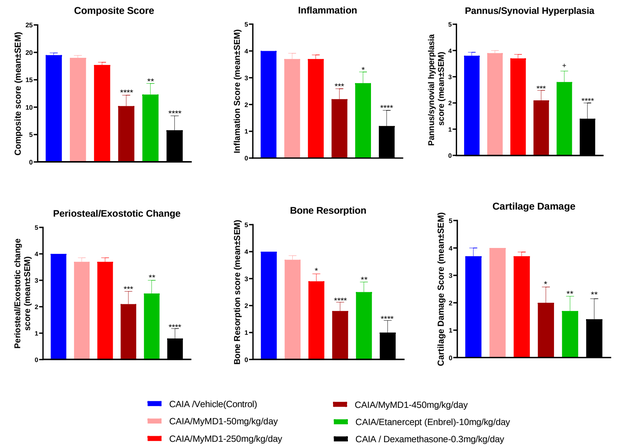
Figure 1: Clinical Score and Paw Volume Measurements



4 HISTOPATHOLOGY RESULTS

Histopathological changes associated with arthritis (inflammation, erosion, synovial hyperplasia, bone degeneration and periosteal changes) were observed in CAIA/vehicle control animals. Disease severity (total composite score) was reduced by 47% with MYMD-1® at 450 mg/kg/day while the reduction was 37% with Etanercept at 10 mg/kg (Figure 2). MYMD-1® at 50mg/kg/day had no reductive effect on the disease state. Scanned images obtained from decalcified left hindlimbs stained with H&E show the thickening of the joint space by pannus and inflammation in the vehicle control when compared to MYMD-1® (450mg/kg) treatment (Figure 3).

Figure 2: Effect of MYMD-1® on histopathology changes



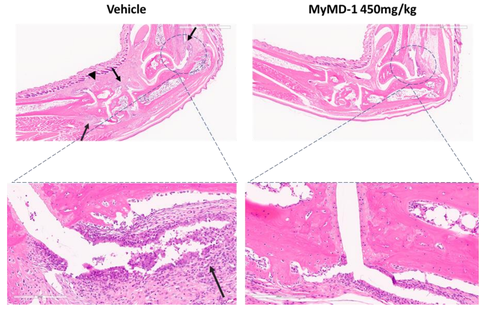


Figure 3: Representativte Hematoxilin Eosin (H&E) staining of decalcified left hindpaw

Upon low and high magnification in the tibio-tarso-metatarsal joint, joint space is thickened by pannus and inflammation (arrows) in vehicle control when compared to MYMD-1® treated animal. Periosteal reaction (bone exostosis) is also noted (arrowhead) in the vehicle control.

5 CONCLUSION

MYMD-1® administration at 450 mg/kg/day inhibited arthritis development in Collagen Antibody Induce Arthritis murine model, with in-life data consistent with histopathological findings. Moreover, no clinical signs or body weight loss was associated with MYMD-1® treatment at 450mg/kg/day. Unlike currently available TNF-α inhibitors, MYMD-1® can be given orally and is a promising drug for rheumatoid arthritis.

6 ACKNOWLEDGMENT

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