Dextran Sulfate Sodium (DSS)-induced Ulcerative Colitis Model in Mice: Comparing the Effects of Two Therapies on Clinical Signs and Colon Cytokines Secretion

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Inflammatory bowel disease (IBD), which affects millions of people world-wide, is a chronic inflammatory condition of the gut caused by microbiome dysbiosis as well as environmental and genetic factors. IBD can be broadly classified as Ulcerative colitis (UC) and Crohn's disease (CD). Among the various animal models that are used to mimic human IBD, the dextran sulfate sodium (DSS)-induced colitis model is more widely used due to its simplicity and recapitulation of several features observed in human ulcerative colitis.

In the present study, we compared the efficacy of two anti-inflammatory therapies in the DSS colitis model in mice by examining their effects on IBD clinical signs and pro-inflammatory cytokines release in colon tissues.

1 Materials and Methods

Animals: C57BL6 Female Mice, 9-11 weeks old at arrival, from Charles River Labs, USA. Animals were acclimated at least 7 days at the test facility before starting the study. All procedures were approved by the adMare Bioinnovations, Montreal Institutional Animal Care and Use Committee (IACUC).

Drugs: Dextran Sulfate Sodium (DSS; Cat–160110; MP Biochemicals USA), Cyclosporine A (CsA, Cat-C988900, Toronto Research Chemicals, Canada), 5-aminosalicylic acid (5-ASA; Cat-M258100, Toronto Research Chemicals, Canada).

Experimental Design: Mice were administrated with DSS solution in drinking water to induce colitis. Cyclosporine A (CsA, 80 mg/kg) or 5-aminosalicylic acid (5-ASA; 75 mg/kg) were given orally to the animals once daily until the terminal day. The disease evolution was monitored daily by measuring weight loss, presence of occult blood in stool (using a Hemoccult kit) and softness of the fecal pellets. Scoring was performed as below:

Body weight loss (BW) score
- 0 = <1% weight loss
- 1 = 1-<5% weight loss
- 2 = 5-<10% weight loss
- 3 = 10-20% weight loss
- 4 = >20% weight loss

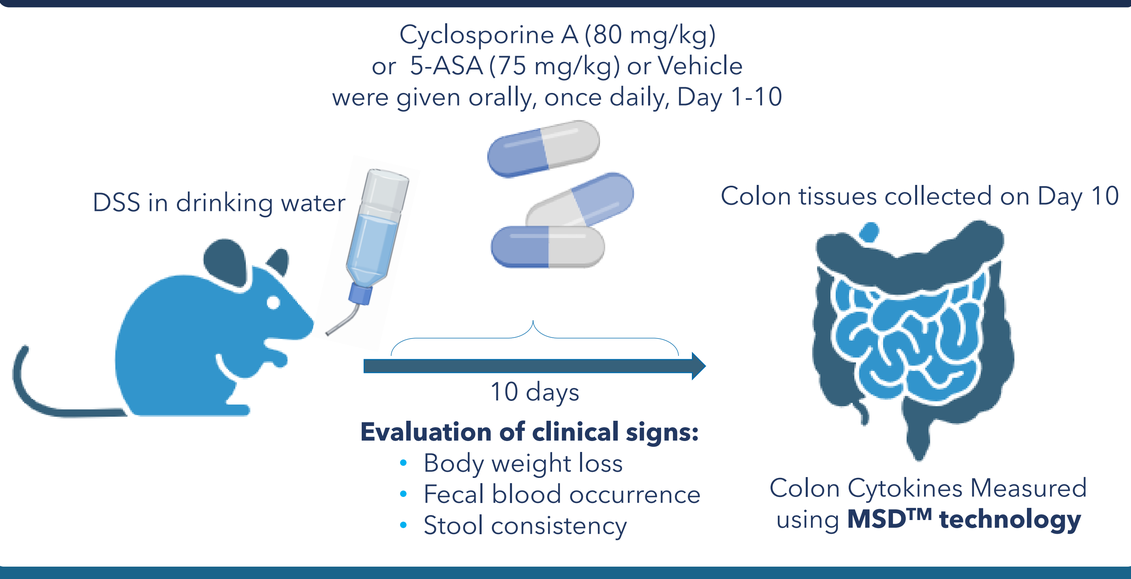
Fecal blood (FB) score
- 0 = Negative hemoccult
- 1 = Positive hemoccult – slight blue color on strip
- 2 = Positive hemoccult – darker blue color on strip
- 3 = Minor Visible traces of blood
- 4 = Major Visible traces of blood

Stool consistency (SC) score:
- 0 = Normal
- 1 = Soft, but still formed
- 2 = Very soft
- 4 = Diarrhea

Disease Activity Index (DAI) score = BW score + FB score + SC score

On the final day, animals were euthanized, the colons were collected. Colon tissues were used for measuring cytokine levels (IL-1B, IL-6, IL-10, IL-17, Eotaxin, GM-CSF, IFN-γ, TNF-α) by Meso Scale Discovery® (MSD) kits.

2 Experimental Design Cartoon



3 DSS Concentration-dependent Colitis Induction in Mice

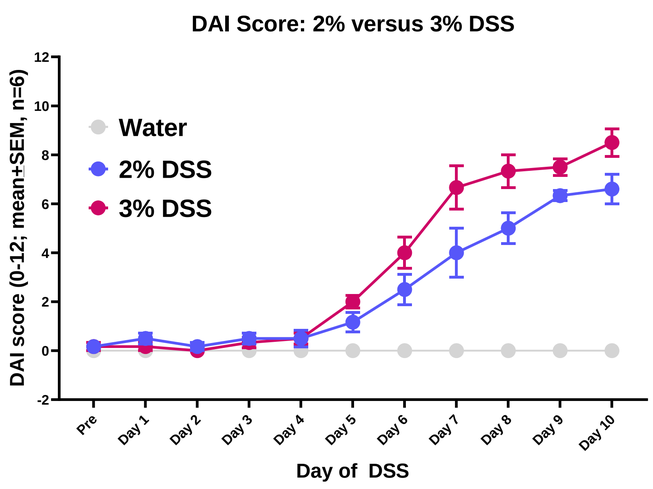


Figure 1: Induction of colitis was evaluated using two different concentrations of DSS (2% and 3%). A DSS concentration-dependent induction of colitis was observed in the mice as evidenced by relatively higher disease scores with 3% DSS compared with 2% DSS. Based on relatively higher and optimal level of colitis induction, 3% DSS was selected to examine effects of the two therapies. BW score, FB score and SC score data are not shown.

4 Effects of CsA and 5-ASA on DSS-induced Colitis Scores

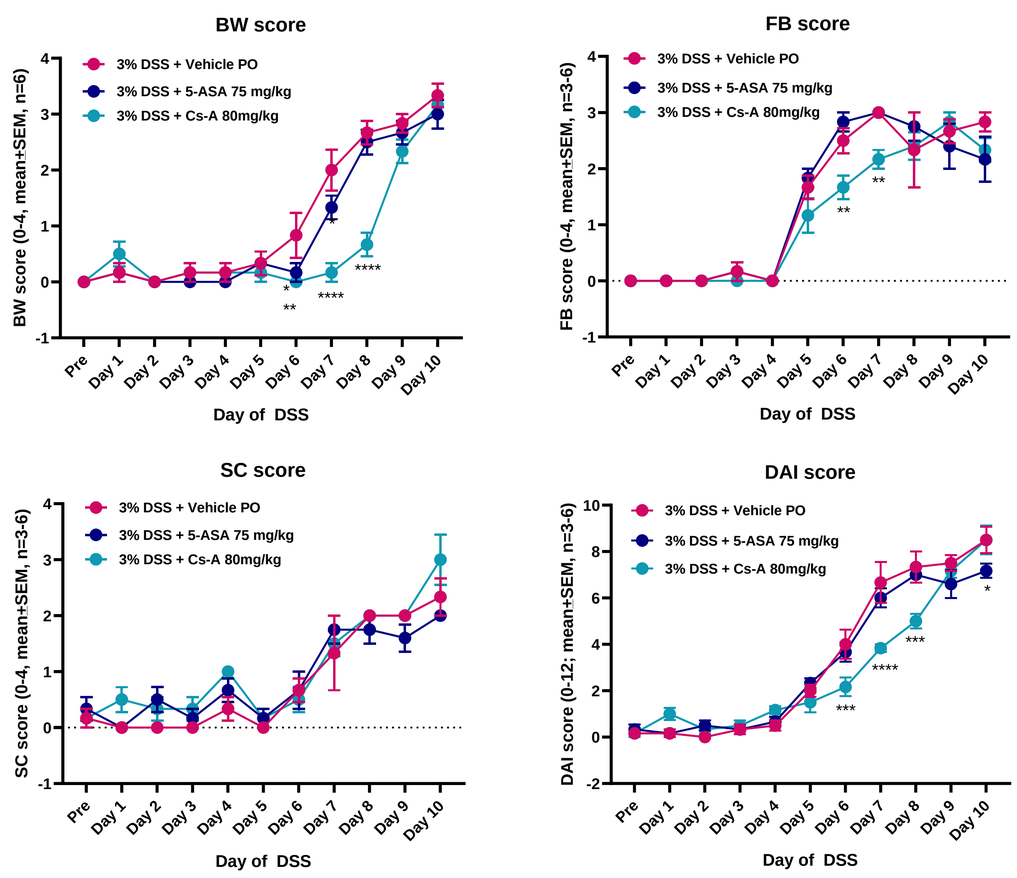


Figure 2: Effects of two clinically used anti-IBD agents, Cyclosporine A (CsA) and 5-amino salicylic acid (5-ASA) were evaluated in the 3% DSS-induced colitis model in mice. While treatment with 5-ASA did not demonstrate a significant protective effect, a significant slowdown in disease progression was observed in mice treated with Cyclosporine A.

5 Effects of CsA and 5-ASA on Colon Cytokine Levels

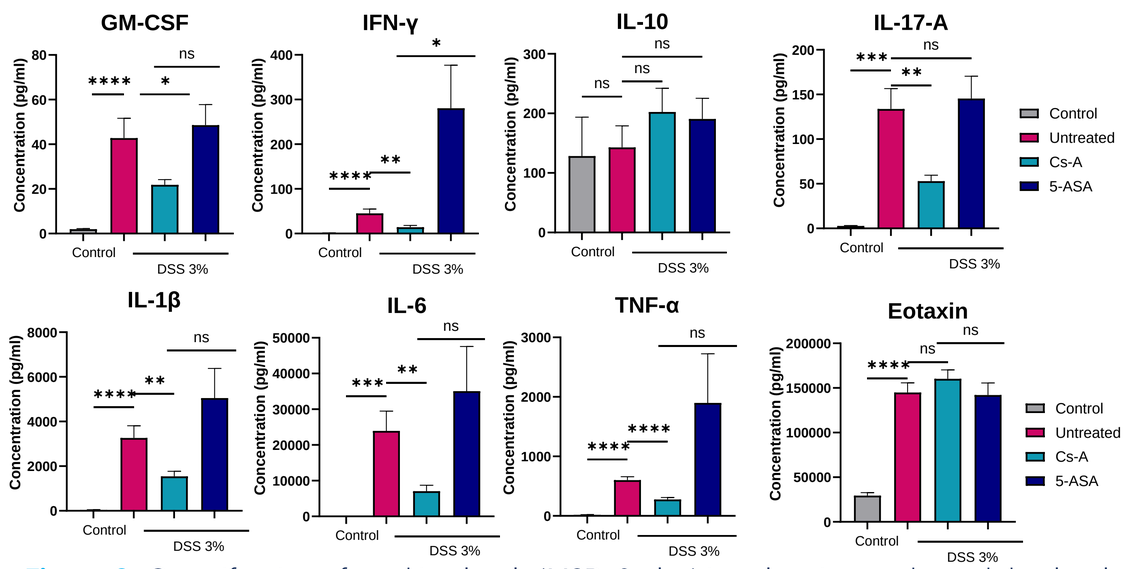


Figure 3: Quantification of cytokine levels (MSD, 8-plex) in colon tissues showed that levels of pro-inflammatory cytokines significantly increased in mice treated 3% DSS compared with control mice. When effects of the two therapies were compared, consistent with in-life data only Cyclosporine A, but not 5-ASA, significantly reduced the cytokines levels in the colon tissues.

6 Summary and Conclusion

Our results showed that

- *ad libitum* administration of DSS can induce colitis in mice with presence of in-life diseases as well as increased expression of pro-inflammatory cytokines in colon tissues.
- When the effects of two anti-IBD therapies were compared, the model seems more sensitive to treatment with Cyclosporine A which is a calcineurin inhibitor immunosuppressant known to act as pan-inflammation inhibitor both locally and systemically. 5-amino salicylic acid, which is poorly absorbed and act locally by inhibiting prostaglandins and leukotrienes release, had no significant effect.
- Local inflammatory cytokines measurement in colon tissues further confirmed the in-life results whereby Cyclosporine A significantly reduced the levels of almost all pro-inflammatory cytokines in colon tissues while 5-ASA had no effect.

References:

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2- Efficacy of drugs used in the treatment of IBD and combinations thereof in acute DSS-induced colitis in mice. Sann H, Erichsen J, Hessmann M, Pahl A, Hoffmeyer A. Life Sci. 2013 Apr 9;92(12):708-18.

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