Development of a Chronic Dextran Sulfate Sodium-Induced Colitis Model in the Nonhuman Primate

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Introduction

- The dextran sulfate sodium (DSS)-induced model of colitis is frequently used as a preclinical model of inflammatory bowel disease (IBD).
- However, some treatments for IBD, such as prednisolone (PSL), show poor efficacy or even worsen colitis in the rodent DSS model.
- Differences in inflammatory/immune mechanisms between humans and rodents are potential sources of this issue.
- In the current study, a nonhuman primate model of chronic colitis was created and the effect of PSL was assessed in this model.

Methods

Animal ethics
Procedures involving macaques were reviewed and approved by the Hamamatsu Pharma Research Animal Care and Use Committee. Environmental management and housing conditions were according to the Guide for the Care and Use of Laboratory Animals, Eighth Ed. (National Research Council, 2011). The facility is fully accredited by AAALAC International.

Animals
Total of eight male cynomolgus macaques (4 years old, 3.6-5.5 kg body weight; EBS Co., Japan).

Experiment design
- Oral administration of 0.25% DSS (M.W. 36,000-50,000; MP Biomedicals, OH, US) in drinking water at a volume of 100 mL/kg.
- 3 cycles 2 weeks on DSS followed by 2 weeks days off DSS.
- Prednisolone (1 mg/body, p.o., BID) administered for 2 weeks.

Modified Mayo score; [from 0 to 12] composed of:
- Stool consistency [0-3]
- Rectal bleeding [0-3]
- Colonoscopy examination [0-3]
- Global assessment [0-3] (Weight loss, Activity, Appetite, Drinking volume, Body temperature)

Rachmilewitz endoscopic index; [from 0 to 12] composed of:
- Granulation [0, 2]
- Vascular pattern [0, 1, 2]
- Vulnerability of mucosa [0, 2, 4]
- Mucosal damage [0, 2, 4]

Fecal calprotectin
- ELISA Kit (Calprotectin Mochida)

Efficacy of Prednisolone (PSL)

Control group
After 2 cycles of DSS
After 3 cycles of DSS

PSL-treated group
After 2 cycles of DSS
After 3 cycles of DSS with PSL for 2W

Conclusions

- A chronic DSS-induced colitis model was developed in macaques that showed similar symptomatic and endoscopic features to those seen in clinical Ulcerative Colitis, including repeated relapse and remission.
- PSL clearly inhibited disease relapse in this model.
- Therefore, the macaque model, compared to the rodent model, could show better predictiveness of clinical outcome of compounds that are currently under evaluation for the treatment of UC.
- Fecal calprotectin correlates with endoscopic activity in this model as well as in human IBD.

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