Longitudinal T_2 relaxometry to monitor repeated cycles of DSS inducing a chronically relapsing inflammation

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Introduction

Most experimental animal models of inflammatory bowel diseases (IBD) fail to accurately reflect the chronically relapsing inflammation underlying the complications of human Crohn's disease. This study investigated whether repeated cycles of dextran sulfate sodium salt (DSS) adequately reflect the effects of chronic transmural healing compared to the acute murine (DSS) colitis model with recovery. Longitudinal T_2 relaxometry at 9.4T was used to monitor the transmural changes during a 2 cycle treatment with DSS.

Materials & Methods

DSS colitis was induced in 6 week-old C57BL6/J mice: a first group (n=8) received 2 cycles of 7 days of DSS followed by 2 weeks of normal drinking water. For histological evaluation, qRT-PCR and macroscopic scoring of the colon, a second group (n=4) received 7 days of DSS followed by a 5 weeks recovery period and third control group (n=3) received normal drinking water only. Mice from the 2 cycle group were monitored longitudinally (day 0, 7, 21, 28 and 42) on a 9.4T MRI system (Bruker Biospin; horizontal bore, 20 cm) equipped with an actively

shielded gradient insert (1200mT/m) and using a 3.5 cm volume resonator (Rapid Biomedical). T_2 weighted images and T_2 maps of the distal colon were recorded (T_2w: RARE; TEeff=52ms, TR=4800ms, FOV=3x3cm, matrix= 256x256; slice thickness = 1mm T_2map:TE=10-100ms, matrix 128x128). Maps were calculated using a plug-in for ImageJ [1]. Regions of interest delineating the colon wall were manually drawn on the T_2w images, acquired with the same geometry as the T_2 map, and then copied to the T_2 map to determine mean T2 values. After scanning and euthanasia, the distal colon was harvested for histology and qRT-PCR. Collagen deposition was quantified with Martius-Scarlett-Blue staining. To compare mean T_2 values at different time points within the 2 cycle group a non-parametric paired (Friedman) test was used with Dunns multiple comparison correction.
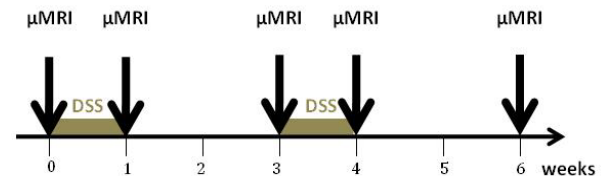
Results

The T_2 after 2 cycles with recovery (day 42) showed a significant decrease compared to the 1 cycle with recovery (21 days) time point (respectively, T_2 =72±8ms and 51±6ms; p<0.05). T_2 values at day 42 also tended to be increased vs. baseline levels (day 0: T_2 = 42±3ms) although not statistically significant with the non-parametric Dunns test.

Mice with 2 DSS cycles had a significant shorter colon (p<0.001), higher colon weight (p=0.001) and higher colon weight/length ratio (p<0.001) vs. 1 cycle mice with recovery and control mice. The colon of the 2 cycle group had a significantly higher macroscopic score than the 1 cycle group (p<0.001). Histology showed a trend towards a higher collagen content in the 2 cycle model compared to the 1 cycle model and a significantly higher value compared to control mice (p=0.046). No significant difference was observed in TGFb, IL13, IL13Ra1 and IL13Ra2 expression. TNFa was significantly higher in the 1 cycle model vs. 2 cycle model and controls (p=0.002).
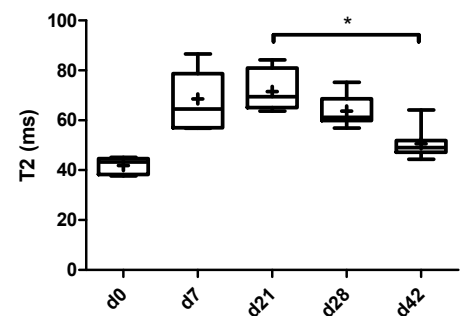
Discussion and Conclusion

Based on macroscopic scoring of the colon and histology the chronic repeated cycle DSS model with relapse and remission is clearly different from the acute DSS model with recovery. The in vivo T_2 relaxometry also showed significant differences between the first and second cycle of DSS making it a promising non-invasive assessment method in IBD. A more detailed statistical analysis relying on the full T_2 histogram at each time point could more accurately reveal these differences. This model opens perspectives to study the effects of healing and fibrosis in Crohn's disease .

References

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