

T₂ relaxometry to assess inflammation and fibrosis in an acute and chronic murine model of inflammatory bowel diseases

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INTRODUCTION

The chronic inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are heterogeneous idiopathic inflammatory disorders of the intestine. CD is in essence a transmural disease and chronic inflammation leads to perforating ulcers and to intestinal wall fibrosis. Both are feared complications that lead to bowel resection and loss of organ function. Studies in experimental, mostly murine, colitis have greatly advanced our knowledge of the pathogenesis and mucosal immune processes underlying IBD, but have generally failed to unravel the pathophysiology of more chronic colitis. Most of the major experimental read outs in experimental colitis models necessitate sacrifice of the animals for histology, mucosal damage scores or cytokines assays. If the more chronic phases of colitis are studied, non invasive imaging tools that can be repetitively applied to the same value would be a major asset. In human CD, the value of MRI and CT enterography as non invasive assessment tools of transmural inflammation and extraluminal complications is increasingly recognized [1]. However, data on MR imaging as a non-invasive screening tool to study murine ileitis or colitis are very limited [2-4] and we could not find an MRI study of a chronic murine model of IBD.

The aim of this study was to determine the feasibility of μ MR imaging in DSS induced colitis to distinguish (and quantify) both inflammatory and fibrotic lesions using in vivo T₂ relaxometry.

METHODS

Animals and experimental procedures:

Six week-old female C57BL/6/J mice were obtained from Harlan (Netherlands). Three conditions were compared: control mice, acute colitis and chronic colitis. Control mice (n=2) received only normal drinking water. Acute colitis mice (n=2) were fed with two percent dextran sulfate sodium salt (DSS) (MPbio) in the drinking water 7 days prior to scanning and the chronic colitis mice (n=2) received two cycles of 7 days of DSS followed by two weeks of normal drinking water (figure 1). All mice were at the same age at time of scanning (figure 1). After scanning, mice were sacrificed and colon was harvested for macroscopic scoring and histology. Collagen deposition was quantified with Martius-Scarlet-Blue staining (MSB). The blue area was measured using ImageJ (Wayne Rasband, NIH, USA). This study was approved by the Institutional Animal Care Commission and Ethical Committee.

MRI acquisition and processing

MR images were acquired with a 9.4T Biospec 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). For planning purposes 2D respiration triggered sagittal and coronal T₂w images were recorded (RARE; TE_{eff}=52ms, TR=4800ms, FOV=3x3cm, matrix= 256x256; slice thickness = 1mm). To determine colon wall thickness 20 axial slices were acquired (at 1.4mm slice distance; other parameters identical). T₂ maps were recorded from the same locations (TE=10-100ms, matrix 128x128, other parameters identical) covering the distal part of the colon. Maps were calculated using a plug-in for ImageJ [5]. Regions of interest (roi) delineating the colon wall were manually drawn on the T₂w images, acquired with the same geometry as the T₂ map, and then copied to the T₂ map. Histograms were created from the T₂ maps from four slice over the distal part of the colon. Colon thickness was evaluated from the area of the roi's drawn on the high resolution T₂w images.

RESULTS

Both the T₂w images as well as histology showed a markedly enlarged colon wall thickness for the acute and chronic model versus the control condition (area ratio acute/control: MRI=1.7, histology=2.2, chronic/control: MRI=1.7, histology=2.9, see figure 2). In this preliminary study, no difference in MRI derived wall thickness was found between the chronic and acute model. However, the histograms of the colon T₂ values showed a clear shift towards higher values for the acute colitis model but less for the chronic colitis versus the control condition (figure 3). This was confirmed by histology, which showed on an increased collagen deposition and more α SMA positive cells for the chronic versus the acute model. Both are indicative of more fibrosis in chronic colitis compared to acute and normal mice.

CONCLUSIONS

These preliminary data suggest a potential role of in vivo MRI T₂ relaxometry in the assessment of chronic intestinal inflammation and fibrosis in a murine IBD model. More importantly, we show that T₂ relaxometry allows distinguishing between the acute and chronic model opening the possibility of monitoring the transition phase of the acute to the, more clinically relevant, chronic condition. Besides previously reported use of DCE-MRI, this T₂ relaxometry approach can also be further development to use MRI as a clinical diagnostic tool, with assessment of T₂ maps in patients with Crohn's disease to quantify fibrosis.

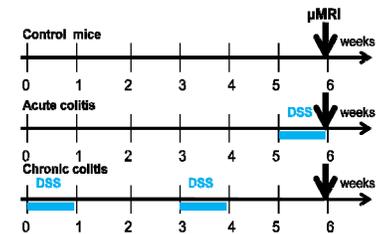


Fig1. Treatment and microMRI for each group

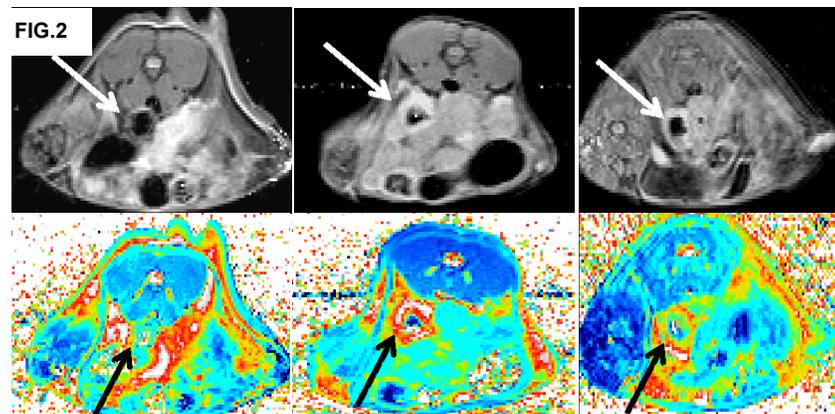
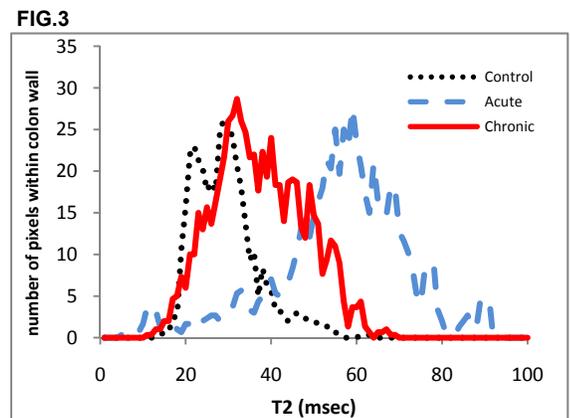


Fig. 2: T₂ weighted (top row) and T₂ maps (bottom) obtained from a mouse in the control, acute and chronic group (L to R)

Fig. 3: T₂ histograms from the colon for the control, acute and chronic condition.



References

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