Development of a Murine Isogenic Graft Model of Endometriosis: Monitoring by dynamic contrast-enhanced MRI

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INTRODUCTION Endometriosis is a common gynaecological condition which is associated with pelvic pain and infertility. The disease is characterised by the presence of ectopic endometrial tissue.

The purpose of our study was to develop non-invasive method of studying endometriosis in a pre-clinical model using magnetic resonance imaging (MRI). In order to investigate the pathological mechanism of endometrial lesion development and to monitor therapy in pre-clinical trials we used dynamic contrast-enhanced MRI (DCE-MRI) in a murine isogenic graft model of endometriosis. Our hypothesis was that DCE-MRI reflects the angiogenic processes underlying lesion development.

METHODS ANIMAL PROTOCOL: C57BL/6J female mice (n = 4 donor, n = 4 recipient; 22-26 g) were maintained in a well-controlled pathogen-free environment. We used a modified version of an isogenic mouse graft model of endometriosis developed by *Pfizer*. Collection of the uterus for grafting from donor animals and its transplantation to a recipient was performed following a strict aseptic technique. One donor animal provided a uterus (two horns) for one recipient. The excised uterus was transferred to Dulbecco's Modified Eagle's Medium prior to preparation. Using a scalpel, each uterine horn was cut into a series of very fine slices. Some medium was expelled onto a chopped uterine horn. The suspension was injected s.c. using a 16 G needle under anesthesia (oxygen/isoflurane). Each animal was imaged on days 3, 7 and 10 after tissue implantation. MRI scans were performed under anaesthesia using isoflurane (1.5 %)/oxygen delivered via a nose cone. Respiratory rate were monitored throughout the imaging experiment and the third scan was performed under terminal anesthesia.

MR PROTOCOL: Data were obtained on a 7T SMIS system employing a quadrature volume coil for excitation and detection. Anatomical images in the axial and coronal planes were acquired using T1-weighted 2D gradient echo (GE) sequences. A T1-weighted 3D GE sequence was used to obtain quantitative data in the coronal plane (FOV= 32 x 32 x 19 mm; acq. matrix 128 x 64 x 17; recon. matrix 128 x 128 x 32; TR/TE=17 ms/5 ms; flip angle = 20^o; 2 averages; acq. time 40 s). Prior to Gd-DTPA injection data were acquired for a T1 measurement using flip angles of 2^o, 10^o and 30^o [1]. The dynamic imaging sequence was run continuously until 25 volumes were acquired, Gd-DTPA was injected into the tail vein (0.25 mmol/kg) after acquisition of the 2^{nd} volume. Regions of interest were selected in the aorta and encompassing the lesion. Mean pixel intensity was recorded then converted to change in 1/T1 (R1) over time as a measure of Gd-DTPA concentration prior to tracer kinetic analysis [2].

RESULTS Endometrial lesions grew rapidly in all animals. An example (at day 7) is shown in Fig. 1. Gd-DTPA uptake was relatively slow but consistent over the three days studied (Fig. 2). Estimates of baseline T1, K^{trans}, v_e (interstitial volume) and k_{ep} (exchange rate) were obtained for each lesion and time point. However, analysis of the data by repeated measures ANOVA indicated that there was no significant within-subject change over time. Good quality data were acquired from the aorta in 6 of the 12 studies performed. These data were averaged (Fig. 3) and a biexponential function was fitted to them to provide a model-specific population arterial input function (AIF) appropriate for subsequent analyses [2].

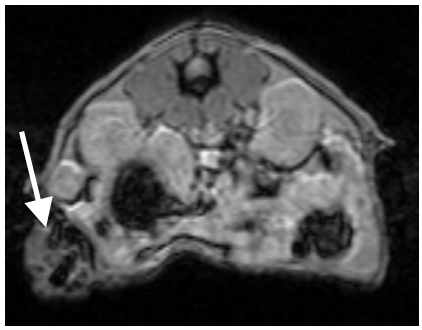

Fig. 1 *T1-weighted axial GE image of endometrial lesion*

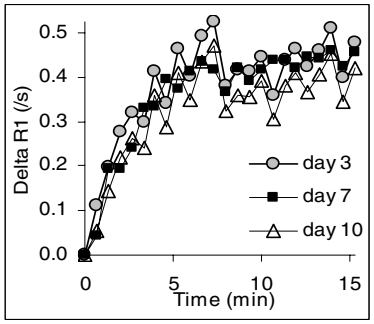

Fig. 2 *Gd-DTPA uptake curves from lesion in Fig. 1 at days 3, 7 & 10*

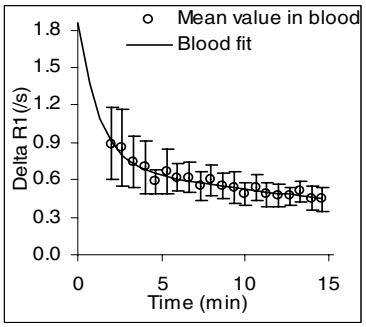

Fig. 3 *Aortic uptake (mean ± SE, n=6) and fitted biexponential population AIF.*

CONCLUSIONS MRI is an appropriate methodology for studying this murine graft model of endometriosis with lesions identifiable as early as 3 days post-implantation. Quantitative DCE-MRI has been shown to provide consistent results but was unable to identify changes in the angiogenic status of the lesion over the time frame studied. Further work is required to compare these results with histology.

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REFERENCES

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