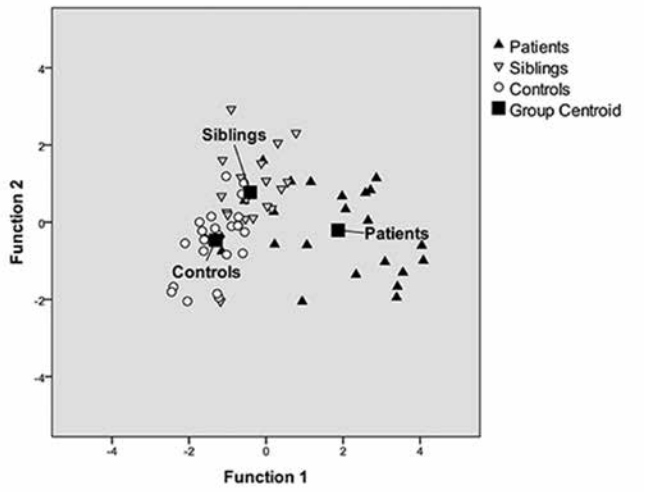
Aims Delineate the genetic, immune and microbial phenotype of patients, siblings and healthy controls (HC); identify factors associated with CD that discriminate siblings from HC.
Methods Faecal microbiota, FC, blood T-cell phenotype, IP and genotype risk over 72 CD risk loci, were measured by qPCR, ELISA, flow cytometry, sugar permeability and Illumina Bead Array respectively, in 22 patients with inactive CD, 21 of their healthy siblings and 25 HC.
Results In addition to genotype risk, siblings shared aspects of the phenotype of CD patients, distinct from HC, as previously reported.[1] Direct discriminant function analysis revealed that the variables maximally separating siblings from HC (Function 2) were: increased β7 integrin expression by circulating naïve $CD4^+$ T-cells and an increased proportion of memory $CD4^+$ T-cells as well as reduced faecal *Roseburia* spp. (Image 1). In contrast, the variables differentiating CD patients from HC (Function 1) were: elevated FC and altered faecal microbiota (reduced *Faecalibacterium prausnitzii*, Cluster IV *Ruminococcus spp. Bacteroides-Prevotella and* Clostridial cluster IV).



Abstract OC-017 Figure 1

Conclusion Healthy siblings of CD patients manifest immune and microbiological abnormalities associated with CD, distinct from their genetic risk. Unaffected siblings of CD patients are an excellent model in which to investigate early CD pathogenesis.
Disclosure of Interest None Declared

REFERENCE

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OC-018 LIMITED LONG TERM TOLERANCE OF METHOTREXATE FOR INFLAMMATORY BOWEL DISEASE: 11 YEARS EXPERIENCE FROM A SINGLE CENTRE

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Introduction Methotrexate (MTX) is used as an immunosuppressive treatment in inflammatory bowel disease (IBD). The aim of the study was to evaluate the long-term tolerability of MTX in adults with IBD from a large, single, tertiary referral centre.
Methods IBD patients who had received MTX at a single centre between 2000 – 2011 were identified from the IBD service database and clinical records reviewed.
Results 137 patients received MTX (Crohn's Disease 105 (77%); ulcerative colitis (UC) 32 (23%)); mean age 44 (range 18–77). The median duration of MTX treatment was 13 months (range 1–127) with an initial dose of 25mg/week (range 10–25 mg) in 127/137 (93%) with 94% commencing MTX intramuscularly. The proportion who continued MTX for ≥ 3, 5, 10 years were 24% (33/137), 10% (14/137) and 1.5% (2/137) respectively.

89/137 (65%) discontinued MTX during the 11 year follow-up. The cessation rate due to lack of effectiveness was 17/137 (12%) by the end of the 2nd year of MTX, after which there were no further discontinuations for this reason. 77/137 (57%) reported ≥ 1 side-effect (SE) attributed to MTX, which was the commonest reason for discontinuing MTX (61/89; 69%). SEs leading to MTX cessation were most frequent during induction (defined as 0–3months): 22/61 (36%); followed by 3–12 months following initiation of MTX: 16/61 (26%). Specific SEs resulting in cessation during the 1st year of MTX were due to ≥ 1 of the following; 15 (40%) gastrointestinal (GI), 12 (32%) neurological (NS), 5 (13%) nonspecific malaise, 5 (13%) abnormal hepatic aminotransferase levels (2-fold increase up to or over the upper limit of normal), 2 (5%) hair loss, 5 other (1 each of sore throat, rash, infection, low platelets, injection site reaction). The incidence of discontinuation due to SEs in successive MTX years fell from commencement of MTX: 10/61 (16%) in the 2nd year, 5/61 (8%) in the 3rd year, 3/61 (5%) in the 4th year and 5 (8%) in total between the 5th-10th years. The most frequent SEs attributed to late discontinuation (> 1year) were GI and NS.

Over 11 years there were 12/137 (9%) reported cases of presumed MTX induced abnormal hepatic aminotransferase levels, of which 8 (67%) resulted in MTX cessation with biochemical resolution. Hepatotoxicity occurred during induction in 7/12 cases (58%) and was stopped in 5 of these (71%). In 5 patients with late abnormal hepatic aminotransferase levels, the median time to detection was 36 months (range 10–100months). MTX was discontinued in 3 of these.
Conclusion In the largest single-centre experience to date, MTX in IBD is limited by high withdrawal rates with a 28% discontinuation rate due to SEs within the 1st year. Late hepatoxicity highlights the need for long term monitoring in maintenance therapy.
Disclosure of Interest None Declared

OC-019 ADAMDEC1: A NOVEL MOLECULE LINKED TO CROHN'S DISEASE, IS ASSOCIATED WITH AN INCREASED SUSCEPTIBILITY TO CITROBACTER RODENTIUM COLITIS IN THE KNOCK OUT MOUSE

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Introduction Innate immunity is attenuated in patients with Crohn's disease (CD), with impaired neutrophil recruitment, delayed clearance of *E. coli*, and defective secretion of pro-inflammatory cytokines from macrophages[1,2]. This primary macrophage defect may result in failure to eradicate bacterial flora entering the tissues and lead to the chronic granulomatous inflammation characteristic of CD. To discover the molecules responsible, transcriptomic profiles were obtained from cultured human macrophages from CD patients and controls. ADAMDEC1 a Disintegrin and Metalloprotease was under-expressed in ~10% of CD patients. This protein is almost exclusively found in macrophages and dendritic cells in the small and large bowel lamina propria. Here we describe the response of *Adamdec1*$^{-/-}$ mice to an enteric bacterial infection with *Citrobacter rodentium*.
Methods *Adamdec1*$^{-/-}$ and wild type mice were administered ~10^8 or 10^9 *C. rodentium* by oral gavage and body weight monitored for three weeks. At intervals mice were sacrificed and samples of serum, stool, colon and spleen were collected. Serum cytokine levels were measured and bacteria counted, in stool and spleen. Bowel inflammation was assessed histologically. Neutrophil and immune cell recruitment to the colon were measured by MPO assay and qPCR respectively.