are few explanations for the wide variation in inter-individual TPMT activities in the wild-type range. Bioavailability of the cofactor *S*-adenosylmethionine (SAM) and RBC age may play a role. The aim of this study was to determine if gender or anaemia influences RBC TPMT activity.

Methods We analysed a retrospective cohort of 6,496 RBC TPMT samples (n = 3804 females, n = 2692 males) measured in the PRL since 2004 and correlated enzyme activity with gender and haemoglobin concentrations.

Results A greater portion of females exhibited intermediate TPMT activity (13.46%) as compared to males (11.07%). The mean TPMT activity was also significantly lower in females (32.94 pmol/mg Hb/h) versus males (34.13 pmol/mg Hb/h; p = < 0.0001, 95% CI 0.7950–1.589). When separated by low, intermediate or normal TPMT activity, this relationship only remained in patients with normal TPMT activity. TPMT activity was significantly higher in female patients with an Hb < 10g/dl (n = 250, mean TPMT 38.06 pmol/mg Hb/h) versus females with an Hb > 12g/dl (n = 2192, mean TPMT 32.46 pmol/mg Hb/h; p = < 0.0001). Similarly TPMT activity was significantly higher in male patients with an Hb < 10g/dl (n = 123, mean TPMT 38.14) versus males with an Hb > 12g/dl (n = 1901, mean TPMT 33.76; p = < 0.0001).

Conclusion TPMT activity in the wild-type range is lower in females than males, suggesting a post-translational influence on TPMT activity related to gender. Lower levels of SAM have been reported in females, which may explain this observation[2]. Re-appraisal of the concordance between TPMT genotype and phenotype, adjusting for gender is therefore indicated. The finding of higher TPMT activity with anaemia may be due to a younger red cell population in this group. The difference in TPMT activities between patients with or without anaemia is clinically relevant, particularly where the TPMT activity is around the cut-off between intermediate (10–25 pmol/mg Hb/h) and normal (≥26 pmol/mg Hb/h) ranges. TPMT genotyping should be considered in such patients.

Disclosure of Interest None Declared

REFERENCES

1. Karas-Kuzelicki, *et al.* Pharmacogenomics 2009. 10:1309–22.
2. Poirier, *et al.* Cancer epidemiology, biomarkers & prevention 2001. 10:649–655.

OC-016 ELEVATED FAECAL CALPROTECTIN PREDICTS DISEASE PROGRESSION IN CROHN'S DISEASE

doi:10.1136/gutjnl-2013-304907.016

[1,*]N A Kennedy, [2]J Chang, [2]M H Guy, [2]T Smith, [2]J T Loh, [2]D Haunschmidt, [2]M Muscat, [2]F Fasci Spurio, [1]H E Drummond, [3]K Kingstone, [2]C L Noble, [2]A G Shand, [1]J Satsangi, [2]I D Arnott, [2]C W Lees. *[1]Gastrointestinal Unit, Molecular Medicine Centre; [2]Department of Gastroenterology; [3]Department of Clinical Biochemistry, Western General Hospital, Edinburgh, UK*

Introduction Historical cohort studies have clearly demonstrated that over time the majority of patients with Crohn's disease (CD) will progress from inflammatory (B1) to stricturing (B2) or fistulating (B3) disease. Emerging data suggest that more intensive treatment targeted towards mucosal healing will help to prevent disease progression. Faecal calprotectin (FC) is an established surrogate biomarker for endoscopic mucosal healing. It has yet to be established whether tailoring therapy to FC levels prevents disease progression.

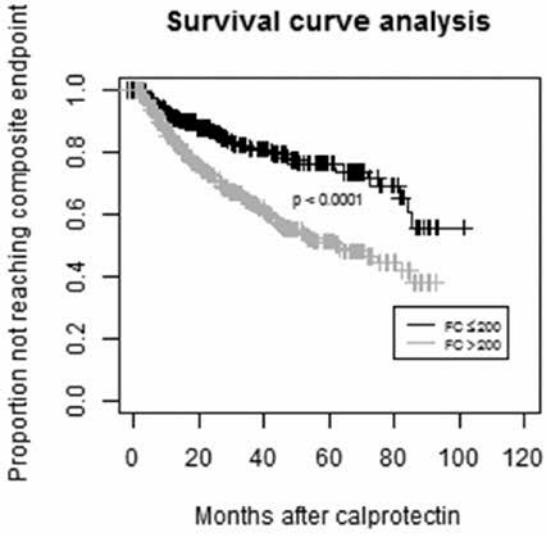
In the present study we aimed to determine whether FC levels in patients with established CD were predictive of disease progression.

Methods The Edinburgh Faecal Calprotectin Registry (EFCR) comprises data on 22,130 FC assays in 16,278 patients from 2005–2012. Detailed phenotypic information was obtained on patients with CD by retrospective casenote review. Data collected included demographics, disease location, disease behaviour over time, CD-related surgery, investigations, hospitalisations and drug therapy. Patients were included in the main analysis if they had at least 12 months' follow-up since first FC. The a priori primary endpoint was a composite of progression in Montreal luminal behaviour, hospitalisation for flare and resectional surgery.

Results There were 881 CD patients identified with at least one FC, of which 723 had at least one year's follow-up, with median follow-up time 40 months (IQR 25–60). The median age was 28y (IQR 20–42) at diagnosis and 40y (28–53) at time of first FC.

239 patients (33%) reached the primary endpoint, of whom 68 had had progression of their Montreal behaviour from B1 to B2 or B3, or from B2 to B3.

The median of the earliest FC was significantly higher in the group that reached the primary endpoint at 586 µg/g (IQR 210–1235) vs. 289 (75–1001) in those that did not (p < 0.0001). Survival analysis (Fig 1) revealed significant differences in time to progression, hospitalisation or surgery with calprotectin ≥ 200 (p < 0.0001).



Abstract OC-016 Figure 1

Conclusion This large single-centre study presents compelling evidence that measurement of FC can be used to predict disease course, which creates the opportunity for physicians to intervene earlier and perhaps alter the disease course.

Disclosure of Interest None Declared

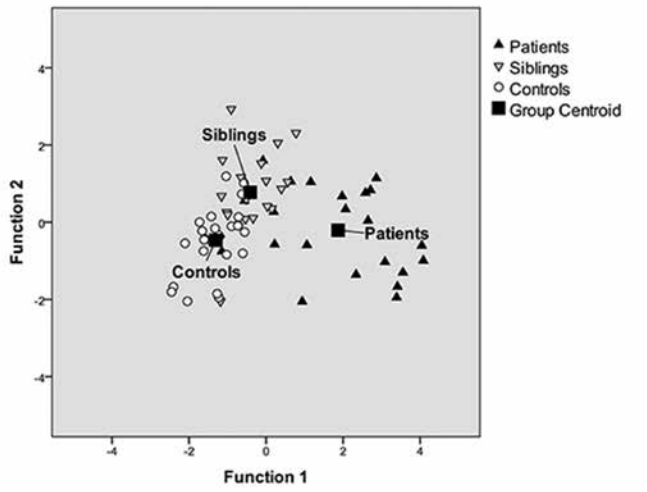
OC-017 A DISCRIMINANT ANALYSIS DEMONSTRATES THAT SIBLINGS OF PATIENTS WITH CROHN'S DISEASE HAVE A DISTINCT MICROBIOLOGICAL AND IMMUNE PHENOTYPE COMPARED WITH HEALTHY CONTROLS: INSIGHTS INTO DISEASE PATHOGENESIS

doi:10.1136/gutjnl-2013-304907.017

[1,2,*]C Hedin, [2]N E McCarthy, [3]P Louis, [3]F Farquharson, [4]S McCartney, [5]K Taylor, [5]N Prescott, [6]T Murrells, [2]A J Stagg, [1]K Whelan, [2]J O Lindsay. *[1]School of Medicine, King's College London; [2]Blizard Institute, Queen Mary, University of London, London; [3]Rowett Institute, University of Aberdeen, Aberdeen; [4]Department for Gastroenterology and Clinical Nutrition, University College Hospitals NHS Foundation Trust; [5]Department of Medical and Molecular Genetics; [6]Florence Nightingale School of Nursing and Midwifery, King's College London, London, UK*

Introduction Crohn's disease (CD) is associated with genetic risk, intestinal dysbiosis, altered blood T-cell phenotype, increased faecal calprotectin (FC) and intestinal permeability (IP). Factors shared by CD patients and unaffected siblings may be implicated in CD pathogenesis.

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

1. Hedin *et al.* Gut 2012; 61: Suppl. 2 A22-A23.

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

doi:10.1136/gutjnl-2013-304907.018

[1,*]A J Brooks, [1]E M Wood, [1]K Robinson, [1]A Wright, [1]M E McAlindon, [1]A J Lobo. [1]*Gastroenterology, Sheffield Teaching Hospitals, Sheffield, UK*

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

doi:10.1136/gutjnl-2013-304907.019

[1,*]N R O'Shea, [1]A M Smith, [1]T Chew, [1]J Dunne, [1]A W Segal. [1]*Medicine, University College London, London, UK*

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.