Oral presentations

Inflammatory bowel disease section free papers

OC-001 ANTI-TNF WITHDRAWAL IN IBD: INITIAL RESULTS FROM A PAN-UK STUDY

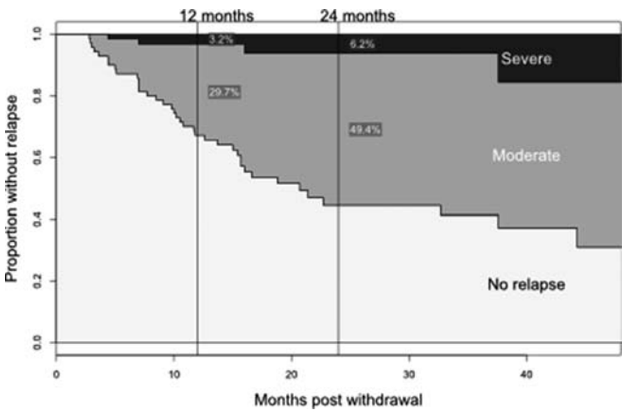
[1]NA Kennedy*, [2]B Warner, [2]E Johnston, [1]C Basquill, [3]R Harris, [4]CA Lamb, [5]A Singh, [6]AS Fadra, [7,8]F Cameron, [9]U Basavaraju, [10]J Mason, [11]K Lithgo, [12]L Penez, [13]C Stansfield, [13]S Lal, [14]F Cummings, [12]A Hart, [11]M Johnson, [8]R Russell, [7]D Wilson, [10]I Gooding, [9]J Thomson, [15]D Gaya, [6]J Lindsay, [5]T Ahmad, [4]J Mansfield, [3]J Gordon, [1]J Satsangi, [2]P Irving, [1]CW Lees. *[1]GI Unit, Western General Hospital, Edinburgh, UK; [2]Department of Gastroenterology, Guy's and St Thomas' Hospital, London, UK; [3]Department of Gastroenterology, Royal Hampshire County Hospital, Winchester, UK; [4]Department of Gastroenterology, Royal Victoria Infirmary, Newcastle, UK; [5]Department of Gastroenterology, Royal Devon and Exeter Hospital, Exeter, UK; [6]Department of Gastroenterology, The Royal London Hospital, London, UK; [7]Department of Gastroenterology, Royal Hospital for Sick Children, Edinburgh, UK; [8]Department of Gastroenterology, Royal Hospital for Sick Children, Glasgow, UK; [9]Department of Gastroenterology, Aberdeen Royal Infirmary, Aberdeen, UK; [10]Department of Gastroenterology, Colchester Hospital, Colchester, UK; [11]Department of Gastroenterology, Luton and Dunstable Hospital, Luton, UK; [12]IBD Unit, St Mark's Hospital, Middlesex, UK; [13]Department of Gastroenterology, Salford Royal, Salford, UK; [14]Department of Gastroenterology, University Hospital, Southampton, UK; [15]Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, UK*

10.1136/gutjnl-2014-307263.1

Introduction Infliximab and adalimumab have established roles in IBD therapy. NICE and SMC guidelines mandate reassessment of disease activity after 12 months. Therapy should ordinarily be discontinued where clinical remission and mucosal healing has been achieved. However, there are presently few data about outcomes of anti-TNF withdrawal.

Methods We conducted a retrospective clinical audit of outcomes following withdrawal of anti-TNF therapy. Inclusion criteria were confirmed diagnosis of IBD; ≥12 m continuous anti-TNF therapy; primary withdrawal reason sustained clinical remission (no corticosteroids for 6 m); ≥12 m follow-up post-withdrawal. Relapse was defined as moderate (oral steroids, immunomodulators, recommencement of anti-TNF agent) or severe (hospitalisation, iv steroids, surgical resection). All UK centres were invited to participate. Demographic and phenotypic data plus clinical, laboratory and endoscopic parameters were recorded.

Results 80 cases (62 infliximab; 18 adalimumab) with a median follow-up time of 26 m post drug withdrawal were included in this analysis (59% female; median age at drug withdrawal 32y). All were in clinical remission at withdrawal; 47/80 had normal laboratory parameters (Hb, WCC, plts, Albumin, CRP, FC) prior to withdrawal. 49/80 had endoscopic re-evaluation with mild disease noted on 9/50 and moderate on 1. 23/70 (33%; 2/23 severe) of patients with Crohn's disease relapsed by 12 months and 49% relapse (3/35 severe) by 24 months (Fig 1, median time to relapse 10.4 m). Younger age at diagnosis (p = 0.017) and elevated WCC (p = 0.025), but not CRP or faecal calprotectin, were predictive of relapse. 4/10 (none severe) with UC/IBDU had relapsed by 12 and 24 months. Anti-TNF therapy was re-introduced in 30 patients following relapse and was successful in 93%.



Abstract OC-001 Figure 1

Conclusion Planned withdrawal of anti-TNF therapy for sustained clinical remission is associated with a moderate relapse of Crohn's disease in up to half of patients by 2 years. Data collection of an expanded cohort is ongoing around the UK to improve power to dissect predictive factors at time of drug withdrawal.

Disclosure of Interest None Declared.

OC-002 PREDICTING OUTCOME IN ACUTE ULCERATIVE COLITIS: COMPARISON OF THE TRAVIS AND HO SCORES USING UK IBD AUDIT DATA

[1]AM Churchhouse*, [1]RW Lynch, [2]A Protheroe, [1]ID Arnott. *[1]GI Unit, Western General Hospital, Edinburgh, UK; [2]CEEu, Royal College of Physicians, London, UK*

10.1136/gutjnl-2014-307263.2

Introduction Patients with severe Ulcerative Colitis (UC) are commonly identified using the Truelove and Witts[1] criteria on presentation. The Travis[2] and Ho[3] scores are subsequently used to identify patients with severe UC who are at high risk of failing medical therapy and needing second line therapy or colectomy. To date there has been no direct comparison between Travis and Ho scores to determine which is superior.

Methods We analysed data from 3049 patients with UC collected during the 2010 round of the UK IBD audit. 984 patients had acute severe UC according to the Truelove and Witts criteria. Those that failed steroid therapy were scored using both Travis and Ho criteria and allocated into either a Travis "high" or "low" risk group *and* either a Ho "high", "medium" or "low" risk group. We assessed whether further medical or surgical intervention varied between groups.

Results Patients requiring surgery did not differ between the high risk groups (Travis 49%, n = 93 and Ho 51%, n = 84, respectively). However, only 35% (n = 53) in the medium risk Ho group, 26% (n = 17) in the low risk Ho group and 32% (n = 65) in the low risk Travis group underwent surgery. Similarly 41% (n = 78) and 38% (n = 63) of patients in the high risk Travis and Ho groups respectively were treated with ciclosporin, whereas only 34% (n = 51) were treated in the medium risk Ho group, 25% (n = 16) in the low risk Ho group and 27% (n = 55) in the low risk Travis group. Resistance to ciclosporin correlated with increasing risk stratification, although this failed to reach statistical significance for all groups. The use of anti-TNFs was the same across all three groups, although like ciclosporin, the tendency to TNF resistance also increased with increasing risk group.

Conclusion The Travis and Ho scores are equally able to identify patients who are at high risk of failing medical therapy and needing colectomy or second line medical therapy. The Ho score may also be able to identify an intermediate risk group which

also has an intermediate response to second line therapy. Both scores are useful tools to aid clinical decision making but do not replace timely multidisciplinary care for these patients.

REFERENCES

1 Truelove SC, Witts DJ. Cortisone in ulcerative colitis. *Br Med J* 1955;2 (4947):1041–1048
2 Travis SPL, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MGW, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996;38(6):905–910
3 Ho GT, Mowat C, Goddard CJR, Fennell JM, Shah NB, Prescott RJ, Satsangi J. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Aliment Pharmacol Ther* 2004;19(10):1079–87

Disclosure of Interest None Declared.

OC-003 GENOME-WIDE EPIGENETIC ANALYSIS IN CHILDHOOD-ONSET CROHN'S DISEASE IMPLICATES MIR21

[1]AT Adams*, [1]NA Kennedy, [2]R Hansen, [1]NT Ventham, [1]KR O'Leary, [1]HE Drummond, [1]CL Noble, [2]E El-Omar, [3]RK Russell, [4]DC Wilson, [1]ER Nimmo, [2]GL Hold, [1]J Satsangi. *[1]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK; [2]Gastrointestinal Research Group, Division of Applied Medicine, University of Aberdeen, Aberdeen, UK; [3]Department of Paediatric Gastroenterology, Royal Hospital for Sick Children, Glasgow, UK; [4]Paediatric Gastroenterology and Nutrition, Child Life and Health, Royal Hospital for Sick Children, Edinburgh, UK*

10.1136/gutjnl-2014-307263.3

Introduction DNA methylation influences transcriptional activity and marks sites of active transcription. Technological developments allow the rapid assessment of methylation state at 450,000 sites across the genome. The aim of this study was to identify genes with a possible role in Crohn's disease pathogenesis, and candidate genes for methylation based diagnostic biomarkers.

Methods Using the Illumina 450k platform we analysed genome-wide DNA methylation in symptomatic children who underwent diagnostic colonoscopy, half of whom were diagnosed with CD and half had no pathology. Replication was performed in children with established CD vs. symptomatic non-disease controls. Further targeted replication by pyrosequencing was performed in adults with CD vs. healthy controls, with qPCR and microarray data to analyse expression.

Results Meta-analysis of the combined paediatric datasets (n = 66) identified 165 individual CpGs with epigenome-wide significance (Bonferroni correction) and 138 differentially methylated regions (DMR). Methylation changes were significantly enriched ($p < 0.0001$) in proximity to loci implicated by genome-wide association studies (GWAS).

The strongest result by each approach was MicroRNA 21, within the autophagy gene VMP1 ($p = 1.2 \times 10^{-14}$), 48 kb from GWAS SNP rs1292053. In adults with CD we replicated MIR21 hypomethylation ($p = 6.6 \times 10^{-5}$, n = 172), and showed increased expression in blood ($p < 0.005$, n = 66). Intestinal expression increased with inflammation in CD ($p = 1.4 \times 10^{-6}$, n = 99) but not controls (n = 73).

Linear discriminant analysis of methylation in the paediatric discovery cohort accurately predicted disease state in the paediatric replication cohort (94% sensitivity, 100% specificity) based on methylation at two CpG sites.

Conclusion MIR21 emerges as a target for further investigation based on methylation and expression, further strengthened by other positive findings – notably dysregulation in dysplasia and colorectal cancer in IBD, an established role in T-cell differentiation, and protection from DSS-induced fatal colitis by MIR21 knockout. These data demonstrate a novel approach for identifying biological variations associated with germ-line variants identified by GWAS, and demonstrate translational potential for biomarker development and therapeutic target discovery.

Disclosure of Interest None Declared.

OC-004 THIOPURINE INDUCED PANCREATITIS IN INFLAMMATORY BOWEL DISEASE: CLINICAL FEATURES AND GENETIC DETERMINANTS

[1]GA Heap*, [1]A Singh, [1]C Bewshea, [1]MN Weedon, [2]A Cole, [3]T Creed, [4]E Greig, [5]P Irving, [6]J Lindsay, [7]J Mawdsley, [8]Z Mazhar, [9]T Orchard, [10]D Reffitt, [11]A Holden, [1]T Ahmad on behalf of The International IBD Genetics Consortium. *[1]University of Exeter, Exeter, UK; [2]Royal Derby Hospital, Derby, UK; [3]University Hospitals Bristol NHS Foundation Trust, Bristol, UK; [4]Taunton and Somerset NHS Foundation Trust, Taunton, UK; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]Barts and the London NHS Trust, London, UK; [7]West Middlesex University Hospital NHS Trust, Isleworth, UK; [8]Basildon and Thurrock Hospital NHS Trust, Basildon, UK; [9]Imperial College Healthcare NHS, London, UK; [10]Lewisham Healthcare NHS Trust, London, UK; [11]International Serious Adverse Events Consortium, Chicago, USA*

10.1136/gutjnl-2014-307263.4

Introduction Pancreatitis is a rare, but important complication of thiopurine treatment. The aims of this project were to a) characterise the clinical features of thiopurine-induced pancreatitis and b) identify clinical useful genetic markers that might predict development of this serious adverse drug reaction.

Methods Patients were identified and recruited from 172 sites (128 UK). Inclusion criteria included a) onset of acute severe abdominal pain within three months of starting thiopurine treatment b) ≥ two-fold rise in amylase or lipase c) medical opinion implicating thiopurine therapy and drug withdrawal.

Results We recruited 303 patients. Following adjudication 48 cases classified as definite (recurrent pancreatitis on rechallenge) and 195 cases classified as probable (temporal relationship and no other cause for pancreatitis) were taken forward for analyses. 46% of patients were smokers at the time of development of pancreatitis. Patients were treated with a thiopurine for a median of 19 days (95% CI: 17 – 21) before development of pancreatitis. Most cases were mild, with only 5 cases developing single organ dysfunction. 70% of patients were hospitalised with a median length of stay of 4 days (95% CI: 3.2 – 4.8). Neither age ($p = 0.08$), drug dose ($p = 0.11$), BMI ($p = 0.73$) nor smoking ($p = 0.59$) predicted length of hospital stay or severity of pancreatitis in multivariate analysis. Using a control cohort of 4,109 Crohn's disease and ulcerative colitis cases we conducted a genome wide association study with these 239 patients. A significant variant was identified in the Class II MHC region (Odds ratio 3.03, $p = 2.63 \times 10–20$). Dedicated HLA and 1000 genome project imputation refined the association within the MHC (R squared > 0.8 and MAF > 0.01). This association was robust to principle component correction. TPMT genotype was not associated with pancreatitis development ($p = 0.99$). A second cohort of 100 cases and 500 independent disease controls treated with thiopurines but screened for pancreatitis has been generated to confirm the association.

Conclusion We describe the largest clinical characterisation of thiopurine-induced pancreatitis to date and use this cohort to undertake a pharmacogenetics genome wide association study that has