identified a significant association within the Class II MHC region.

Disclosure of Interest None Declared.

OC-005 NOVEL PATHWAY-CENTRIC ANALYSIS REVEALS VARIANTS ASSOCIATED WITH TOXICITY AND RESPONSE TO THIOPURINES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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10.1136/gutjnl-2014-307263.5

Introduction Thiopurines remain the first line immunosuppressants recommended in the management of inflammatory bowel disease (IBD). Unfortunately, 30–40% of patients prescribed these agents develop adverse drug reactions or fail to derive therapeutic benefit. Candidate gene studies have identified loci that explain some of these treatment failures; however a substantial fraction of the genetic contribution remains undefined. Using whole thiopurine pathway analysis the aim of this study was to identify novel loci associated with toxicity and response to azathioprine (AZA)/mercaptopurine (MP) in patients with IBD.

Methods Genomic DNA was extracted from EDTA blood samples of 472 well-characterised IBD patients treated with AZA/MP. We examined exome array data using the Illumina HumanExome Beadchip and restricted the analysis to variants associated with the thiopurine pathway as defined by the KEGG database (100 genes, 639 single nucleotide polymorphisms). Using a case-control design we firstly tested for genetic associations between patients with (n = 154) and without (n = 258) adverse drug reactions, and secondly for polymorphisms differentiating patients with (n = 188) and without (n = 141) response to thiopurines after 12 months of treatment. One year intervention-free clinical response was defined by 3 investigators (PB, PI, JS).

Results Following adjustment for principal components, the minor alleles at *ADK* rs946185 (p = 0.0078; OR 1.675), *SLC28A1* rs2242046 (p = 0.0168; OR 1.600) and *ABCA1* rs4149268 (p = 0.033; OR 1.487) were associated with the development of drug toxicity, whereas the minor alleles at *ABCB5* rs2301641 (p = 0.0170; OR 0.608), *ABCC4* rs4148549 (p = 0.027; OR 0.652) and *AOX1* rs55754655 (p = 0.038; OR 0.549) protected against it. The minor allele at *RRM2* rs1130609 ($p = 3.80 \times 10^{-5}$; OR 0.461), which codes a subunit of ribonucleotide reductase involved in the conversion of thioguanine nucleotide to deoxy-thioguanine nucleotide, and a higher normalised dose of AZA/MP were associated with protection from non-response. Conversely, the minor allele at *ABCA1* rs2230808 (p = 0.008; OR 2.585) and Crohn's disease (p = <0.001; OR 5.007) were associated with non-response to treatment at 12 months.

Conclusion High-throughput sequencing using exome array technology has revealed new loci, other than thiopurine-*S*-methyltransferase, explaining toxicity and response to thiopurines. Validation of these markers in separate cohorts will allow the development of biomarker panels to predict outcomes prior to the start of treatment.

Disclosure of Interest None Declared.

OC-006 SAFETY AND EFFICACY OF LOW DOSE AZATHIOPRINE AND ALLOPURINOL CO-THERAPY: A LARGE SINGLE CENTRE EXPERIENCE

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10.1136/gutjnl-2014-307263.6

Introduction The effectiveness of full dose azathioprine (FDA) for inflammatory bowel disease (IBD) has been questioned in recent scientific literature. A popular strategy to improve its outcomes recommends the use of low dose azathioprine with allopurinol co-therapy (LDAA) for patients profiled as "hypermethylators" (30% of non-responders). The aim of this study was to determine the safety and efficacy of LDAA without using thiopurine metabolite (TM) profiling.

Methods Records of IBD patients treated with LDAA were retrospectively analysed.

Patients who had poor response and/or side-effects to FDA were offered LDAA by all Consultants whilst a single IBD physician also offered LDAA to thiopurine-naïve patients. Azathioprine dose was reduced to 25% of the thiopurine methyl transferase (TPMT) adjusted dose (0.5 mg/kg for wild type and 0.25 mg/kg for heterozygotes) followed by conventional haematological monitoring. Non-adherence was assessed by TM measurements. Full response (FR) was defined as steroid free remission (Harvey Bradshaw index ≤3, Truelove-Witts normal) for greater than 3 months after a 3 month induction period for LDAA.

Results Of 300 LDAA patients, adequate data was available for 295 cases. Group 1 (G1) were treated 1st line (n,105) and Group 2 (G2) were switched from FDA to LDAA (n,190). Overall, for both groups, there were 207 (70%) full responders (FR), 20 partial responders (PR) and 68 non-responders (NR). Full response rate was 78% in G1 and 66% in G2. The commonest indication for switching to LDAA was non-response to FDA (n,118).

Analysis of haematological indices revealed significant changes (p < 0.05) in erythrocyte sedimentation rate, white cell count and platelet count after therapy induction.

Myelotoxicity occurred in 5 patients (all NR, WCC >2 and <3.5) and 12 patients had asymptomatic hepatotoxicity (ALT range: 100–700) which resolved by increasing allopurinol to 200 mg in 9 patients (all FR).

Time on treatment: 208 patients took LDAA for more than twelve months with a median length of therapy of 24 months.

Conclusion Appropriately dosed LDAA therapy delivers a therapeutically effective dose of azathioprine without the

Abstract OC-006 Table 1

	Clinical response (n)			
Indication	**FR**	**PR**	**NR**	**Total**
AZA/6MP Naive (LDAA without FDA exposure)	82	7	16	105
Switched from FDA to LDAA	125	13	52	190
Poor response	81	10	27	
GI intolerance	16	n/a	11	
Hepatotoxicity	7	1	3	
Myelotoxicity	13	2	1	
"Flu-like" symptoms	3	n/a	1	
Other	5	n/a	9	