OTU-006 THE INTERLEUKIN-6 RECEPTOR AS A DRUG TARGET IN INFLAMMATORY BOWEL DISEASE; A MENDELIAN RANDOMISATION STUDY

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Introduction Excessive production of interleukin-6 is associated with active inflammatory bowel disease (IBD).¹ Blockade of the interleukin-6 receptor (IL6R) with a monoclonal antibody (tocilizumab) is licensed for treatment of rheumatoid arthritis.² Clinical trials of IL6R inhibitors in IBD have been small in numbers, with varying efficacy.³ The *IL6R* SNP rs2228145 associates with a similar pattern of effects to tocilizumab therapy (higher soluble IL6R, lower c-reactive protein and fibrinogen), making it an attractive genetic instrument for drug target validation.⁴

Methods We performed a two sample Mendelian randomization study using rs2228145 (a variant associated with impaired IL6R signalling) to evaluate the role of IL6R inhibition for primary prevention of IBD. Gene – soluble IL6R biomarker associations were estimated in 1650 individuals, as a proxy for defective IL6R signalling.⁵ Gene – IBD associations were estimated in 49 833 cases and 61 630 ancestry matched controls from publically available IBD genome wide association study (GWAS) summary statistics.^{6, 7}

Results In a fixed effects meta-analysis of 26 788 cases with Crohn's disease (CD), 23 045 with ulcerative colitis (UC) and 61 630 controls, genetically elevated soluble IL6R was associated with decreased odds of Crohn's disease (CD) (odds ratio (OR) 0.87, 95% CI 0.82–0.92, $p=0.0001463$) and ulcerative colitis (UC) (OR 0.92, 95% CI 0.89–0.99, $p=0.0378$) per 2-fold increment.

Abstract OTU-006 Figure 1 Forest plot of odds ratios (OR) for Crohn's disease (CD) and ulcerative colitis (UC) per doubling of soluble IL6R, used as a proxy for defective IL6R signalling as described elsewhere⁸

Conclusions On the basis of genetic evidence in human beings, defective IL6R signalling seems to protect against the

development of both CD and UC; its inhibition is an attractive drug target suitable for further exploration. Genetic studies in populations could be used more widely to help validate and prioritise novel drug targets or to repurpose existing agents for new therapeutic and preventive uses.

REFERENCES

- Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol.* 2015;**16**(5):448–457. doi:10.1038/ni.3153
- Neurath MF. Current and emerging therapeutic targets for IBD. *Nat Rev Gastroenterol Hepatol.* 2017;**14**(5):269–278. doi:10.1038/nrgastro.2016.208
- Coskun M, Vermeire S, Nielsen OH. Novel Targeted Therapies for Inflammatory Bowel Disease. *Trends Pharmacol Sci.* 2017;**38**(2):127–142. doi:10.1016/j.tips.2016.10.014
- Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes M V, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet.* 2012;**379**(9822):1214–1224. doi:10.1016/S0140-6736(12)60110-X
- IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet.* 2012;**379**(9822):1205–1213. doi:10.1016/S0140-6736(11)61931-4
- Liu JZ, van Sommeren S, Huang H, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* 2015;**47**(9):979–986. doi:10.1038/ng.3359
- de Lange KM, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet.* 2017;**49**(2):256–261. doi:10.1038/ng.3760
- Hartwig FP, Borges MC, Horta BL, Bowden J, Davey Smith G. Inflammatory Biomarkers and Risk of Schizophrenia. *JAMA Psychiatry.* November 2017. doi:10.1001/jamapsychiatry.2017.3191

OTU-007 TREATING ILEOCOLONIC CROHN'S STRICTURES WITH REMOVABLE-SEMS – EFFICACY AND SAFETY, A LARGE SINGLE CENTRE EXPERIENCE

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Introduction Crohn's patients have a greater than 70% lifetime risk of developing ileocolonic anastomotic strictures. (Rieder et al 2013) The usual management of these strictures has been with surgery or endoscopic balloon dilatation (EBD). Both risk complications, with a reported perforation rate of 4% to 11% with EBD. (Morar et al. 2015) Stenting is a new alternative. We present the largest UK series of Crohn's patients undergoing removable self-expanding-metal-stent' (SEMS) and report on the efficacy and safety of this technique.

Methods Crohn's patients were identified following MR Enterography. Ileocolonic fibrostenotic strictures were assessed for stenting within an IBD MDT setting. Strictures were examined at colonoscopy and stenting not attempted if the stricture was inaccessible, or stenting inappropriate based on endoscopist judgement. Strictures ≤ 6 cm lengths were stented, with the Hannaro Diamed 'HRC-20-080-230, 80 mm length' stent under combined endoscopic and fluoroscopic guidance. Stents were removed between 6 and 10 days post insertion. Demographic and disease data was collected. All patients were followed up post-procedure median 70 (Range – 18 to 122) weeks. Stenting success was defined as successful placement when endoscopically attempted. Therapeutic success was defined by whether the stented stricture could be crossed colonoscopically at stent retrieval.

Results Eighteen patients were considered for stenting. Four were not suitable – 2 had inflammatory strictures, 1 had an