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

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Abstract

Background

The Interleukin-6 receptor (IL6R) and its ligand Interleukin-6 (IL6) have an established role in the immune system and in inflammatory processes. Genetic studies of non-synonymous variants in the IL6R confirmed its role in susceptibility to inflammatory bowel diseases. Here we aimed to test the biological plausibility of these associations, and prioritise novel drug targets or to repurpose existing agents for new therapeutic and preventive uses.

Methods

We performed a two sample Mendelian randomization study using rs2228145 (a variant associated with defective 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. Gene – IBD associations were estimated in 49833 cases and 61630 controls, genetically elevated soluble IL6R was associated 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.

Results

In a fixed effects meta-analysis of 26788 cases with active inflammatory bowel disease (IBD), blockade of the interleukin-6 receptor (IL6R) with a monoclonal antibody (tocilizumab) is licensed for treatment of rheumatoid arthritis. Clinical trials of IL6R inhibitors in IBD have been small in numbers, with varying efficacy. 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.

Conclusions

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


Abstract OTU-007 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 elsewhere.

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 under- going 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 ≤0.5 cm lengths were stented, with the Hannar-Diagmed ‘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...
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inaccessible stricture (treated with balloon dilatation) and 1 had no apparent luminal stenosis. Fifteen SEMS were placed for 14 patients. Stented patients had median 1 (range 0 to 6) prior surgery. Eleven patients had had prior right hemicolectomy, while 3 had ileal resection only. Attempted SEMS placement was successful in 100% of cases but could not be attempted in one case. Three adverse events were noted. There were 2 patients admitted for abdominal pain, with pain resolving upon stent removal. There was a single asymptomatic stent migration. There were no bleeding events, perforations or any need for emergency surgery. On extended follow up (n=11) 9 of 11 patients reported symptom resolution or improvement. To date none of the patients (n=14) has required surgical intervention during follow up, with a single patient electing for re-stenting. (Ref. Figure 1)

Conclusions In this series, removable SEMS therapy for Crohn’s ileocolonic strictures was effective both endoscopically and in relieving symptoms. The absence of perforations appears favourable when compared to rates reported with endoscopic balloon dilatation though a larger controlled study would be needed to test this finding. Observed long term benefit, a low re-intervention rate and no need for surgery during follow up in this series is notable. Safety and comparative efficacy against EBD should be further established with Randomised Control Trial evidence.

Abstract OTU-007 Figure 1

OTU-008 GROWTH IN PARTICIPATION, REGISTRATIONS AND DATA MATURITY IN THE UK IBD REGISTRY: FOCUS ON BIOLOGICS

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Introduction The UK IBD Registry (IBD-R) provides a standardised dataset and alternative methods for local teams to record structured electronic data in routine care. The infrastructure enables collection of data for local use and upload of anonymized data centrally (each quarter). Registry participation allows sites to demonstrate engagement with national audit (e.g. Biologics Audit, listed on the NHS Quality Accounts) and access to centrally-developed analytics and reporting.

Methods To evaluate growth in establishment of local biologics registers using the IBD-R, we analysed three uploads of data (March, June and Sept 2017) with a focus on key data items required for producing site-level reports for patients treated with these agents (from a basic to more granular-level detail, using the ‘biologics events’ dataset). We generated Quarterly Reports and distributed to centres, seeking feedback to inform future iterations.

Results Participating centres grew by 59% (32 to 51) and number of sites contributing biologics events more than doubled (16 to 37). Total registered patients in the IBD-R increased from 24 633 to 31 613.

Biologics Events For adults with CD, submitted initiation events increased >6 fold (472 to 3126 patients), post-induction review ~3 fold (709 to 2,022) and 12 month review >19 fold (22 to 437). Agents used for adult CD [UC]: Remicade 1423 [450]; Humira 1675 [311]; Inflectra 345 [236]; Remsima 398 [225]; Vedolizumab 186 [201]; Ustekinumab 16 [0]. Data completeness varied by item, e.g. recording of ‘naïve’ status (y or n) was static at ~50%; categorization of clinical indication consistently high at >80% of cases.

Outcome measures The number of clinical indication consistently high at >80% of cases. Disease activity indices (HBI or SCCAI) remained static at around 10%. The next upload (Feb 2018) contains almost 40 000 records from 63 sites and confirms continuing growth (analysis in progress).

Conclusions There has been significant increase in participation and in the breadth and depth of data being submitted to the UK IBD-R, particularly for biological therapies. Patterns of outcome data collection suggest clinical teams favour simple global outcome measures to formal activity indices – likely reflecting the added burden of administering and recording the data. However, the feasibility of site-level reporting to support local biologics registries is now established.

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OTU-009 MODELLING CASELOAD STANDARDS FOR IBD SPECIALIST NURSES IN THE UK

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Introduction The national standards for IBD care defined the numbers of nurse specialists required as 1.5 FTE per 2 50 000 population. The aim was to publish a new, robust, validated national standard and caseload.

Methods A consensus workshop of 15 IBD nurse specialists from across the UK met to check assumptions regarding workload and activity of this group. A 24-item questionnaire, exploring demographic data, caseload, workload and experience was developed. This was distributed through the RCN IBD Nursing Network. Data was modelled using descriptive statistics and pattern recognition.

Results 164 responses were received (55% response rate). 76% were from England. Responses were received from all four countries of the U.K. Most respondents covered a single (60%) or two (25%) hospital sites. 38% of respondents had less than 3 years experience working with IBD patients. 62% having four years plus experience. 32% had over ten years experience. 90% of the responding CNS were working solely in IBD. 82% reported spending 80% to 100% of their time on IBD. 51% worked with adult and transition patients. 72%