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Original research

Neutralising autoantibodies against IL-10 and HLA-DRB1*01:03 in paediatric patients with inflammatory bowel disease

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ABSTRACT

Background Interleukin-10 (IL-10) is an essential regulator of intestinal immune homeostasis. Neutralising autoantibodies against IL-10 (anti-IL-10) have been identified in children and also adult patients with IBD. Positivity for anti-IL-10 autoantibodies was associated with carriage of HLA-DRB1*01:03 allele.

Objective To determine the prevalence of anti-IL-10 in paediatric IBD and assess the associated clinical phenotype.

Design We conducted a cross-sectional multicentre study across paediatric IBD cohorts from four countries. Anti-IL-10 antibodies were investigated in serum and plasma from paediatric patients with IBD (mean age of IBD onset 11.2±3.8 years). IL-10-neutralisation capacity was confirmed by functional IL-10 reporter assay, competitive ELISA and cytokine release assay. Clinical data were analysed to evaluate disease phenotype and treatment outcomes, with comparison with matched controls. HLA-DRB1*01:03 analysis was performed.

Results Anti-IL-10 positivity was identified in 26/1045 paediatric patients with IBD (2.5%) (Crohn's disease n=6, UC n=19, IBD unclassified n=1; IBD diagnosis age of 13±3 years). Anti-IL-10 autoantibodies were of the IgG class and amplified pro-inflammatory cytokine responses in vitro. Anti-IL-10-positive patients exhibited more severe disease compared with matched controls, including an increased prevalence of difficult-to-treat disease (23% vs 6%, p=0.03), higher rate of acute severe UC (26% vs 6%; p=0.038) and higher rates of colectomy (27% vs 6%, p=0.01). Eighty percent (16/20) of anti-IL-10-positive patients with available HLA data carried the HLA-DRB1*01:03 allele, compared with 1.5% in the anti-IL-10-negative group.

Conclusion Anti-IL-10 autoantibodies are present in a subgroup of paediatric patients with IBD and are associated with difficult-to-treat disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Interleukin-10 (IL-10) is an essential cytokine for intestinal immune homeostasis.
⇒ Anti-IL-10 neutralising autoantibodies were initially identified in two children with very early-onset IBD and were subsequently detected in a small fraction of patients with adult-onset and paediatric-onset IBD.
⇒ Positivity for anti-IL-10 autoantibodies was associated with carriage of the HLA-DRB1*01:03 allele.

INTRODUCTION

The incidence of IBD is increasing worldwide, suggesting that in addition to genetic susceptibility, environmental and acquired factors contribute to disease pathogenesis.[1 2] Similar to adult IBD, an increase in the incidence of paediatric-onset IBD has been observed across multiple regions during recent decades.[3] Paediatric-onset IBD is a heterogeneous disease group defined by disease onset

WHAT THIS STUDY ADDS

⇒ This international multicentre study identified 26 patients (2.5%) positive for anti-IL-10 autoantibodies among 1045 paediatric individuals with IBD.
⇒ Most patients with anti-IL-10 disease presented as adolescent-onset IBD.
⇒ The neutralising IgG class anti-IL-10 autoantibodies amplify inflammatory cytokine responses in vitro.
⇒ In a high proportion of patients positive for anti-IL-10 autoantibodies, multiple mechanisms of advanced therapies failed, and patients underwent colectomy, indicating a severe, therapy-refractory disease course.
⇒ The strong association between anti-IL-10 positivity and HLA-DRB1*01:03 allele carriage was validated in this paediatric study (80% of anti-IL-10-positive patients carrying the DRB1*01:03 allele).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Neutralising anti-IL-10 autoantibodies affect a small but clinically meaningful proportion of paediatric patients with IBD (2.5%).
⇒ This autoimmune acquired defect in IL-10 signalling has potential therapeutic implications and may support targeted genetic and functional screening, with the potential to guide personalised treatment strategies.

from infancy to adolescence.[1 4] Paediatric-onset IBD can have significant consequences for patients as active disease affects growth, pubertal development, bone health and education.[1 4] At the youngest end of this spectrum, infantile-onset IBD, defined as disease presenting before 2 years of age, represents a biologically informative subgroup enriched for monogenic forms of IBD, where disease is driven by disruption of core immune regulatory pathways, host defence mechanisms or barrier dysfunction.[4 5] Recent monogenic IBD taxonomies and consensus guidelines have defined a gene and pathway-based mechanistic concept of rare subforms of IBD, rather than relying solely on conventional Crohn's disease (CD) or ulcerative colitis (UC) labels.[6 7]

Interleukin-10 (IL-10) is a central anti-inflammatory cytokine that controls intestinal immune responses to luminal microbes.[8] Human genetics provides strong evidence for the non-redundant role of this pathway in gut homeostasis.[8–11] Biallelic loss-of-function variants in *IL10*, *IL10RA* or *IL10RB* cause severe infantile-onset colitis, often with perianal or fistulising disease.[9–11] The clinical response to allogeneic haematopoietic stem-cell transplantation confirms that defective IL-10 signalling in haematopoietic cells is the disease-driving mechanism.[9 10]

Similarly to genetic variants, acquired disruption of cytokine pathways can occur through neutralising anti-cytokine autoantibodies. Anti-IL-10 autoantibodies represent an acquired defect of a central immune regulatory pathway. We previously described two children with neutralising anti-IL-10 autoantibodies and very early-onset IBD.[12] One child presented with severe colitis closely resembling inherited IL-10 pathway deficiency and improved following rituximab-mediated B-cell depletion, with disappearance of the autoantibody, whereas the second exhibited a milder clinical course.[12] Subsequently, we identified anti-IL-10 autoantibodies in 3.5% of patients with IBD (mean age of IBD diagnosis at 32±13 years) and demonstrated a strong association between anti-IL-10 positivity and carriage of the HLA-DRB1*01:03 allele (OR >24).[13] This is particularly relevant because HLA-DRB1*01:03 is the strongest HLA marker associated with IBD.[14–16] Most recently, an independent study identified neutralising anti-IL-10 autoantibodies in five of 239 patients with paediatric-onset IBD (2.1%).[17] The prevalence of IL-10 autoantibodies across geographically diverse paediatric cohorts needs to be shown, and the association between IL-10 autoantibodies and HLA-DRB1*01:03 and clinical outcomes requires validation studies.

We investigated the prevalence of neutralising anti-IL-10 autoantibodies across international paediatric IBD cohorts and examined their association with clinical phenotype and disease severity. We assessed whether acquired disruption of IL-10 signalling due to neutralisation of IL-10 by autoantibodies identifies a distinct subgroup of paediatric IBD with mechanistic and potentially therapeutic significance. We assessed the carriage rate of HLA-DRB1*01:03 allele in a subset of paediatric patients with IBD with and without anti-IL-10 autoantibodies.

METHODS

Design

We performed a cross-sectional multicentre study to determine the seroprevalence of neutralising anti-IL-10 autoantibodies in paediatric IBD. Samples were assessed using four complementary assays of IL-10 binding and neutralisation (IL-10 bead assay, IL-10 reporter assay, competitive ELISA and cytokine secretion assay), followed by detailed clinical phenotyping (figure 1A).

Patient cohorts and ethics

We included patients with paediatric-onset IBD, defined as diagnosis below 18 years of age. Patients with confirmed or suspected monogenic IBD based on prior genetic testing were not included. Samples were collected from four countries, including five paediatric IBD cohorts (serum: UK IBD BioResource (IBD-BR), n=330; Boston, n=94; Jerusalem/Petah Tikva, n=62; Toronto, n=76; lithium-heparin plasma: Southampton, n=483) (figure 1B). These cohorts included children with CD, UC and IBD-unclassified (IBDu).

Patient and public involvement

Parent representatives were involved in the establishment of the PIBD BioResource and served on the Investigator Steering Group.

IL-10 reporter assay and competitive ELISA

Serum and lithium-heparin plasma samples were screened using a HEK-Blue IL-10 reporter assay (InvivoGen, #hkb-IL-10), with confirmatory testing by competitive ELISA.

In the HEK-Blue assay, IL-10-induced STAT3-dependent reporter activity was measured following stimulation with recombinant human IL-10 in the presence or absence of patient serum or lithium-heparin plasma. The assay quantifies downstream IL-10 receptor signalling, and reduced reporter activity in the presence of patient serum or lithium heparin plasma indicates inhibition of IL-10 signalling consistent with functional neutralisation by anti-IL-10 autoantibodies (online supplemental information).

In the competitive ELISA, recombinant human IL-10 was pre-incubated with patient serum or plasma to allow antibody binding and epitope masking (online supplemental information). Residual detectable IL-10 was quantified using a commercial capture ELISA. Reduced signal indicated functional neutralisation of IL-10. Assay performance was validated using

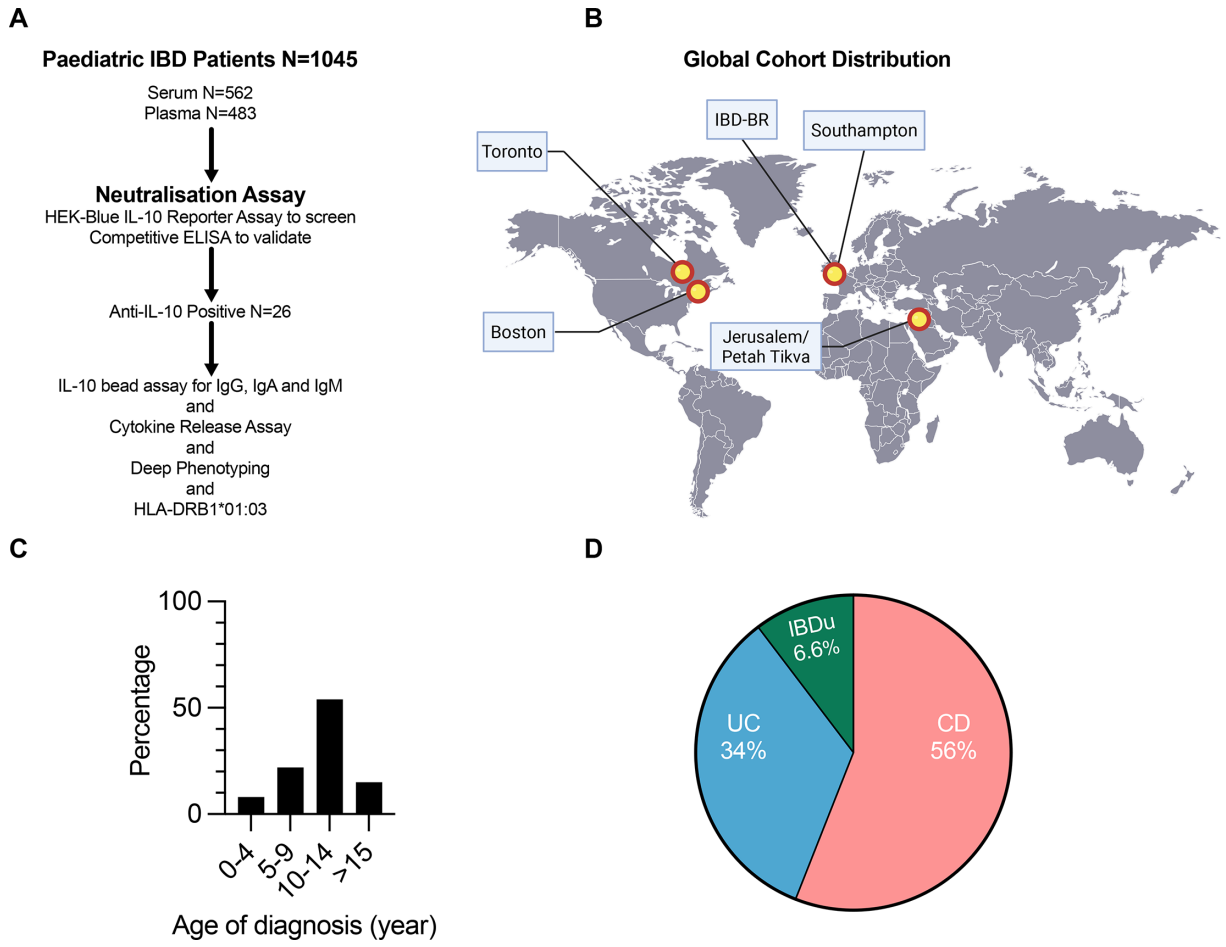

Figure 1 Overview of the international paediatric IBD study cohort. (A) Screening of paediatric patient serum and plasma to detect anti-interleukin-10 (IL-10) autoantibodies via HEK-Blue IL-10 reporter assay and competitive ELISA followed by validation via cytokine release assay. (B) Geographical distribution of the paediatric IBD cohorts. (C) Age at IBD diagnosis of the study population. (D) Proportion of Crohn's disease (CD), UC and IBD-unclassified (IBDu) in the study population. IBD-BR, IBD BioResource.

recombinant IL-10 titration and IL-10-specific monoclonal blocking antibodies.

Anti-IL-10 positivity was defined based on functional evidence of IL-10 neutralisation in the HEK-Blue IL-10 reporter assay as well as competitive ELISA. A prespecified threshold of <72% detectable exogenous recombinant IL-10 was used to define positivity. This threshold was determined in prior analysis based on 1006 paediatric and adult individuals without IBD.[13]

Cytokine release assay

As previously described,[12 13] serum or lithium-heparin plasma samples were investigated by cytokine release assay. This assay measured neutralisation of endogenous IL-10 produced by peripheral blood mononuclear cell (PBMC)-based that were stimulated by lipopolysaccharide (LPS) stimulation. After 20 hours, cytokine levels in the culture supernatants were measured using a bead-based multiplex assay (#740809, BioLegend; online supplemental information).

IL-10 bead assay

To determine the predominant immunoglobulin isotype of anti-IL-10 autoantibodies, a bead-based flow cytometry assay was performed using IL-10-coupled magnetic beads (online supplemental information).

Anti-integrin αvβ6 antibody ELISA

Anti-integrin αvβ6 antibodies (anti-αvβ6) were measured in serum and lithium-heparin plasma samples from anti-IL-10-positive patients (n=26) and anti-IL-10-negative IBD controls (n=23) using a commercial ELISA kit (MBL International, Woburn, Massachusetts, USA; #7670E) according to the manufacturer's protocol. This ELISA has been used and validated previously.[18 19] The cut-off of 1.7 U/mL has been suggested based on the company protocol and previous investigation.[18] Comparisons were performed between IBD subgroups and between patients with anti-IL-10-positive and anti-IL-10-negative IBD.

Clinical phenotyping and outcome definitions

The clinical phenotypic analysis was conducted in two parts: a baseline demographic description of the entire cohort and a subsequent case-control deep-phenotype analysis of the anti-IL-10-positive patients and matched subgroup. For the case-control analysis, anti-IL-10-negative controls were matched to positive patients in a 3:1 ratio per centre (2:1 ratio if inadequate matches found). Controls were selected from the corresponding clinical sites and matched based on sex, IBD subtype and age at diagnosis (±1 year).

Basic demographics were obtained for all patients and included age at IBD diagnosis, age at blood sample collection, sex and IBD subtype. Deep phenotyping was performed for all

anti-IL-10-positive patients and a group of matched anti-IL-10-negative patients through structured healthcare record review at each site. Variables collected included the Paris classification,[20] changes of diagnosis, family history of IBD, extraintestinal manifestations, treatment history, immunomodulators, advanced therapy, colectomy and follow-up duration.

Advanced therapy was defined as treatment with biologic agents (eg, antitumour necrosis factor (anti-TNF), vedolizumab, ustekinumab) and/or small-molecule advanced therapy (Janus kinase inhibitor). For IBD-related operation, we primarily collected colectomy (partial, total or proctocolectomy) and other surgical procedures (fistula-related procedures, ileostomy formation and pouch creation).

Acute severe UC (ASUC) was recorded based on clinical documentation consistent with paediatric UC activity index criteria, including hospitalisation for a UC flare, acute disease requiring urgent surgical intervention or severe inflammatory activity with markedly elevated C reactive protein prompting treatment escalation. This definition was aligned with paediatric acute severe colitis consensus guidance.[21]

Difficult-to-treat (D2T) IBD was defined according to the International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) consensus criteria,[22] describing patients with persistent disease activity despite sequential use of advanced therapies (failure was defined by non-responsiveness to more than two biologics or small molecules with different mechanisms of action) or intolerance to available therapeutic options.

HLA typing

A subset of patients from the IBD-BR cohort (n=71) underwent genotyping with HLA imputation. Genotyping was performed using the Affymetrix Axiom UK Biobank Array, and HLA alleles were imputed using HLA Imputation using attribute BAGging (HIBAG)[23] with prefitted models specific to the corresponding array platform.

In addition, high-resolution long-range HLA class II sequencing was performed in 16 patients with positive anti-IL-10 autoantibody status in an ISO-accredited laboratory in Oxford. Clinical-grade HLA typing was conducted using next-generation sequencing (NGS) with the AllType FASTplex NGS kit (Thermo Fisher Scientific).

Statistical analysis

Continuous variables are presented as mean (SD) or median (IQR), as appropriate, and categorical variables as n (%) with 95% CIs. For between-group comparisons of continuous variables, the Mann-Whitney U test was applied. For comparisons involving more than two groups, the Kruskal-Wallis test followed by Dunn's multiple comparisons correction was used. Where multiple testing was performed, p values were adjusted to control the false discovery rate using the two-stage step-up procedure of Benjamini, Krieger and Yekutieli. For categorical variables, χ^2 test or Fisher's exact test were used as appropriate. ORs and corresponding 95% CIs were calculated to assess the association between anti-IL-10 autoantibody positivity and HLA-DRB1*01:03 carriage. Kaplan-Meier analysis with log-rank test and Cox proportional hazards analysis were used to evaluate longitudinal survival outcomes. All tests were two-sided and p value <0.05 was considered statistically significant. Analyses and visualisation were performed using GraphPad Prism and BioRender.

RESULTS

Detection of anti-IL-10 autoantibodies in paediatric IBD

We analysed 1045 paediatric IBD samples obtained from five international cohorts, comprising 562 serum samples and 483 lithium-heparin plasma samples (figure 1A,B and online supplemental figure S3). The mean age at IBD diagnosis was 11.2±3.8 years (median 12 (IQR 9.2, 14.1) years; range 0–18 years) (figure 1C). The whole cohort consisted of 585 patients with CD, 352 with UC and 108 with IBDu (figure 1D).

Based on positive cellular IL-10 reporter assay and subsequent positive competitive ELISA, 26 of 1045 paediatric IBD samples demonstrated neutralising anti-IL-10 activity, corresponding to a seroprevalence of 2.5% (95% CI 1.7% to 3.6%). IL-10-neutralisation-positive samples were detected in four cohorts, including Southampton (16/483, 3.3%), UK IBD-BR (7/330, 2.1%), Boston (2/94, 2.1%) and Toronto (1/76, 1.3%), and were not detected in the cohort from Israel (0/62) (figure 2A–C).

Using a bead-based assay, we demonstrated that the IL-10 neutralising activity detected by the reporter assay and the competitive ELISA was significantly associated with high levels of anti-IL-10 IgG, supporting IgG as the predominant isotype linked to IL-10 neutralising activity. Anti-IL-10 IgA binding did not differ significantly between groups. Anti-IL-10 IgM binding was significantly lower in patients with anti-IL-10-positive IBD than in patients with anti-IL-10-negative IBD (figure 2D–F). These findings indicated that neutralising IgG autoantibodies against recombinant human IL-10 can be observed across several geographically distinct paediatric IBD cohorts.

Neutralising IL-10 activity towards endogenous IL-10 amplifies pro-inflammatory responses

To assess the effect of anti-IL-10 autoantibodies on endogenous human IL-10, PBMCs from a healthy donor were stimulated with LPS in the presence or absence of anti-IL-10-positive serum or plasma samples and cytokines were measured in culture supernatants (figure 3). In control experiments, a monoclonal neutralising IL-10 antibody reduced immunoreactive IL-10 and increased pro-inflammatory cytokines (particularly IL-23, IL-6 and TNF) (figure 3).

Samples from paediatric patients with anti-IL-10 activity reduced detectable IL-10 following LPS stimulation, consistent with the neutralisation of endogenously produced IL-10, and this was associated with a marked increase in pro-inflammatory cytokine secretion (particularly IL-23, IL-6, TNF and IL-1β) (figure 3 and online supplemental figure S1). This effect occurred despite low baseline levels of these proinflammatory cytokines in the serum or lithium-heparin plasma samples (online supplemental figure S1B). By contrast, other cytokines, including IL-8, interferon-α2, monocyte chemoattractant protein-1 were not significantly increased (online supplemental figure S1A). These findings suggest that patient samples with high anti-IL-10 activity selectively amplify a subset of pro-inflammatory cytokine responses.

To assess the presence of another colonic IBD-associated serological marker in patients with anti-IL-10 autoantibodies, we measured anti-αvβ6 integrin antibodies in samples from patients with anti-IL-10-positive IBD and anti-IL-10-negative IBD controls. As expected, anti-αvβ6 concentrations were significantly higher in patients with UC compared with CD phenotype (p=0.0009; online supplemental figure S2). However, anti-αvβ6 concentrations were not significantly different between patients with anti-IL-10-positive IBD and patients with anti-IL-10-negative IBD (p=0.0898), nor between patients with

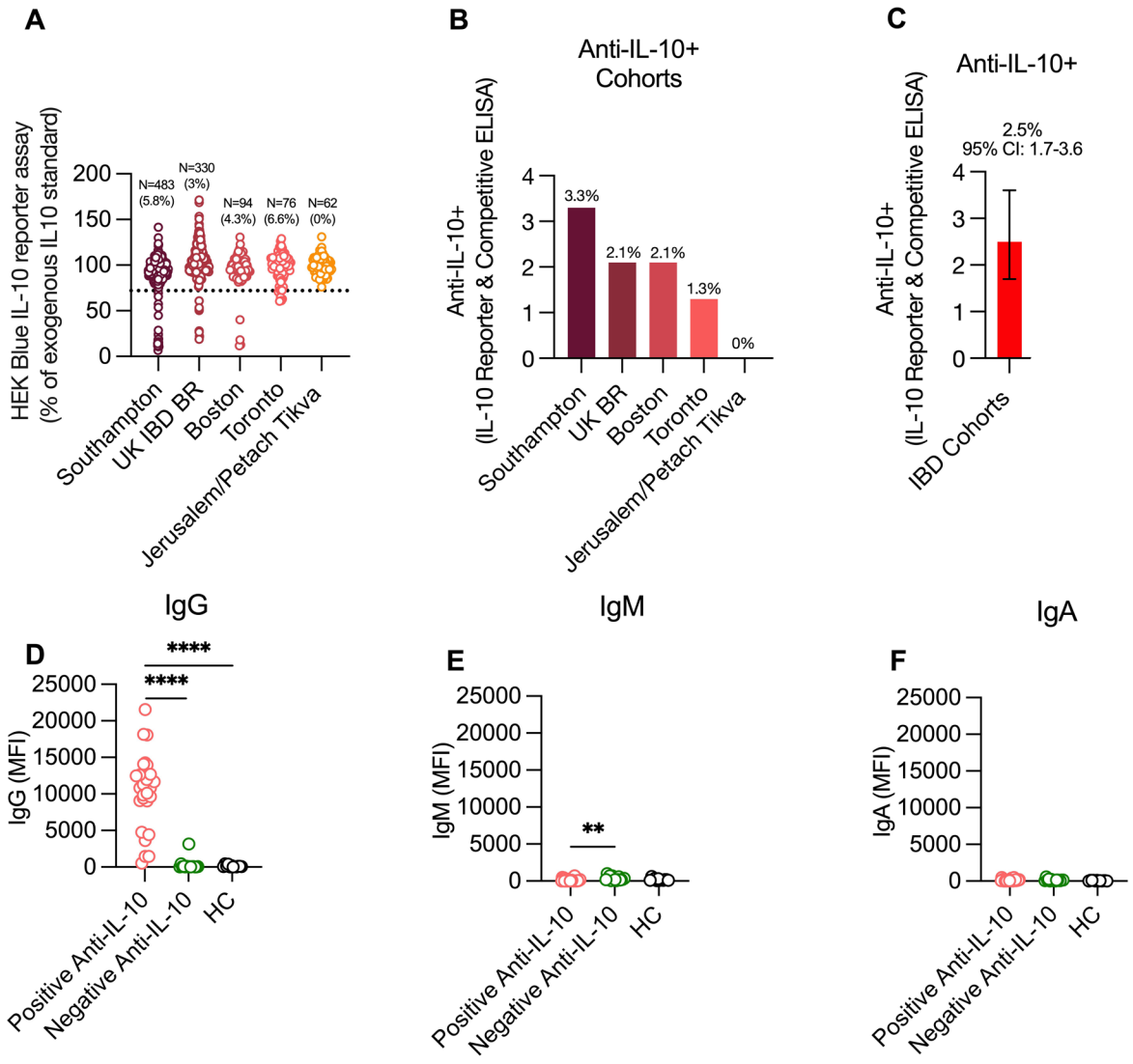

Figure 2 Neutralising anti-interleukin-10 (IL-10) autoantibodies in paediatric IBD. (A) Distribution of anti-IL-10 assay results across paediatric cohorts. Results are expressed as percentage of exogenous IL-10 standard. Each symbol represents one sample; cohort size and assay-related positivity rate are shown above each group. The dotted line marks the positivity threshold. (B) Percentage of anti-IL-10-positive samples in each cohort. (C) Overall frequency of anti-IL-10 positivity in paediatric patients with IBD, with 95% CI. (D–F) Immunoglobulin isotype analysis of anti-IL-10 autoantibodies using an IL-10 bead-based assay. Binding of (D) IgG, (E) IgM and (F) IgA to IL-10-coated beads is shown for patients with positive anti-IL-10 IBD, patients with negative anti-IL-10 IBD and non-IBD healthy controls (HC). Statistical comparisons were performed using the Kruskal-Wallis test followed by Dunn's multiple comparisons correction. **P<0.01, ****p<0.0001. MFI, median fluorescence intensity; UK-BR, UK IBD BioResource.

anti-IL-10-positive UC and patients with anti-IL-10-negative UC (p=0.4890; online supplemental figure S2). Among patients with CD, anti-αvβ6 concentrations were higher in the anti-IL-10-positive group than the anti-IL-10-negative group (p=0.0293), likely reflecting the enrichment of colonic phenotype in the anti-IL-10-positive patients.

Anti-IL-10 autoantibodies are associated with a clinically distinct subgroup of paediatric IBD

Regarding baseline demographics, the anti-IL-10-positive group (n=26) showed a higher prevalence of female sex (65% vs 39%, p=0.0143) and UC diagnosis (73% vs 33%) compared with the anti-IL-10-negative cohort (n=1019) (online supplemental table S1).

In the anti-IL-10-positive group (n=26), there were nine male and 17 female (35% vs 65%) participants. The age of IBD diagnosis was 13±2.7 years (median 13.1; IQR 11.3, 15.5), while the age of blood sampling was 14.6±2.3 years (median 15.1; IQR 12.8, 16.2). Three patients with anti-IL-10 were diagnosed before 10 years of age (Paris A1a) and none had very early-onset disease (figure 4A). The average follow-up time from IBD diagnosis was 6.5±4.7 years (median 5; IQR 3.8, 8.3). The initial IBD diagnoses were UC (73%), CD (23%) and IBDu (4%). Patients exhibited a predominantly colonic disease phenotype, including all the patients with CD. Patients with CD and anti-IL-10 autoantibodies had colonic involvement (L2 or L3), and 50% had concurrent upper GI tract involvement (L4), although the colonic disease was predominant. Among patients with UC

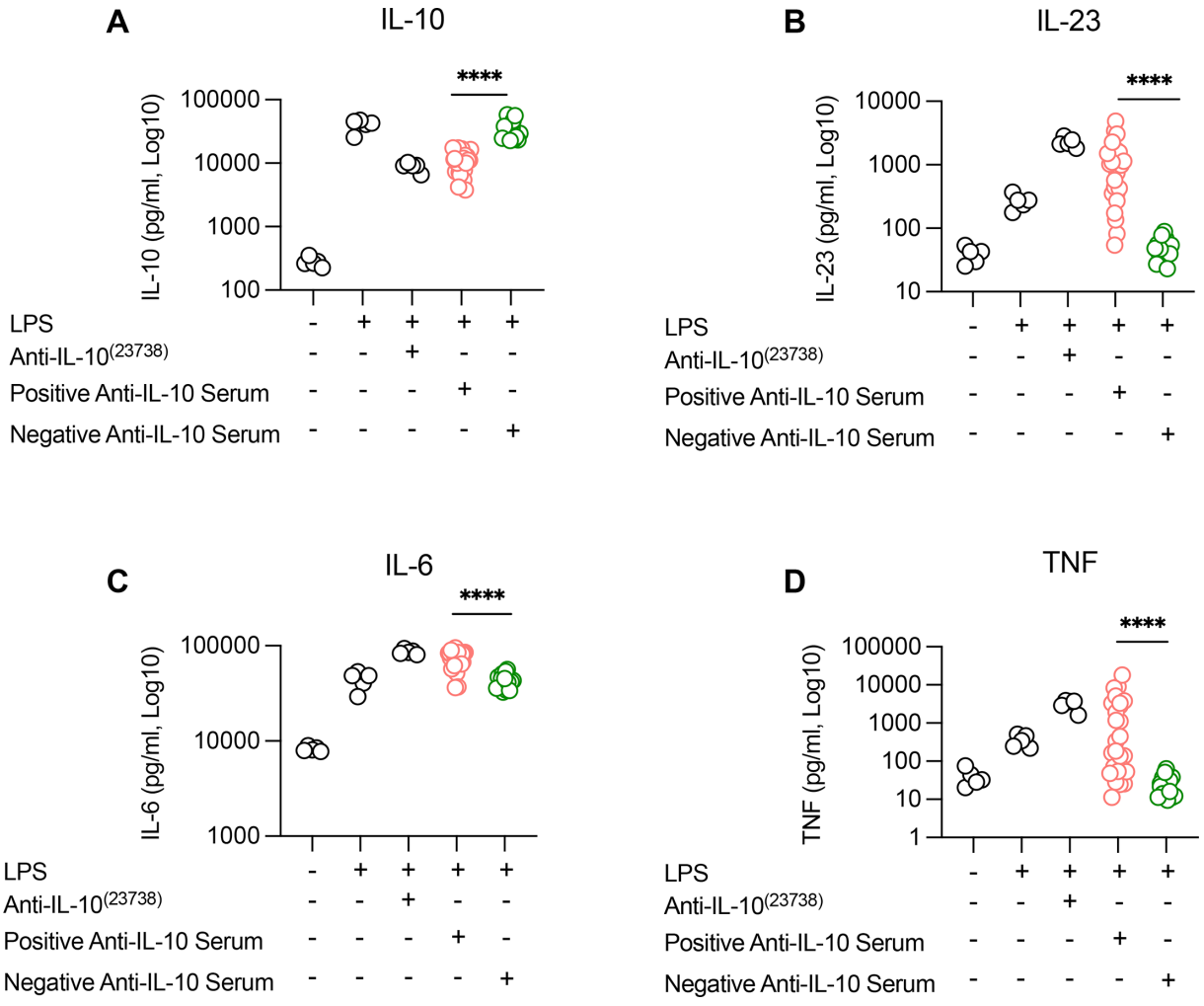

Figure 3 Inflammatory capacity of patient sera with anti-interleukin-10 (IL-10) autoantibodies. Cytokine release assay of peripheral blood mononuclear cells from a healthy donor following lipopolysaccharide (LPS) stimulation in the presence or absence of anti-IL-10-positive serum. Cytokine levels were quantified using a cytokine bead assay. Monoclonal IL-10 neutralising antibody (clone 23738) was included as control. (A) IL-10, (B) IL-23, (C) IL-6, (D) tumour necrosis factor (TNF). Statistical analysis was performed using multiple Mann-Whitney U tests. ****P<0.0001.

and anti-IL-10 autoantibodies, 59% presented with extensive colitis (E3 or E4) (figure 4B).

Anti-IL-10-positive patients had different clinical course compared with matched controls

To investigate the impact of anti-IL-10 autoantibodies on clinical pattern, we compared anti-IL-10-positive patients (n=26) with a matched control group (n=66) of anti-IL-10-negative patients (table 1). The matching of sex, diagnosis (UC and CD subtype) and age were statistically confirmed. The follow-up durations of the two groups were similar (p=0.1374). Additionally, the two groups were not significantly different in terms of family history of IBD or extraintestinal manifestations.

While the two groups were matched by IBD subtype, 31% of the patients in the control group presented with L1 (terminal ileal and/or limited caecal disease) or exclusive L4 (isolated upper tract disease) disease, whereas the anti-IL-10-positive group presented entirely with colonic involvement.

During follow-up, anti-IL-10-positive patients with UC or IBDu encountered a higher incidence of ASUC compared with the negative group (25% vs 6%, p=0.0376). Furthermore, three of the patients with initial UC (16%) developed subsequent CD-like features: two of them changed diagnosis from UC to CD (one with enterocutaneous fistula), while the other remained with a diagnosis of UC, but had a history of presacral abscess formation with associated fistula.

Medical management showed a trend towards higher medical utilisation in the anti-IL-10-positive group, including immunomodulators (85% vs 62%, p=0.0466) and advanced therapies (81% vs 65%, p=0.2084) (table 1 and figure 4C). The anti-IL-10-positive group had a greater proportion of patients requiring three or more advanced therapies (38% vs 18%, p=0.0570), reaching borderline statistical significance. Within the positive group, types of advanced therapy included anti-TNF agents (n=20), vedolizumab (n=12), ustekinumab (n=5), risankizumab (n=2) and the small molecule upadacitinib (n=4). The median time from IBD diagnosis to the initiation of the first advanced therapy was 1 year for both groups. The longitudinal trajectory to advanced therapy confirmed a trend towards more progressive in the positive group (log-rank p=0.1340, HR 1.44; 95% CI 0.85 to 2.44) (figure 4D).

Based on the IOIBD consensus criteria, there were significantly more patients with D2T criteria (ie, who failed at least two advanced therapies with different mechanisms of action) in the anti-IL-10-positive group compared with the controls (23%, 6%, OR 4.7, 95% CI 1.3 to 15.5, p=0.0277).

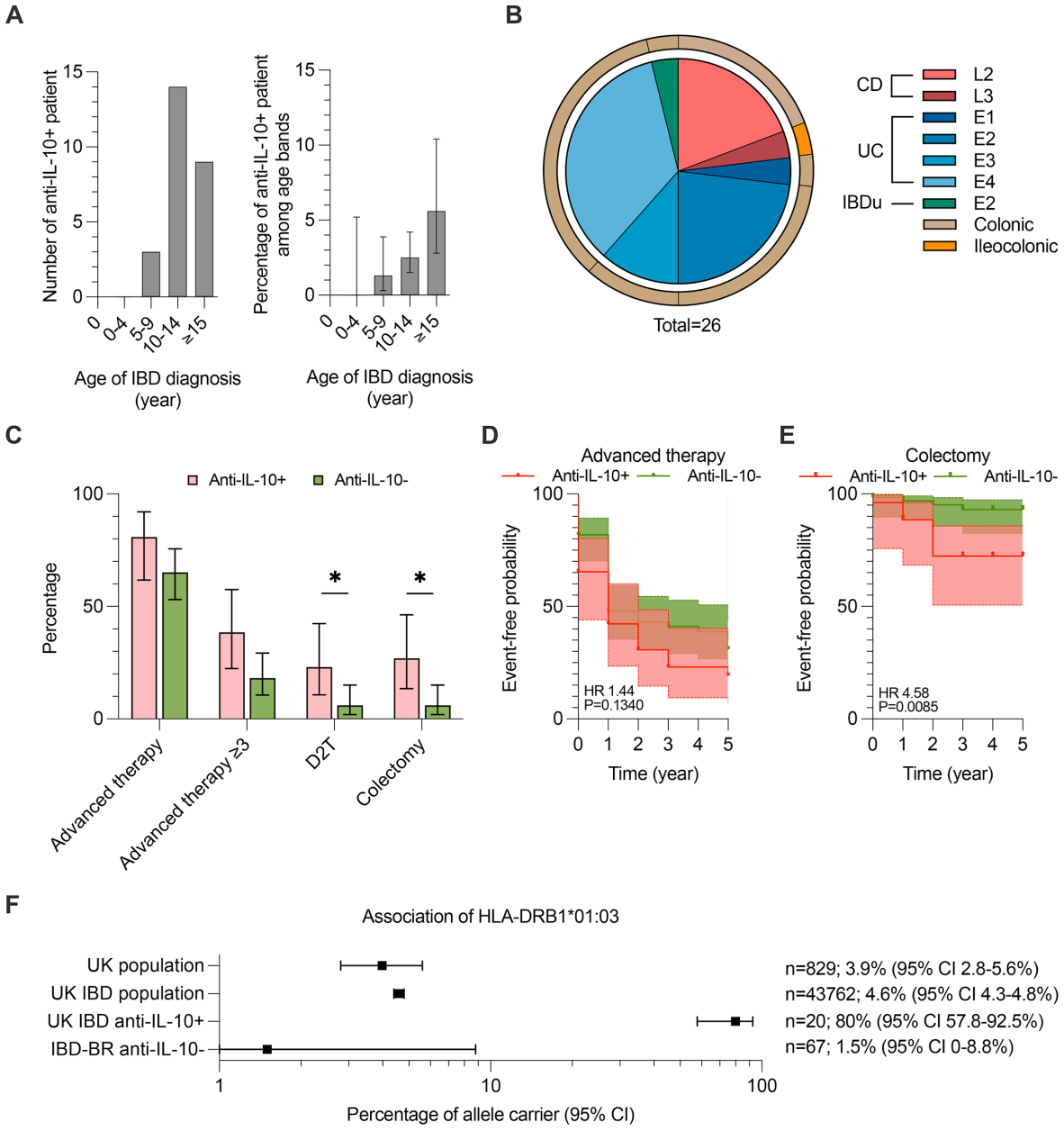

Figure 4 Clinical phenotype, therapeutic trajectory and HLA association of anti-interleukin-10 (IL-10)-positive paediatric patients with IBD. (A) Age at IBD diagnosis in anti-IL-10-positive patients (left) and the percentage (with 95% CI) of anti-IL-10-positive patients among all screened patients across different age bands (right). (B) Disease subtypes (central circle) and colonic involvement (outer ring) at IBD diagnosis in anti-IL-10-positive patients, stratified by Paris IBD classification. (C) Percentages (with 95% CI) of patients receiving advanced therapy, ≥3 types of advanced therapies, difficult-to-treat (D2T) status and colectomy. (D) Event-free probability (with 95% CI) of patients requiring advanced therapy until 5-year follow-up after IBD diagnosis. (E) Event-free probability (95% CI) of patients requiring colectomy until 5-year follow-up after IBD diagnosis. (F) Percentage (with 95% CI) of persons with HLA-DRB1*01:03 carrier status among general population and IBD groups in the UK; UK population is the summary of three English population studies (England-Northwest, England-Bedfordshire and England-Pop6) derived from allele frequency net database (https://allelefrequencies.net); UK IBD population is derived from cohort study (Zhang *et al*[16]); UK IBD anti-IL-10 group comprises HLA typing data available for anti-IL-10-positive patients identified from the IBD BioResource (IBD-BR) cohort (n=4) and the Southampton cohort (n=16). Statistical analysis was performed using Mann-Whitney U tests. *P<0.05; n represents number of studied individuals in each group. CD, Crohn's disease; IBDu, IBD-unclassified.

Colectomy was also more frequent in anti-IL-10-positive patients compared with the anti-IL-10-negative patients. Seven (27%, six UC and one CD, four females) in the anti-IL-10-positive and four patients in the anti-IL-10-negative group (6%, one UC and three CD, four females) underwent colectomy (OR 5.7, 95% CI 1.5 to 18.5, p=0.0103) with median time from IBD diagnosis to operation of 2 and 1 year, respectively (online supplemental table S2). The longitudinal progression was also worse in the anti-IL-10-positive group (log-rank p=0.0085, HR 4.58; 95% CI 1.34 to 15.7) (figure 4E). Pouch creation was performed in three patients in the positive group: one patient developed pouchitis, and another had presacral abscess with fistula noted 6 years after the pouch creation.

Table 1 Deep phenotypic comparison between anti-IL-10-positive and anti-IL-10-negative group

	Anti-IL-10 positive (n=26)	Anti-IL-10 negative (n=66)	OR (95% CI)	P value
Sex (male/female) (n (%))	9/17 (35/65)	25/41 (38/62)		0.8149
IBD subtype (n (%))				
CD	6 (23)	16 (24)		0.7910
L1/L2/L3/L4	0/5/1/3	4/4/7/6		
UC	19 (73)	49 (74)		
E1/E2/E3/E4	1/6/3/9	5/12/7/25		
IBDu	1 (4) (E2)	1 (1) (E4)		
Subtype change	2 (8)	0 (0)		
Age of diagnosis (years)				
Mean±SD	13±2.7	13±2.8		0.8852
Median (IQR)	13.1 (11.3, 15.5)	13.6 (11.7, 15.4)		
Paris A1a (n (%))	3 (12)			
VEOIBD (n (%))	0 (0)			
Age of sampling (years)				
Mean±SD	14.6±2.3	14.4±2.3		0.6186
Median (IQR)	15.1 (12.8, 16.2)	14.5 (13.2, 16.0)		
Follow-up (year)				
Mean±SD	6.3±4.6	5.2±4.5		0.1374
Median (IQR)	5 (3.3, 7)	4 (2, 6.3)		
Presentation (n (%))				
Family history	5 (19)	19 (29)	0.6 (0.2 to 1.8)	0.4349
EIM	4 (15)	9 (14)	1.2 (0.4 to 3.7)	1.00
ASUC (% of UC)	5 (26)	3 (6)	5.2 (1.1 to 21)	**0.0376**
Immunomodulator	22 (85)	41 (62)	3.4 (1.1 to 9.7)	**0.0466**
Advanced therapy	21 (81)	43 (65)	2.2 (0.8 to 6.0)	0.2084
≥3 types	10 (38)	12 (18)	2.8 (1.1 to 7.1)	0.0570
D2T (IOIBD)	6 (23)	4 (6)	4.7 (1.3 to 15.5)	**0.0277**
Colectomy	7 (27)	4 (6)	5.7 (1.5 to 18.5)	**0.0103**
Pouch creation	3 (12)	0 (0)		
Time to first advanced therapy (mean±SD, median (IQR))	1.6±3.2 (year) 1 (0, 2)	1.7±2.9 (year) 1 (0, 1)		0.5123
Time to first IBD operation (mean±SD, median (IQR))	1.4±0.8 (year) 2 (1, 2)	1.5±1.3 (year) 1.5 (0.3, 2.8)		0.9091

Significant values are in bold.
ASUC, acute severe UC; CD, Crohn's disease; D2T, difficult-to-treat; EIM, extraintestinal manifestations; IBDu, IBD-unclassified; IOIBD, International Organisation for the Study of Inflammatory Bowel Disease; VEOIBD, very early-onset IBD.

Anti-IL-10 positivity was associated with HLA-DRB1*01:03 allele carriage

In the IBD-BR cohort, imputation-based HLA typing data were available for a subset of patients. The proportion of HLA-DRB1*01:03 allele carriers in the anti-IL-10-positive group was highly enriched relative to the anti-IL-10-negative group (OR 66, p=0.007). To validate this finding in additional patient samples, high-resolution sequencing-based HLA typing was performed in 16 anti-IL-10-positive patients, of whom 87.5% (14/16; 95% CI 62.7 to 97.8%) carried the HLA-DRB1*01:03 allele. Combining data from the two UK cohorts, 80% of anti-IL-10-positive patients with IBD carried the HLA-DRB1*01:03 allele (95% CI 57.8% to 92.5%), a frequency substantially higher than that reported in the UK IBD population (4.6%) and in the UK non-IBD population (4%)[16] (figure 4F).

DISCUSSION

In this international multicentre study, neutralising anti-IL-10 autoantibodies were identified in a small but clinically relevant subgroup of paediatric patients with IBD. An independent paediatric-onset IBD cohort reported a similar prevalence of anti-IL10 antibodies (5/239; 2.1%),[17] providing external replication. Together, these findings support anti-IL-10 autoimmunity as a mechanistically defined subgroup of paediatric IBD. The neutralising activity of anti-IL-10 IgG was confirmed using multiple functional assay systems, and anti-IL-10 positivity was associated with a D2T clinical phenotype. Furthermore, our findings provide independent validation for the recently reported association between anti-IL-10 positivity and carriage of the HLA-DRB1*01:03 allele.[13]

Anti-IL-10-positive paediatric patients with IBD experienced severe and therapy-refractory disease, consistent with the severe phenotype in patients with inborn errors of IL-10 signalling.[9 10] In our study, this was indicated by an advanced therapy utilisation rate of 81% and 27% requirement for colectomy within a median of 5 years of follow-up after diagnosis. Only four (15%) anti-IL-10-positive patients remained free of both advanced therapy and colectomy. Nearly half of advanced therapy-exposed patients required a third advanced therapy, reflecting the therapeutic refractoriness in this patient group. Compared

with matched anti-IL-10-negative controls, disease severity was significantly higher in the anti-IL-10-positive group, as suggested by a higher proportion of patients with D2T disease and a more aggressive progression towards surgical intervention. While reported rates of advanced therapy utilisation in paediatric IBD cohorts range from 43% to 66.5%,[24 25] the rate observed among anti-IL-10-positive patients in our study highlighted a notably more severe disease phenotype. As for colectomy, previous paediatric studies reported <20% of patients required an operation in paediatric UC up to 12 years of follow-up.[26] These findings suggest that anti-IL-10 positivity may identify a subgroup of patients with a more progressive disease course fulfilling the D2T criteria of the IOIBD. This clinical association requires validation in larger prospective cohorts. While the data presented in this study suggest significant differences in disease progression, further studies are required to inform clinical decision-making. However, the severe phenotype observed in patient with anti-IL-10 positivity is plausible since it is consistent with the known phenotype of patients with HLA-DRB1*01:03.[16]

We noted clear phenotypic similarities between inborn errors of IL-10 signalling and their autoimmune counterpart while the age of disease onset differs. Inherited IL-10 pathway deficiency classically presents in infancy,[9 10] whereas anti-IL-10-positive patients in this cohort presented in the paediatric age range, with a median age at diagnosis of 13 years. The delayed onset suggests that additional genetic, developmental or environmental factors may contribute to anti-IL-10 development and/or its clinical expression. Because samples were obtained after diagnosis in most patients, the temporal relationship between anti-IL-10 emergence and disease onset cannot be determined. Once present, however, anti-IL-10 positivity is associated with a distinct disease course.

The biological plausibility of IL-10 as a causative factor of disease is strong. Genetic dissection of monogenic IBD has established that disruption of the IL-10 pathway is sufficient to cause severe intestinal inflammation.[9 10] Recent comparisons between IL-10 and IL-10 receptor deficiencies in paediatrics further support this framework, emphasising complete penetrance of intestinal inflammation in IL-10 signalling defects, early severe disease and the central role of dysregulated innate immune responses.[27] This reinforces the relevance of acquired anti-IL-10 autoimmunity as a phenocopy of a genetically defined pathway rather than a non-specific inflammatory antibody response.[27] Consistent with the therapeutic efficacy of allogeneic stem cell transplantation in IL-10 receptor-deficient patients,[9 28] experimental models further demonstrate that macrophage-restricted IL-10 receptor deficiency is sufficient to induce severe spontaneous colitis, placing failure of myeloid IL-10 sensing at the centre of disease pathogenesis.[29]

Previous transcriptional analyses in paediatric IBD have suggested a state of IL-10 non-responsiveness, characterised by persistent expression of pro-inflammatory cytokines despite high IL-10 transcription.[30] While impaired downstream signalling of the IL-10 receptor during bacterial translocation is one explanation of those findings,[30] anti-IL-10 autoantibodies can also provide an additional mechanistic explanation, linking transcriptional signatures of IL-10 resistance to a defined humoral immune defect.[13 30]

We showed that anti-IL-10 autoantibodies impaired recombinant IL-10 activity in the functional reporter assay and reduced detectable recombinant IL-10 in the competitive ELISA assay, indicating functional neutralisation of IL-10. Similarly, in the cytokine release assay, anti-IL-10 autoantibodies reduced detectable endogenous IL-10 and amplified IL-6, IL-1β, TNF and IL-23 release after LPS stimulation. This pattern fits our prior studies, indicating that acquired and genetic IL-10 resistance converge on an IL-1-centred inflammatory network regulating IL-23 in IBD.[30] It is also consistent with work showing that IL-1β is a key effector in IL-10 receptor deficiency.[31] Anti-IL-10-mediated blockade of IL-10 signalling is therefore not simply causing more inflammation but is associated with increased secretion of a selective subset of myeloid cytokines. This provides a mechanistic basis for the severe and treatment-refractory phenotype.

Anti-IL-10 autoantibodies have been described previously. While earlier reports of anti-IL-10 reactivity in patients with IBD did not show variable neutralising activity[32 33] or were limited to case reports,[12] recent studies with increasingly comparable assay systems demonstrate neutralising function of anti-IL-10 across several cohorts with emerging evidence for a severe clinical phenotype.[13 17]

These data support targeted testing in children with severe or refractory disease, where identifying anti-IL-10 may help define a subgroup for mechanism-based treatment strategies. In proof-of-concept observations, reduction of autoantibody production through B-cell depletion resulted in clinical improvement, supporting a causal role for anti-IL-10 in disease pathogenesis.[12] Emerging CD19 chimeric antigen receptor T-cell therapies also highlight the potential of targeting autoreactive B cells but remain investigational in this context.[34 35] In our cohort, the high rate of treatment escalation and frequent failure of multiple biologic therapies suggest that targeting downstream inflammatory pathways alone may be insufficient and targeting B or plasma cells or the pathogenic IgG may represent a rational therapeutic avenue in selected patients.

Anti-IL-10 autoantibodies define a distinct small group within the evolving autoantibody landscape associated with IBD. Established serological markers, including Perinuclear antineutrophil cytoplasmic antibodies (pANCA), anti-*Saccharomyces cerevisiae* antibodies (ASCA) and Anti-CBir1 flagellin antibodies (anti-CBir1), may support a degree of disease classification, but their pathogenic roles remain uncertain.[36 37] Antigranulocyte-macrophage colony-stimulating factor (anti-GM-CSF) autoantibodies have been associated with complicated ileal CD.[38] Anti-αvβ6 have been associated with UC and colonic CD and may precede the development of UC.[39] However, such antibody signatures in IBD are interpreted primarily as biomarkers of immune dysregulation rather than direct mediators of intestinal inflammation.[40] In contrast, neutralising anti-IL-10 autoantibodies target IL-10 and show measurable functional neutralisation, supporting a plausible pathogenic mechanism. As this study is cross-sectional, the temporal relationship between anti-IL-10 emergence and disease onset cannot be established; however, anti-IL-10 autoantibodies were detected within the first 2 years following diagnosis, that is, early in the disease course.

Anti-αvβ6 is an established serological marker associated with UC and colonic CD.[39 41] As expected, we observed elevated concentrations of anti-αvβ6 antibody in anti-IL-10-positive patients, in keeping with their colonic phenotype. However, anti-αvβ6 titres did not differ significantly between anti-IL-10-positive and anti-IL-10-negative patients overall, or within the UC subgroup. In a previous study, we did not observe broad co-occurrence of anti-IL-10 autoantibodies with other anti-cytokine autoantibodies, such as anti-GM-CSF.[13] Systematic profiling of pANCA, ASCA, anti-CBir1 and other IBD-associated antibodies was not possible because of limited residual sample availability. Future prospective studies, including anti-IL-10 testing alongside broader serological profiling in larger cohorts, will determine whether anti-IL-10 autoimmunity represents

an independent immunological endotype or partially overlaps with established antibody-defined IBD subgroups. Future work should also address the relevance of anti-IL-10 in more diverse populations and the extent to which this is driven by HLA-DRB1*01:03 distribution and environmental exposure.

Differences in prevalence of anti-IL-10 positivity across cohorts may reflect variations in age and genetic background and environmental exposures. Consistent with previous findings from the adult cohort study,[13] the current paediatric cohort confirms the strong association between anti-IL-10 autoantibody positivity and carriage of the HLA-DRB1*01:03 allele. Population-level variation in the frequency of the HLA-DRB1*01:03 allele may partly account for the differing rates of anti-IL-10 autoantibody positivity across geographical regions. As this study is cross-sectional, the temporal relationship between anti-IL-10 emergence and disease onset cannot be established; however, anti-IL-10 autoantibodies were detected within the first 2 years following diagnosis.

Our findings can also be interpreted within the framework of anticytokine autoantibodies.[42] Neutralising autoantibodies against interferons and other cytokines (eg, IL-12, IL-23, IL-6 and IL-27) are established causes of severe infectious and inflammatory syndromes, demonstrating that disruption of a single cytokine axis can be sufficient to drive infectious disease susceptibility or immune-mediated disease.[42]

In summary, anti-IL-10 autoantibodies in paediatric IBD are associated with a predominantly colonic phenotype and a severe clinical trajectory. The identification of an acquired anticytokine autoimmune pathogenesis for anti-IL-10 disease, showing phenotypic similarities to monogenic IL-10 signalling defects, unifies these aggressive phenotypes within a single mechanistic framework. This suggests that anti-IL-10 is not merely an inflammation-associated autoantibody, but a mechanistically defined biomarker for a distinct high-risk endotype of paediatric IBD.

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Contributors NG and P-JY contributed equally to this work and performed laboratory experiments, analysed and interpreted the data and prepared the figures. NG, P-JY and HU drafted the manuscript. KV, Madeleine Coy (MC) and LK contributed to laboratory work and data acquisition. Mian Chen (MC), MB, QZ, LF, CAA and JJA contributed to the HLA analysis. All authors contributed to patient recruitment, sample collection, clinical phenotyping or the critical interpretation of data, critically revised the manuscript, approved the final version and agree to be accountable for all aspects of the work. HU is the guarantor of the study and accepts full responsibility for the integrity of the work as a whole, from inception to publication.

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