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Ruxolitinib: Targeted Approach for Treatment of Autoinflammatory Very Early Onset- Inflammatory Bowel Disease

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Keywords

ruxolitinib; Very Early onset- inflammatory bowel disease; pediatric; genetic etiology

Introduction:

Very early onset-inflammatory bowel disease (VEO-IBD), diagnosed <6 years old, can be genetically and phenotypically distinct and more refractory than older-onset IBD. Identified causal monogenic defects have been targeted therapeutically in a small subset of VEO-IBD (1), however for the majority of these children, treatment strategies such as phenotypic profiles are critically needed to improve outcomes.

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Most of the >70 monogenic defects identified in children with VEO-IBD involve immune response and epithelial barrier function (1, 2), including aberrant activation of the JAK-STAT pathway and interferon (IFN)-mediated autoinflammatory disease (AID)(3, 4). This phenotype is characterized by recurrent fevers, elevated inflammatory markers, increased cytokine production, and severe intestinal and systemic disease(2). Therapies targeted to IFN production have shown promising results in some AIDs(5). Ruxolitinib, a selective JAK1/2 inhibitor, is approved to treat polycythemia vera, myelofibrosis, and graft versus host disease. It has also shown potential in immune dysregulation disorders such as interferonopathies caused by *STAT1* and *STAT3* GOF mutations(6, 7). While efficacy for intestinal symptoms has not been established (8), we hypothesized it would be effective in patients with VEO-IBD who have an autoinflammatory phenotype (AIP).

Our aim was to describe treatment with ruxolitinib in patients with severe and refractory VEO-IBD with AIP in the absence of identified monogenic defects.

Methods:

This was a single-center retrospective study of patients with refractory VEO-IBD with AIP treated with ruxolitinib following informed consent for at least six months. VEO-IBD diagnosis was confirmed through endoscopic, histologic, laboratory and clinical evaluation in children <6 years of age at presentation. AIP was defined by persistent fevers, leukocytosis and elevation of ≥2 cytokines: soluble IL-2 receptor (sIL-2R), IL-8, IL-6, and interferon signature including chemokine ligand 9 (CXCL9) or IFN-γ in the absence of infection. Clinical data were collected at: 1) baseline 2) three months and 3) six months post-ruxolitinib initiation as outlined in Table 1. Response was measured by improvement in extraintestinal manifestations (EIMs), laboratory studies, nutritional status, stool frequency, and steroid taper.

Results:

Six patients with autoinflammatory VEO-IBD were included: 50% diagnosed at <1 year, 33% with Crohn disease, 83% with inflammatory phenotype, and histologic findings of chronic active colitis (66%) or duodenitis (33%). Severity of disease was demonstrated by multiple, prolonged hospitalizations (median number of hospitalizations (IQR): 4.5 (3,12), median hospital days (IQR): 84.5 days (55.5, 98.5)), steroid dependence (n=5) or steroid refractory (n=1), and failure of at least one biologic (n=6). Two patients had prior surgeries: 1) diverting ileostomy 2) ileocecectomy, stricturoplasty, and diverting colostomy (Supplementary Table 1).

At baseline, all patients had severe gastrointestinal symptoms: diarrhea (n=6), intractable vomiting (n=2) and malnutrition (n=6), with total parenteral nutrition (TPN) requirement (n=4). EIMs included prolonged fevers (n=6), arthritis (n=3), and oral ulcers (n=1). Laboratory studies demonstrated hypoalbuminemia (n=3), anemia (n=4), leukocytosis (n=5), and elevated ESR (n=4). Cytokine profiles revealed elevated sIL-2R (n=5), IL-8 (n=3), IL-6 (n=5), IFN-γ (n=4) and CXCL9 (n=3) (Table 1). Trio whole exome sequencing and immunophenotyping were unrevealing for all patients.

The average starting dose of ruxolitinib was 5.6 mg/m^2/dose twice daily (6). It was added as dual therapy in five patients with IL-1 blockade (n=3) or anti-tumor necrosis factor alpha therapy (n=2) (Supplementary Table 2), with stable doses of concomitant therapies. Initial response, most remarkably in fevers and stool frequency, was seen within 1 week. Over 6 months, further clinical response included resolution of EIMs, steroid taper and nutritional status improvement with TPN weaned in all patients (Table 1). Additionally, all patients had improvement in laboratory studies. No hospitalizations for IBD-related illness occurred in the six-month study period. Three patients underwent repeat endoscopy: 1 demonstrated deep mucosal healing and 2 showed endoscopic improvement. Minimal adverse effects included *C. difficile* infection (n=1) and uncomplicated acute otitis media (n=2), and notably, no patients showed evidence of cytopenia.

Discussion:

This is the first study describing targeted use of ruxolitinib in patients with VEO-IBD with AIP without an identified genetic defect. Ruxolitinib was predominantly used as dual therapy when primary treatment failed to achieve complete response. All patients demonstrated clinical improvement without TPN or steroid requirement. Three mild infections occurred while on ruxolitinib, but bone marrow suppression was not evident. Additional potential benefits of ruxolitinib include lack of immunogenicity, quick onset of action, and short half-life. Furthermore, ruxolitinib is administered enterally and clinical response was achieved in this cohort with severe intestinal disease, suggesting adequate enteral absorption. The limitations include small sample size, lack of a comparative control cohort, and limited available data for each timepoint; however, it demonstrates a much-needed targeted therapeutic option in VEO-IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AID	autoinflammatory disease
AIP	autoinflammatory phenotype
CBC	complete blood count
EIM	extraintestinal manifestations

ESR	erythrocyte sedimentation rate
GOF	gain of function
IBD	inflammatory bowel disease
IFN	interferon
IL	interleukin
IQR	interquartile range
JAK-STAT	Janus kinase/signal transducers and activators of transcription
TPN	total parenteral nutrition
VEO-IBD	Very Early onset-inflammatory bowel disease
WBC	white blood cell

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Table 1:

Clinical Response over 6 months

	Baseline	3 months	6 months
Growth			
Weight-for-age Z-score, median (IQR)	−2.85 (−3.6– (−1.7))	−0.88 (−1.62–(−0.46))	−0.34 (−2.16– (−0.1))
TPN requirement, n (%)	4 (67)	1 (17)	0
Stool frequency (n=4)			
1–3 stools per day, n (%)	1 (25)	2 (50)	3 (75)
4–6 stools per day, n (%)	1 (25)	1 (25)	1 (25)
>6 stools per day, n (%)	2 (50)	1 (25)	0
Ostomy Output (n=2)			
Severely increased (>2L/day), n (%)	2 (100)	0	0
Normal (600–1200ml/day), n (%)	0	2 (100)	2 (100)
Extra-intestinal manifestations			
Prolonged fevers, n (%)	6 (100)	2 (33)	0
Arthritis, n (%)	3 (50)	1 (17)	0
Standard Biochemical Markers			
WBC, K/uL, median (IQR)	19.5 (13.7–27.0)	8.4 (7.3–12.2)	9.7 (7.0–12.2)
Hemoglobin, g/dL, median (IQR)	8.6 (7.8–11.1)	11.7 (11.1–11.8)	11.4 (9.4–11.8)
Albumin, g/dL, median (IQR)	2.6 (1.9–3.6)	4.2 (3.8–4.2)	4.1 (3.9–4.3)
ESR, mm/hr, median (IQR)	77.5 (20.0–120.0)	20.0 (11.0– 59.0)	25.0 (15.0–39.0)
CRP, mg/dL, median (IQR)	3.75 (3.1–12.5)	1 (0.8–2.7)	0.5 (0.5–0.8)
Cytokines			
IL- 2 soluble receptor<= 1033 pg/ml, median (IQR)	1859 (1520– 10940)		530.6 (245.4–1673.2) *
IL- 6 <=5 pg/ml, median (IQR)	15.0 (8–23)		2.0 (2.0–2.1) *
IL- 8 <=5 pg/ml, median (IQR)	6.5 (5–10)		3.0 (2.5–6.5) *
IFN γ <4.2 pg/ml, median (IQR)	4.6 (4.2–9)		4.2 (4.2–5) *
CXCL9 <= 121pg/ml, median (IQR)	240.5 (99.5, 402.5) **		69.5 (43, 103.5) **

* Cytokine panels were obtained in only four patients at 6 months.

** CXCL-9 leve was only obtained in four patients.

IQR: interquartile range, TPN: total parenteral nutrition, WBC: white blood count, ESR: erythrocyte sedimentation rate, CRP: c-reactive protein, IL: interleukin