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REVIEW ARTICLE

Linking Genetic Diagnosis to Therapeutic Approach in Very Early Onset Inflammatory Bowel Disease: Pharmacologic Considerations

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Abstract

Very early onset inflammatory bowel disease (VEO-IBD) is diagnosed in children < 6 years of age, and in rare cases may be due to an identifiable monogenic cause. Recent advances in genetic testing have allowed for more accurate diagnosis, with as many as 100 genes now known to be associated with monogenic inflammatory bowel disease. These genes are involved in many immune pathways and thus may represent potential avenues for targeted precision medicine with pharmacologic treatments aimed at these. This review describes the broad classifications of monogenic disorders known to cause VEO-IBD, as well as empiric and disease-specific medical therapies. These include immune-modulating or immunosuppressant medications, nutritional therapy, surgery, and hematopoietic stem cell transplantation. We aim to provide an overview of the current state of targeted therapy for VEO-IBD.

Key Points

Very early onset inflammatory bowel disease (IBD) represents a unique category of pediatric IBD, requiring special considerations regarding genetic testing and therapeutic decision making.

Current treatments directed at specific immune pathways, such as anti-interleukin (IL)-1 and anti-IL18, are becoming increasingly available for some disorders, allowing for reductions in broader immunosuppressants and, in some cases, acting as a bridge to definitive cure with hematopoietic stem cell transplantation (HSCT).

In the future, more genes will be identified, and their functions determined, opening the door for further immune-targeted agents as well as potential gene therapy.

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1 Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC), Crohn's disease (CD), and IBD–unspecified (IBD-U), is an immune-mediated disease that causes chronic intestinal inflammation. Although the exact pathogenesis of IBD is as yet unknown, it is thought to involve dysfunctional interactions between the host immune system, microbiome, and genetic factors. In the pediatric population, a growing cohort of patients presents before the age of 6 years. These patients are considered to have very early onset IBD (VEO-IBD), which can be further subclassified into infantile IBD for children diagnosed before age 2 years, and neonatal IBD for those diagnosed by 28 days of life [1]. In contrast to older children and adolescents with IBD, those with VEO-IBD often have more severe refractory disease and are more likely to have a causative monogenic defect underlying their disease [1, 2]. Many of these monogenic defects represent primary immune deficiencies, and as such, lend themselves to treatment targeted at specific immune pathways. However, the majority of VEO-IBD does not have an identifiable genetic cause, requiring an empiric approach to treatment. This review will discuss the epidemiology and genetics of VEO-IBD, as well as gene-targeted pharmacologic therapies focused on addressing underlying immune dysregulation.

The incidence of pediatric IBD, and with it VEO-IBD, has been rising over the last 20 years [3]. Recent data from Canada suggests that 6–15% of pediatric IBD presents

before age 6, and that incidence has risen from 1.3 to 2.1 per 100,000 from 1994 to 2009, with a mean annual incidence of 7.2% [4]. However, this varies from country to country, suggesting that other factors, such as environmental exposures, are at play. VEO-IBD as a proportion of pediatric IBD ranges from just 3% in France [5] to 20% in Singapore [6].

To date, more than 100 genes have been found to be associated with monogenic forms of IBD [7], and a recent consensus statement from the Pediatric IBD Porto Group included 75 genes in their recommended diagnostic algorithm [8]. Although very rare, an underlying monogenic cause of VEO-IBD may be identified in up to 20% of cases [1, 8]. In monogenic IBD, infantile IBD makes up 28.2% of those diagnosed by age 18 years, and 63.4% are diagnosed by age 6 years [9]. Rates of detection may vary across centers and depend on the manner of testing (targeted panel sequencing versus whole exome or whole genome sequencing) [8]. Functional immunologic assays, such as protein testing and flow cytometry, may be needed in the event of detection of a variant of unknown significance or novel gene mutation [10]. The monogenic variants identified thus far can be classified broadly as epithelial barrier defects, phagocytic defects, defects of adaptive immunity, T regulatory defects, interleukin (IL)-10 pathway disorders, and autoinflammatory conditions [10–13]. As some of these disorders may have implications for indicated treatments, a high level of suspicion should be maintained in VEO-IBD patients and appropriate testing done with the assistance of a multidisciplinary team including geneticists and immunologists.

2 Monogenic Defects Associated with Very Early Onset Inflammatory Bowel Disease (VEO-IBD)

2.1 Epithelial Barrier Defects

The intestinal epithelium is a physical barrier between the immune system and both commensal and pathogenic bacteria. Epithelial defects often involve both the gut and the skin. Disorders of this type include X-linked ectodermal dysplasia and immunodeficiency, due to *IKBKG* gene mutation and subsequent deficiency of NF-κB regulatory protein NEMO [14], dystrophic epidermolysis bullosa with *COL7A1* mutation [15], psoriasiform rash with *ADAM17* deficiency [16], and Kindler syndrome, which presents with skin blistering and atrophy due to *FERMT1* mutation [17]. Other disorders in this class affect more systems and include greater immune dysfunction. These include Loeys-Dietz syndrome, due to *TGFB1* and *TGFB2* mutations, which presents with skeletal and craniofacial abnormalities as well as vascular involvement [18], and *TTC7A* deficiency leading to multiple intestinal atresias, enterocolitis, and severe combined immunodeficiency (SCID) [19].

2.2 Phagocytic Defects

Pathogenic bacteria that breach the intestinal epithelium are neutralized by intestinal phagocytes, most importantly neutrophils. Patients with VEO-IBD due to phagocyte defects have either defective degranulation, as in the case of chronic granulomatous disease (CGD), or impaired migration of granulocytes into the tissue, such as with leukocyte adhesion disorder (LAD). CGD is due to defects in the NADPH oxidase complex (*CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4*) and leads to defective clearance of bacteria as neutrophils are unable to produce hydrogen peroxide to kill phagocytized organisms [20]. The clinical manifestations of CGD are variable, ranging from skin and soft tissue abscesses to severe systemic bacterial and fungal infections, and includes Crohn's-like intestinal inflammation and perianal disease in up to 40% of cases [21]. Patients with mutations in *ITGB2* have LAD type 1, resulting in Crohn's-like disease with strictures, as well as peripheral neutrophilia, recurrent bacterial infections, delayed umbilical cord separation, and oral/dental disease (lip ulcers, gingivitis, and periodontitis) [22–24].

2.3 Adaptive Immune Defects

Disorders affecting T- and B-cell function can cause IBD-like enterocolitis as part of primary immunodeficiencies such as SCID. Many genes that have been implicated in SCID also underlie VEO-IBD, such as *ZAP70*, *RAG2*, *LIG4*, *ADA*, and *DCLRE1C*/*ARTEMIS* [25–29]. Wiskott Aldrich Syndrome (WAS) also leads to disordered B- and T-cell responses, presenting with a triad of eczema, thrombocytopenia, and immunodeficiency. WAS patients tend to have UC-like disease confined to the colon [30]. Bruton's or X-linked agammaglobulinemia is a B-cell disorder due to mutations in *BTK* and manifests as recurrent infections (notably sinusitis and otitis media) as well as colitis [31]. Common variable immunodeficiency (CVID) due to *ICOS* and other mutations could also present with recurrent infections and enterocolitis [32].

2.4 T Regulatory Defects

T regulatory cell defects cause enterocolitis with notable small bowel villous atrophy, in addition to other systemic symptoms. The most common of these disorders is immunodysregulation, polyendocrinopathy, and enteropathy X-linked syndrome (IPEX), due to mutations in *FOXP3*, a transcription factor necessary for the development of a subset of CD4+ T regulatory cells [33]. These patients have

severe diarrhea, diabetes, and dermatitis, as well as frequent infections [33, 34]. Disorders in other steps of the T regulatory pathway can present with IPEX-like VEO-IBD syndromes. *CTLA4* mutations lead to deficiency of an inhibitor of T regulatory cells [35], while *LRBA* mutations lead to deficiency of a protein needed for normal T regulatory function [36]. Finally, gain of function mutations in *STAT1* and *STAT3* [37], and CD25 deficiency due to *IL2RA* mutations can also present as IPEX-like syndromes [38].

2.5 Hyperinflammatory and Autoinflammatory Disorders

A VEO-IBD phenotype is not an uncommon presentation of autoinflammatory or hyperinflammatory conditions. Most notably, up to 20% of patients with loss-of-function mutations in X-linked inhibitor of apoptosis (*XIAP*), leading to X-linked lymphoproliferative syndrome, develop severe fistulizing Crohn's-like disease [39]. *XIAP* deficiency leads to defects in pathogen sensing and killing, as well as hyperinflammation with elevated cytokine levels, especially of IL-18. Not only does this contribute to intestinal inflammation, but also leaves these patients at risk of severe hemophagocytic lymphohistiocytosis (HLH) due to Epstein Barr virus or other infections [40]. Other disorders of this kind include mevalonate kinase deficiency (*MVK*) [41], *NLRC4* mutations [42], and *TRIM22* mutations [43].

2.6 IL-10 and IL-10R Disorders

Finally, defects in IL-10 production and function lead to defects in numerous anti-inflammatory pathways, manifesting as severe Crohn's-like inflammation with perianal fistulas, arthritis, and skin involvement [44, 45]. Loss-of-function mutations in both *IL10* ligand and the receptor α and β chains (*IL10RA* and *IL10RB*) cause VEO-IBD with onset generally in the first months of life. Severity of disease ranges from mild disease responsive to 5-aminosalicylates to life-threatening fulminant colitis [45]. Patients with these disorders are also predisposed to develop large B-cell lymphoma later in life [46].

3 Pharmacologic Considerations

Despite the multitude of monogenic disorders now known, the large majority of children with VEO-IBD ultimately do not have a genetic disorder identified. In the absence of a treatment-guiding diagnosis, these children are treated in a similar manner to older pediatric patients diagnosed with IBD without genetic defects. Empiric treatments for IBD include corticosteroids, 5-aminosalicylates, immunomodulators, biologics, and antibiotics. There are currently no randomized controlled trials in VEO-IBD to guide therapy choice, in large part due to the rarity of each monogenic disorder and the difficulty of conducting such trials in young children [12, 13]. Moreover, several small studies suggest that VEO-IBD patients may have a more severe, refractory disease course than older children and adolescents with IBD, making their management even more challenging. In patients with identified monogenic disorders, however, there are now a number of therapies available targeting specific pathways (Table 1).

3.1 Immunomodulators

Immunomodulatory medications such as azathioprine and methotrexate have long been used, both as monotherapy and in combination with biologics and corticosteroids, to treat IBD. VEO-IBD patients often require higher doses of azathioprine to achieve therapeutic levels, increasing the risk of drug toxicity [13, 47]. There are no large studies examining the efficacy of methotrexate in this population, though it is used not infrequently [13].

3.2 Anti-TNF Antibodies

Monoclonal antibodies directed against tumor necrosis factor alpha (TNFα), such as infliximab and adalimumab, are widely used as the first-line biologic treatment for pediatric IBD. Infliximab has an excellent response rate in the general pediatric population, with nearly 60% in remission by week 10 of treatment and up to 65% maintaining remission at 1 year [48]. Studies in younger children demonstrate reduced response to infliximab, however; of 33 children diagnosed with IBD and started on infliximab aged 7 years or younger, 36% remained in remission at 1 year and only 12% at 3 years [49]. Another recent study found similar response rates, with 28.6% in remission at 14 weeks and 15.8% at 1 year [50]. The difference in response has been attributed to a number of factors, including different immune pathways of disease in VEO patients, as well as differences in pharmacokinetics in younger patients [13]. A study from the ESPGHAN Porto group found that IBD patients aged < 10 years required significantly higher doses of infliximab to maintain therapeutic trough levels and had increased risk of developing anti-infliximab antibodies [51]. Nonetheless, infliximab continues to be a useful tool in treating some varieties of VEO-IBD, both those with identified monogenic disorders and those without. One case report suggests that infliximab could have good response in X-linked ectodermal dysplasia and immunodeficiency secondary to NEMO, especially since the pathogenesis of colitis in this disorder is suggested to be due to increased TNFα [52]. Similarly, a case report of one child with Hermansky-Pudlak syndrome type 1 with Crohn's-like colitis suggests these patients could

Table 1 Medications and therapeutic targets in very early onset inflammatory bowel disease (VEO-IBD)

Medication	Monogenic disorder(s) targeted	Proposed mechanism/immune pathway	References
Azathioprine 6-mercaptopurine	Undifferentiated	Purine analog, blocks DNA replication and proliferation of T cells; possible inhibition of CD28 T-cell co-stimulation	[13, 47]
Infliximab Adalimumab	Undifferentiated, X-linked ectodermal dysplasia and immunodeficiency, Hermansky-Pudlak syndrome	Anti-TNFα	[13, 48–53]
Vedolizumab	Undifferentiated, CGD, CTLA4	Anti-α4β7 integrin; blockade of MAdCAM-1 directed lymphocyte traffic to intestinal Peyer's patches	[55–58]
Ustekinumab	Undifferentiated, CGD	Anti-IL12 and IL-23	[59–62]
Cyclosporine Tacrolimus	Undifferentiated	Suppression of IL-2, TNFα, and interferon-c production in T cells	[63–69]
Tofacitinib Ruxolitinib	*STAT3* GOF and *IL2RA* IPEX-like syndromes	JAK-STAT pathway inhibition, with downstream effects on CD4+ Th cell proliferation	[70–72]
Anakinra Canakinumab	CGD MKD IL-10 & IL-10R	Competitive inhibition of IL-1 receptor binding	[73–83]
Recombinant human IL-18 binding protein	*NLRC4* XIAP	IL-18 blockade and inhibition of IFNγ production	[84–87]
Abatacept	*LRBA* *CTLA4*	Enhanced CTLA4 trafficking and proliferation of FOXP3+ T regulatory cells	[88–90]

CTLA4 cytotoxic T lymphocyte antigen-4, *CGD* chronic granulomatous disease; *GOF* gain-of-function, *IFNγ* interferon gamma, *IL* interleukin, *IPEX* immune dysregulation, polyendocrinopathy, enteropathy X-linked, *MKD* mevalonate kinase deficiency, *XIAP* X-linked inhibitor of apoptosis, *TNFα* tumor necrosis factor alpha

respond well to infliximab, as this child remained in remission after 22 months of therapy [53]. However, infliximab is not appropriate for all patients with VEO-IBD, and in particular should be used with caution in patients with chronic granulomatous disease. Although it is effective in closure of fistulae, it has been linked with severe infections and death due to over immunosuppression in these patients [54]. Thus, a thorough workup at presentation to determine etiology is important in this patient cohort.

3.3 Vedolizumab

Vedolizumab is a gut-specific humanized anti-α4β7 integrin monoclonal antibody that prevents migration of T cells into tissue, thus reducing intestinal inflammation. A Polish review of 16 VEO-IBD patients without known monogenic diagnoses showed that vedolizumab was safe and effective at inducing remission of disease in 56% after failure of anti-TNF therapy [55]. It has been used with varying degrees of success in small studies as a treatment for certain monogenic variants of VEO-IBD as well. In a case study of an adult with CGD colitis and perianal disease, the subject had sustained remission on vedolizumab [56]. However, a US National Institutes of Health (NIH) study of 11 pediatric CGD patients was not promising. Although more than half the patients had subjective improvement in symptoms and some were able to decrease doses of chronic steroids, none had sustained mucosal healing [57]. In CTLA4 deficiency, one case report of an adult patient suggested that sustained remission of colitis on vedolizumab may be possible; however, pediatric studies of its use in this disorder are lacking [58].

3.4 Ustekinumab

Ustekinumab is a fully humanized monoclonal antibody against IL-12 and IL-23 that is used increasingly in pediatrics for maintenance of remission in IBD patients who are non-responsive to anti-TNF medications. While it has been shown to be safe and efficacious in both biologic-exposed and naïve patients [59, 60], its use in the VEO population has been limited and there are no large-scale trials. There is limited evidence to suggest that it can safely induce remission in some patients with CGD-related VEO-IBD. A case report from Stanford followed one patient with *CYBB* mutation X-linked CGD who achieved clinical remission and was able to decrease the dose of chronic steroids while on ustekinumab [61]. A follow up study from the NIH followed nine CGD patients treated with ustekinumab, of whom six had clinical response with four achieving clinical remission. However, none of those followed up endoscopically had mucosal healing [62].

3.5 Calcineurin Inhibitors

Cyclosporine A and tacrolimus are calcineurin inhibitors that have been used for successful induction of remission in fulminant, steroid-refractory colitis in children [63]. Calcineurin inhibitors suppress transcription of cytokines such as IL-2, TNFα, and interferon-c in T cells, thus exerting an immunosuppressive effect [64]. While pediatric IBD studies have shown response rates up to 60–80% [65], their use in the VEO population has had mixed results. Small case series have shown varying degrees of success using cyclosporine for treatment of VEO-IBD. In a study of 10 children with VEO-IBD with onset in the first 12 months of life, one patient received cyclosporine as a second-line therapy after becoming steroid-refractory and achieved clinical remission; however, the patient relapsed within a year [66]. In a review of 16 patients in Italy diagnosed before age 2 years, one patient found to have VEO-IBD secondary to CGD and another with a UC-like phenotype achieved remission on a combination of corticosteroids and cyclosporine. However, others were refractory to cyclosporine therapy, including one patient with a fatal outcome [67]. Finally, in a review of eight patients with neonatal-onset VEO-IBD in the United Kingdom, none of the three patients treated with cyclosporine achieved remission of their disease [68]. A review of XIAP patients treated with tacrolimus found that 92% of patients were refractory to treatment with combination corticosteroids and tacrolimus, as well as cyclosporine and azathioprine [69].

3.6 Janus Kinase Inhibitors

Ruxolitinib and tofacitinib are small molecules that respectively inhibit JAK1/2 and JAK1/3 in the JAK/STAT pathway. A recent retrospective study of six patients with refractory VEO-IBD with autoinflammatory phenotypes from Children's Hospital of Philadelphia suggests that patients treated with ruxolitinib for refractory colitis may see improvement in clinical symptoms and laboratory parameters. Three of the six patients showed improvement on endoscopic reevaluation [70]. A single patient with IPEX-like syndrome due to gain of function *STAT3* mutation who was refractory to steroids, tacrolimus, azathioprine, ustekinumab, and tocilizumab had sustained remission at 1 year with ruxolitinib therapy [71]. Although tofacitinib has not been used directly in patients with IPEX-like disorders, a single study using resected colonic tissue from a patient with refractory colitis due to *IL2RA* IPEX-like syndrome suggests there could be a role for its use in these patients. Exposure of diseased tissue in vitro to tofacitinib led to subsequent normalization of CD25 and reduction in IL-2 and interferon gamma (IFNγ) secretion [72]. However, in vivo follow-up studies are so far lacking.

3.7 IL-1 Blockade

IL-1 is a pro-inflammatory cytokine, and its release is triggered by activation of the inflammasome, cytosolic sensors of environmental stress, pathogens, and cell damage [73, 74]. Canakinumab and anakinra are recombinant IL-1 receptor antagonists, which act by competitive inhibition of IL-1 binding to its receptor. Canakinumab can be used in a variety of autoinflammatory disorders, including cryopyrin-associated periodic fever syndrome (CAPS). In a case report, a patient with CAPS was trialed on canakinumab and developed IBD, requiring change in therapy to infliximab. However, she continued to have elevated inflammatory markers and associated rash thereafter [75]. In patients with chronic granulomatous disease, mutations in the NADPH complex leads to defective autophagy due to minimal reactive oxygen species production. Defects in autophagy and dysregulated activation of the inflammasome have been linked [76], with resultant increased IL-1β release, inflammation, and enterocolitis. De Luca et al. described two patients with CGD colitis who seemed to respond to anakinra, though only one achieved remission, and subsequently relapsed when it was stopped [76]. Hahn et al. described five patients aged 6–30 years treated with anakinra, of whom only two had modest clinical improvement but did not achieve remission. The remaining three had no change in symptoms despite treatment with anakinra [77].

Patients with mevalonate kinase deficiency (MKD) have also been treated with anakinra. MKD has two phenotypes, mevalonic aciduria (MA), with minimal residual function of the mutated enzyme, and hyperimmunoglobulinemia D syndrome (HIDS), with up to 28% residual function [78]. Symptoms generally develop in infancy, and include recurrent fevers, failure to thrive, diarrhea, splenomegaly, and abdominal pain [79]. MKD leads to inflammasome activation and IL-1β secretion [78]. Case studies suggest that MKD colitis may respond to anakinra. Levy et al. reported two infants who achieved remission, one of whom had documented endoscopic healing after 3 months of treatment [79]. Peciuliene et al. described a patient with neonatal MKD whose symptoms were well controlled with anakinra, though required dose escalation due to breakthrough symptoms [78]. Campanilho-Marques and Brogan further reported two sisters with MKD who had partial improvement in their symptoms with anakinra, though again required dose escalation and had breakthrough symptoms [80]. Finally, a recent review of ten MKD patients with IBD across eight centers suggested that MKD patients could have improvement of their IBD with the addition of anakinra [81].

IL-10 is an important immunoregulatory cytokine that mediates anti-inflammatory and immunosuppressive pathways via its receptor on immune cells. Mutations in the receptor genes *IL10RA* and *IL10RB* lead to VEO-IBD in

infancy [45, 82]. These patients are frequently refractory to corticosteroids, azathioprine, biologics, and calcineurin inhibitors, and many require surgical resection to control their disease [82]. Recent work by Shouval et al., suggests a potential role for IL-1 blockade in this population. Using a murine model, they showed that innate IL-1 production allowed CD4+ T cells to induce colitis in IL10R-deficient mice. Human in vivo studies showed that IL-10R-blocked macrophages stimulated with lipopolysaccharide had increased IL-1b production and inflammasome activation. Finally, two patients with *IL10RA* mutations and severe VEO-IBD were treated with anakinra and had improvement in symptoms and histologic healing [83]. Both patients eventually underwent hematopoietic stem cell transplantation, but anakinra therapy was a steroid-sparing bridging therapy.

3.8 IL-18 Blockade

As previously discussed, inflammasome activation leads to secretion of pro-inflammatory cytokines, including IL-1β and IL-18. Mutations in *NLRC4*, an inflammasome component, have been shown to cause macrophage activation syndrome (MAS) and severe neonatal-onset enterocolitis [42, 84]. These patients have very high levels of IL-18, a pro-inflammatory cytokine whose downstream effects include secretion of IFNγ [85]. Canna et al. described a 6-week-old patient who developed MAS and severe enterocolitis due to *NLRC4* mutation. The patient had a refractory clinical course despite treatment with corticosteroids, infliximab, cyclosporine, vedolizumab, and anakinra. She was then treated with recombinant IL-18 binding protein (rhIL-18BP), with improvement in inflammatory markers and clinical symptoms [85]. However, rhIL-18BP is not yet approved by the US Food and Drug Administration for human use and was only made available in this case via an emergency compassionate-use Investigational New Drug authorization. Other potential uses for rhIL-18BP include XIAP, which features inflammasome activation and significant elevation in IL-18 as well [13]. A recent phase II clinical trial of the rhIL-18BP drug tadekinig alfa demonstrated safety and early signs of efficacy in patients with adult-onset Still's disease, a hyperinflammatory disorder also involving high levels of IL-18 [86]. Pediatric phase II trials are ongoing of MAS825, an anti-IL-1b/IL-18 monoclonal antibody, examining its safety and efficacy in patients with *NLRC4* gain-of-function mutations causing autoinflammation and infantile enterocolitis [87].

3.9 CTLA4-Ig

Abatacept is a cytotoxic T lymphocyte antigen-4 (CTLA4) immunoglobulin fusion drug that has shown efficacy in treating enteropathy due to LRBA deficiency. LRBA is involved in intracellular trafficking of CTLA4, which is an inhibitory immune checkpoint protein expressed on FOXP3+ T regulatory cells [88]. Patients with LRBA deficiency have very low CTLA4 expression, which manifests as an IPEX-like syndrome with enteropathy, autoimmune hemolytic anemia (AIHA), type I diabetes, interstitial lung disease, and splenomegaly [10, 12, 88]. A Turkish study of 22 pediatric patients with LRBA deficiency who were treated with abatacept suggested that it may have a therapeutic effect in this disorder. Of 14 patients with a chronic diarrhea-predominant phenotype, complete remission was achieved in 11 and partial in 3 patients. The majority of patients were able to stop steroids and other immunosuppressive agents as well [89]. Patients with CTLA4 haploinsufficiency may also respond well to abatacept, with improvement in two reported cases of refractory colitis [90].

4 Non-Pharmacologic Therapies

Non-pharmacologic treatments for VEO-IBD include nutrition, surgery, and hematopoietic stem cell transplantation (HSCT). Nutritional therapy, including exclusive enteral nutrition (EEN), is recommended as a first-line therapy to induce remission in pediatric Crohn's disease and is equally as effective as corticosteroids [91, 92]. While the efficacy of EEN in VEO-IBD is less clear, a case study of two infants with bloody diarrhea and endoscopic findings of chronic inflammation showed that treatment with EEN, one using intact cow's milk protein-based formula and the other using an amino acid-based hypoallergenic formula, led to clinical remission [93]. Surgery can improve symptoms and quality of life in treatment-refractory VEO-IBD, but carries risks of perforation, pouchitis, anastomotic stricture, and fistula formation [13]. VEO-IBD patients are more likely than older patients to require surgery, most commonly colectomy or diverting ileostomy, with rates ranging from 29 to 50% [13, 94]. A recent systematic review of monogenic IBD showed that 29.9% of patients with VEO-IBD required surgery, with patients carrying diagnoses of IL-10R or TTC7A deficiency undergoing surgery earlier in their disease course [9].

Allogenic HSCT can improve intestinal disease and even be curative in some monogenic VEO-IBD disorders but should be used with caution in others. Conditions in which HSCT improves both the underlying immune disorder and associated colitis include IL10R, IPEX, Wiskott-Aldrich, some forms of SCID, XIAP, CGD, LRBA, CTLA4, and DOCK8 [12]. However, in patients with underlying epithelial barrier disorders, HSCT may not be efficacious for IBD symptoms. In particular, patients with X-linked ectodermal dysplasia with immunodeficiency due to NEMO mutation may see improvement in their immune function after HSCT, but several studies have shown that these patients may

continue to have colitis or even develop IBD de novo after transplant [95, 96]. This is theorized to be due to continued epithelial apoptosis and bacterial translocation, with a vigorous response from the transplanted immune system leading to chronic intestinal inflammation [96]. Similarly, patients with TTC7A deficiency who undergo HSCT continue to have epithelial cell defects and enteral symptoms despite amelioration of the immune dysregulation [97]. Costs and benefits of HSCT must be carefully weighed in VEO-IBD patients, as risks of the procedure include engraftment failure, sepsis, graft-versus-host disease, and secondary malignancy, among others [12].

5 Conclusions

Very early onset IBD represents a unique category of pediatric IBD, requiring special considerations regarding genetic testing and therapeutic decision making. As the incidence of VEO IBD increases, the need to understand the genetic underpinnings of the disease becomes more urgent in order to develop targeted therapies. Current treatments directed at specific immune pathways, such as anti-IL1 and anti-IL18, are becoming increasingly available for some disorders, allowing for avoidance of broader immunosuppressants and, in some cases, acting as a bridge to definitive cure with HSCT. Going forward, more genes will be identified, and their functions determined, opening the door for further immune-targeted agents as well as potential gene therapy. A multidisciplinary care team including genetics, gastroenterology, immunology, nutrition, and others is needed in order to care for this complex and challenging population and their families. VEO-IBD represents a new frontier in personalized precision medicine.

Declarations

Ethics Declarations None.

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Conflict of interest DLS is co-founder and Chief Medical Officer of NiMBAL Health, a digital Health Platform for IBD and is an Inventor for MicrobiomX. AEL and HBZ have declare they have no conflict of interest.

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