New Insights and Advances in Pathogenesis and Treatment of Very Early Onset Inflammatory Bowel Disease

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Very early onset inflammatory bowel disease (VEO-IBD) is characterized by multifactorial chronic recurrent intestinal inflammation. Compared with elderly patients, those with VEO-IBD have a more serious condition, not responsive to conventional treatments, with a poor prognosis. Recent studies found that genetic and immunologic abnormalities are closely related to VEO-IBD. Intestinal immune homeostasis monogenic defects (IIHMDs) are changed through various mechanisms. Recent studies have also revealed that abnormalities in genes and immune molecular mechanisms are closely related to VEO-IBD. IIHMDs change through various mechanisms. Epigenetic factors can mediate the interaction between the environment and genome, and genetic factors and immune molecules may be involved in the pathogenesis of the environment and gut microbiota. These discoveries will provide new directions and ideas for the treatment of VEO-IBD.

Keywords: microRNA, circular RNA, biologics, immunity, gut microbiota

INTRODUCTION

Very early onset inflammatory bowel disease (VEO-IBD) refers to a subgroup of pediatric patients diagnosed with IBD before the age of 6 years (1); it includes subclasses of infantIBD and neonatal IBD diagnosed before the age of 2 years and 28 days, respectively. Epidemiological data show that the incidence of VEO-IBD has been increasing rapidly, and one study showed that the incidence had reached 7.2% (2). The increasing incidence of VEO-IBD suggests that it is urgent to understand its pathogenesis. The latest and largest genetic association study collected genome-wide association data for over 75,000 patients and controls and identified 163 susceptibility loci for IBD. Interestingly, twin and family studies of IBD showed that for a child with an affected sibling, the risk increases 26 times for Crohn’s disease (CD) and increases 9 times for ulcerative colitis (UC). This suggests that both genetic and environmental factors may affect the pathogenesis of VEO-IBD. However, the pathogenesis of VEO-IBD is still not fully clear. To help solve the existing problems, this narrative review starts from the genetic pathogenesis of VEO-IBD, systematically and comprehensively summarizes the existing pathogenesis and treatment, and provides a potential breakthrough point for the therapeutics of VEO-IBD.
GENETIC FACTORS

Gene Abnormalities
Owing to technological progress in genetic testing and DNA sequencing, many genome-wide association studies (GWAS) have been improved, showing new single nucleotide polymorphisms (SNPs) (3). However, the explainable susceptibility loci and genetic risk factors discovered thus far only account for 20–25% of the heritability (genetic risk) (4). Moreover, monogenic mutations have been found mostly in children aged under 6 years, and most conventional polygenic IBD patients are older than 7 years.

Discovered in 2001, nucleotide-binding oligomerization domain containing 2 (NOD2) was the first susceptibility gene for CD. It encodes a protein that acts as an intracellular receptor for bacterial products in monocytes and transduces signals activating NFκB. Polymorphisms in NOD2 are one of the greatest genetic risk factors for Crohn’s disease. Three different non-synonymous NOD2 polymorphisms, R702W, G908R, and L1007fsinC, account for ~80% of all NOD2-associated cases of Crohn’s disease and they have been reported to cause a loss of receptor function in response to muramyl dipeptide (MDP) stimulation (5). It has been shown that the perception of NOD protein on bacteria is associated with the induction of autophagy (6). DCs from CD patients with susceptibility variants in the NOD2 gene are deficient in autophagy induction, and the localization of bacteria in autophagolysosomes is reduced (7). Additionally, the genome map of CD patients shows that NOD2 deficiency and mutations are related to CD in the ileum. Therefore, the interaction between ileal microflora and mucosal immunity is changed by NOD2 mutation, which is a high-risk factor for multiple complications of ileal CD and indicates increased susceptibility to CD.

miRNA Abnormalities
CD and UC have differences not only in the tissue miRNA spectrum but also in the peripheral blood miRNA spectrum. Recently, several studies have analyzed the differential expression of miRNAs in tissue samples and blood between IBD patients and healthy controls, showing that miRNAs may be regarded as novel biomarkers of these diseases (8). Therefore, the recognition of different miRNA expression profiles may provide a method to determine the course of the disease at an early stage.

Serum miR-146a and miR-146b decrease with IFX treatment and long-term glucocorticoid (GC) treatment (weeks) but not with short-term GC treatment (days) (9). Previous studies have shown that miR-146a and miR-146b are responsive to endotoxin, while increasing miR-146a or miR-146b is dependent on inflammatory stimuli (10). miR-146b was previously described as a monitoring biomarker for IBD, positively correlated with endoscopic disease activity, and more specific than serum C-reactive protein (9). In this study, serum miR-320a was found to decrease in response to both infliximab (IFX) treatment and long-term steroids (weeks) but not to decrease during shorter courses of GC treatment. In the resting colonic mucosa of patients with UC and CD, the levels of miRNA miR-320a were higher than those in controls, which may be caused by the sensitivity of the resting colonic mucosa to environmental factors (11).

Normally, miRNA miR-126 decreases with anti-TNF-α and shows a decreasing trend with GCs. A previous study also showed that miR-126 expression is higher in IBD biopsies than in controls and in vitro, and overexpression of miR-126 leads to intestinal mucosal barrier dysfunction (12). After the miRNA differential expression changes are confirmed, miRNA may also become a target of future treatment.

Circular RNAs
Non-coding RNAs (ncRNAs), circular RNAs (circRNAs) produced by reverse splicing of exons from precursor mRNAs, are ncRNAs that mainly act as elements of regulation. Increasing evidence has shown that cyclic RNAs can regulate gene expression through adsorption of miRNAs or interactions with other molecules at the transcriptional or posttranscriptional level. Furthermore, the evolutionary conservation of cyclic RNAs and their specific loop structure formed by phosphodiester ‘5 to 3’ leads to their resistance to nucleic acid exonucleases, causing a relatively stable expression in the cytoplasm. These features suggest that cyclic RNAs may be ideal biomarkers.

Several studies have shown that circRNA expression dysregulation plays a role in the progression of some cancers and some specific autoimmune diseases (13). CircRNA-004662 has been found to be a better and possible diagnostic biomarker for CD in terms of IBD pathogenesis and it may be a new candidate gene to differentiate CD from UC (14). It has also been found that circRNA-103765 in peripheral blood mono-nuclear cells (PBMCs) of patients with active IBD is significantly upregulated, and IFX treatment can significantly reverse circRNA-103765 expression. In vitro studies have shown that TNF-α induces circRNA-103765 expression and it promotes apoptosis, while silencing circRNA-103765 protects against TNF-α-induced apoptosis of human intestinal epithelial cells (ECs). Thus, blocking circRNA-103765 may be a novel approach for the treatment of IBD patients (15). A study found that the expression of circRNA-102685 was upregulated in the colonic tissue of CD patients compared to healthy controls. Therefore, in CD pathogenesis, circRNA-102685 may regulate the expression of target genes through miR-146 (16). HuR (encoded by the Elav1 gene) has become the main posttranscriptional regulator of intestinal epithelial homeostasis and it is a widely studied RNA binding protein (RBP) (17). To regulate ATG16L1 translation, HuR regulates autophagy by interacting with circPABPN1 in intestinal epithelial cells. Autophagy is generally considered to benefit cell, tissue, and organ homeostasis and it is involved in intestinal mucosal defense and barrier function (18). It has been shown that transcription of CDKN2B-AS1 into circular RNA with specific functions increases cell proliferation, increases cell adhesion, and decreases apoptosis (19, 20). Some studies have found that in UC patients, CDKN2B-AS1 is significantly downregulated, whereas linear and circular CDKN2B-AS1 affects the proliferation of colonic epithelial cells. A decrease in the expression of CDKN2B-AS1 enhances the formation of the colonic epithelium monolayer barrier by destroying...
Claudin-2 expression (21). Inspired by these studies, a new direction for the targeting of therapeutic drugs is provided by these circRNAs.

**IMMUNE DYSREGULATION**

The gastrointestinal tract is the largest immune organ in the human body, so it is not surprising that people with immunodeficiency have an increased risk of developing IBD. The progress of high-throughput sequencing technology helps describe single gene abnormalities, which change the intestinal dynamic balance through multiple mechanisms, including dysfunction of the epithelial barrier, abnormalities of T and B lymphocytes, a decrease in neutrophils, a defect in the phagocyte ability to kill bacteria and a lack of intestinal innervation.

**Cytokines and Their Receptors**

IL-10 was originally described as a soluble factor released by CD4+ Th2 cells that can preclude the release of CD4+ Th1 cytokines, such as IL-2 and IFN-γ (22) (Figure 1). Subsequently, it was found that IL-10 is secreted by a variety of cells and has multiple effects on T and B lymphocytes, bone marrow cells, etc. In 2009, mutation of IL-10RA-IL-10RB was found in infants with IBD, providing a new comprehension of the pathogenesis of IBD (23), which is consistent with the conclusion of previous studies that the lack of an anti-inflammatory effect of IL-10 causes the activation of an explosive intestinal immune response. These mutations are associated with severe intestinal inflammation, especially in neonatal or infantile VEO-IBD with a phenotype of severe enterocolitis and perianal disease (24). IBD-like immunopathology appears in all patients with IL-10 signaling blocking mutations, showing that these defects are a single gene form of IBD with a penetrance of 100% (24, 25). According to recent immunological studies, IL-10R1 is expressed in many cells involved in innate immunity or acquired immunity, while IL-10RB is an integral part of the receptors of IL-22, IL-26, IL-28 and IL-28β, and it is expressed in immunocytes or non-immunocytes (26). IL-10 polymorphism is associated with the risk of colitis (27), implying that genetic variation in the IL-10-dependent pathway may be related to the pathogenesis of inflammatory bowel disease.

TGFβ constitutes a key factor in the differentiation of regulatory T cells (Tregs) and Th17 cells. TGFβ is non-redundantly required for the generation of Tregs (28) but essential for the development of Th17 cells (29). IL-1β can take the place of TGFβ in IL-6-mediated generation of Th17 cells (30). In the absence of pro-inflammatory signals, such as IL-6 produced by microbial-activated dendritic cells (DCs) or IL-21 secreted by IL-6-stimulated T cells, priming of naïve CD4+ T cells in an environment rich in TGFβ promotes the development of iTregs (31) in response to antigens. In contrast, activation in an environment wherein both TGFβ and IL-6 are available promotes Th17 development, at least at mucosal sites (32). At low concentrations, TGFβ synergizes with IL-6 and IL-21 to increase
IL-23 receptor (IL-23R) expression, favoring Th17 differentiation (33, 34), whereas at high concentrations, TGFβ represses IL-23R and favors Foxp3+ Tregs, which in turn restrains RORγt function (35). In contrast, the amelioration of IL-21 and IL-23 toward Foxp3-mediated inhibition of RORγt facilitates Th17 differentiation (Figure 2).

In a controlled clinical trial, altered methylation of interleukin (IL-6) and transforming growth factor β1 (TGF-β1) was detected. The logistic regression analysis showed that a combination of 14 CpGs in TGF-β1 and 4 CpGs in IL-6 provides a new way to identify children with CD and that CpGs, and the proximal fragment of the promoter of the TGF-β1 gene, discriminated quite accurately between children with UC and controls. The results of this controlled trial suggest that a combination of DNA methylation of TGF-β1 and IL-6 could provide very high accuracy in distinguishing between CD and control patients and that further expansion of the sample content could detect even more accurate variations. This provides a new way of diagnosing and classifying children with VEO-IBD (36).

**T and B Lymphocytes and Complex Function Defects**

Loss of LRBA function mutations causes multiple defects in the immune cell population, which ultimately leads to the VEO-IBD phenotype (37). Arp2/3 and CARMIL2, also known as RLTPR, regulate the cytoskeleton, endocytosis, and cell migration by controlling actin polymerization (38). This study noted that CARMIL2 deficiency can produce an IBD-like phenotype, which may be related to the significant decrease in Foxp3+ Tregs in patients with CARMIL2 deficiency. Moreover, providing another important molecular example for PID to show the characteristics of VEO-IBD, this study placed great emphasis on the important role of CARMIL2-mediated immunity in regulation of the balance of the intestinal environment. The results of this study also suggested that the lack of a serious autoimmune phenotype in CARMIL2 deficiency may be caused by the deficiency of memory T cell differentiation and CD28-mediated dysfunction of effector T cell activation, but further research on CARMIL 2 is required to confirm this hypothesis.

Based on the relevant research results, we have summarized the existing and relatively comprehensive research conclusions, providing intuitive and useful conclusions (Table 1).

**Epithelial Barrier Function Defects**

Villous blunting or atrophy barely occurs in adult IBD coteries but it occurs in as many as 20% of VEO-IBD coteries (51). Junctional adhesion molecule-A (JAM-A) constitutes a key structure of tight junctions and it is essential for the control of cell migration into the underlying tissues. Moreover, studies of CD tissue specimens revealed a loss of epithelial JAM-A expression (64). In line with these findings, decreased levels of other tight junction proteins, such as claudins, were observed in CD (62).
### TABLE 1 | List of gene mutations associated with monogenic VEO-IBD and IBD-like colitis.

| Genes | Clinical syndromes | Studies |
|-------|---------------------|---------|
| **Immune dysregulation** | | |
| NOD2 | Susceptibility gene | Travassos et al. (6) |
| ATG16L1 | Susceptibility gene | Homer et al. (39) |
| TRIM22 | NOD2 signaling defects | Li et al. (40) |
| IL-10 | Neonatal or infantile VEO-IBD | Kotlarz et al. (24) |
| IL-10RA | Neonatal or infantile VEO-IBD | Glocker et al. (23) |
| IL-10RB | Neonatal or infantile VEO-IBD | Glocker et al. (23) |
| FOXP3 | IPEX | Torgerson and Ochs (41) |
| **Hyperinflammatory and autoimmune disorders** | | |
| XIAP | X-linked lymphoproliferative syndrome 2 | Latour and Aguilar (42) |
| SLC11A1 | Susceptibility gene | Sechi et al. (43) |
| CTLA4 | Autoimmune lymphoproliferative syndrome | Kuehn et al. (44) |
| PLCG2 | Autoinflammation and PLCγ2-associated antibody deficiency, and immune dysregulation (APLAID) | Zhou et al. (45) |
| STAT3 | Multisystem autoimmune disease | Duer et al. (46) |
| IL23R | Susceptibility gene | Duer et al. (46) |
| CCR6 | Susceptibility gene | Duer et al. (46) |
| TNFSF15 | Susceptibility gene | Duer et al. (46) |
| SHP2 | Susceptibility gene | Xiao et al. (47) |
| mIR-320a | CD and UC | Fasseu et al. (11) |
| let-7c | CD and UC | Banerjee et al. (48) |
| **T cell, B cell, and complex function defects** | | |
| LRBA | CD1d 8 | Alangari et al. (37) |
| ZAP70 | ZAP70 deficiency | Chan et al. (49) |
| WAS | Wiscott-Aldrich syndrome | Catucci et al. (50) |
| CARML2 | VEO-IBD, SCID | Magg et al. (38) |
| RAG2 | Omenn syndrome | Kelsen et al. (51) |
| RAG1 | Omenn syndrome | Villa et al. (52) |
| DCLRE1C/ARTEMIS95 | Omenn syndrome | Villa et al. (52) |
| MALT1 | SCID | Punwani et al. (63) |
| DOCK8 | Hyper immunoglobulin E syndrome | Sanal et al. (64) |
| CD40LG | Hyper immunoglobulin M syndrome | Levy et al. (65) |

(Continued)

### TABLE 1 | Continued

| Genes | Clinical syndromes | Studies |
|-------|---------------------|---------|
| AICDA | Hyper immunoglobulin M syndrome | Quartier et al. (56) |
| **Epithelial barrier function defects** | | |
| COL7A1 | Dystrophic epidermolysis bullosa | Zimmer et al. (57) |
| ADAM17 | ADAM17 deficiency | Chalaris et al. (58) |
| IKBKG | X-linked ectodermal immunodeficiency (NEMO) | Karamchandani-Patel et al. (59) |
| FERM1T | Kindler syndrome | Sadler et al. (60) |
| TTC7A | TTC7A deficiency | Avitzur et al. (61) |
| GUCY2 | Familial diarrhea | Uhlig (4) |
| CDKN2B-AS11 | UC | Rankin et al. (21) |
| CrcRNA_103765 | IBD | Ye et al. (15) |
| Oaudin2 | IBD | Zeissig et al. (62) |
| HLR | Colitis | Pott et al. (19) |
| mIR-126 | IBD | Chen et al. (12) |
| **Others** | | |
| FUT2 | Susceptibility gene | McGovern et al. (63) |

Defects in intestinal epithelial barrier function can be involved in VEO-IBD processes, including loss-of-function mutations in ADAM17 resulting in ADAM17 deficiency (65), IKBKG (encoding NEMO) mutation producing X-linked ectodermal dysplasia and immunodeficiency (59), and COL7A1 mutation causing dystrophic epidermolysis bullosa (57). FERM1T mutation results in Kindler syndrome (66), and TTC7A (61) or gain-of-function mutations in GUCY2 cause familial diarrhea (4, 67).

### INTESTINAL ENVIRONMENTAL FACTORS

It has been proven that the interaction between the gut microbiota, metabolites, and the gut immune system is essential for maintaining a healthy gut (68). Specific alterations in the composition and function of the gut microbiota may be used as microbial biomarkers for the diagnosis of IBD, disease activity, response to therapy, and prediction of outcomes.

For newly diagnosed children with IBD, an increase in the number of *Proteobacteria* in the intestinal microbiota and a decrease in the number of *Faecalibacterium prausnitzii* appear to be associated with a complex disease phenotype and a subsequent need for biological therapy or surgery (69). The most common finding was an increase in adherent-aggressive *Escherichia coli* in the gut of IBD patients. This infectious agent can adhere to and cross the intestinal mucus barrier and invade the upper intestinal cortex. Second, compared with
non-gastroenteritis patients. Salmonella fecal culture-positive gastroenteritis patients were significantly associated with an increased risk of new UC and CD. The most recent national case-control study from Sweden also demonstrated a positive association between a Salmonella diagnosis and the likelihood of IBD, and this study found that Clostridium difficile was associated with higher rates of UC and CD (70). Additionally, the latest and most comprehensive meta-analysis found a 57% lower risk of Helicobacter pylori exposure and inflammatory bowel disease, including CD and UC (71), and a meta-analysis that included only Asian studies reported consistent results (72). This protective association may be mediated, at least in part, by the specific components of H. pylori strains through immune regulation.

In addition to bacteria, some studies have found that VEO-IBD is also linked to enteroviruses. In a study of enterovirus, norovirus G-I, norovirus G-II, rotavirus, astrovirus, and sand wave virus RNA in fecal samples from 33 children with IBD and 17 children without IBD, viral RNA was detected only in children without IBD (3% vs. 0%) (73). Given changes in the intestinal microbiota in IBD patients, current clinical guidelines recommend testing for C. difficile in all IBD patients with exacerbating or newly emerging diarrhea and testing for cytomegalovirus in severely active IBD patients, especially when steroids and medications are used together to treat refractory disease.

Patients with CD exhibit significant differences in their gut metabolome, including lower concentrations of short-chain fatty acids (74, 75), higher concentrations of amino acids (75), and a dysregulated bile acid composition, including higher concentrations of conjugated bile acids and lower concentrations of secondary bile acids (76). In a cohort study, a strong association was found between an increase in the number of antibiotic prescriptions in the first year of life and the onset of IBD in childhood. In this study, the use of antibiotics, particularly in infancy, could lead to changes in the gut microbiota, suggesting they have a vital role in development of the immune system (77).

**THERAPEUTIC METHODS**

**Medications**

The standard therapeutic choices for VEO-IBD include 5-ASA, steroids, immunomodulators (6MP, azathioprine, methotrexate), and anti-TNF antibodies. At present, there are few studies that have been carried out in the pediatric patient population, and the relevant clinical data are insufficient, most of which are similar to polygenic IBD. It is more important to understand the data on drug-related dosage and adverse reactions (Table 2). Among the available medications, infliximab, vedolizumab, and ustekinumab are used in the treatment of VEO-IBD.

Monoclonal antibodies against tumor necrosis factor α (TNF-α), such as infliximab (IFX) or adalimumab (ADA), are safe and effective in inducing and maintaining remission in moderate-to-severe pediatric Crohn’s disease (CD), and ulcerative colitis (UC) patients (78, 79). Based on the experience of a tertiary center in Japan, IFX treatment seems to be more effective for non-ulcerative colitis type (NUCT) and non-ulcerative colitis type without perianal disease (NUC-NPD) patients, and it seems that their height and weight are improved after treatment (80). However, the use of TNF inhibitors is limited, even among TNF responders, because of systemic side effects, including immunosuppression and cardiotoxicity. In addition, up to one-third of patients do not respond to TNF-α antagonist therapy, and ~20% of primary responders may experience response loss each year (81, 82). Therefore, in recent years, the FDA has approved some bio-similars of TNF-α antagonists for the treatment of VEO-IBD. The biosimilar agent infliximab is an immunoglobulin G (IgG) anti-TNF-α monoclonal antibody that binds to soluble and transmembrane forms of TNF-α, which can further impede its interaction with the TNF receptors TNFR1 (P55) and TNFR2 (P75) on the surface of target cells. Therefore, it can be used to treat pediatric IBD (83, 84). Nonetheless, the biosimilar adalimumab has not yet been approved for pediatric IBD (85).

Vedolizumab (VDZ) is a humanized monoclonal antibody that specifically identifies lymphocyte integrin 4β7 receptors and prevents them from migrating from the blood vessels into the intestinal mucosa, thereby reducing the flow of white blood cells into inflammatory tissues. As an intestinal selectivity anti-integrin drug, it has been reported to have a low risk of infection (86, 87). In the first study of VDZ in children with VEO-IBD, this anti-integrin agent was shown to be safe and effective in the study population. Similarly, in the Porto group study, 16 pediatric patients found VDZ was safe and well-tolerated—1 developed upper respiratory tract infection (6.3%), and two developed joint pain (12.5%) (88). Conrad et al. also evaluated VDZ for severe IBD in children with similar results (89). Another multicenter study published in 2016 demonstrated the efficacy and safety of VDZ in the pediatric population (90). VDZ is not approved for pediatric patients but has demonstrated clinical efficacy for pediatric IBD. Its remission rates of UC and CD are 76 and 42%, respectively (89, 90).

Ustekinumab, a therapeutic human IgG1 monoclonal antibody (mAb) targeting the interleukin (IL)-12/IL-23 shared p40 subunit, is approved in adolescents (12 years of age and older) for the treatment of moderate and severe psoriasis, as well as for the treatment of adult celiac disease and UC (91) while celiac disease currently has gluten-free diet as the only therapy. In a multicenter prospective cohort of children, the effectiveness of ustekinumab in treating refractory UC was demonstrated (92), which is similar to the results of a retrospective study of pediatric IBD, suggesting that ustekinumab is effective and safe in children with IBD (93). Some case reports suggest that 50% of children with IBD have a clinical response to ustekinumab (94, 95). In a cohort of pediatric patients with CD, patients using ustekinumab had significant improvements in their abbreviated pediatric CD activity index (aPCDAI) scores, clinical remission rates, albumin, and hematocrit, and 89.5% of patients had no significant adverse events (96). The use of off-label drugs is increasing in children with IBD and generally they are being reported as safe and effective (93).
| Therapy                        | Therapeutic doses                                                                 | The time interval                  | Adverse effects                                                                 |
|-------------------------------|-----------------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------|
| Exclusive enteral nutrition therapy | Starting from 10–20 ml/(kg*d), the speed of increasing 10–20 ml/(kg*d)             | Total treatment: 6 weeks, then 2-week course of EEN tapering and gradual introduction of a habitual diet | Anatomical extension, perianal disease, stricturing behavior, diarrhea, vomiting, constipation, dehydration, feeding tube blockage, dyspnea and hypoxia, aspiration pneumonia. |
| Ustekinumab                   | 90 mg                                                                             | Every 8 weeks/every 4 weeks         | Arthralgia, skin eruption, cough, spondylarthrits, cardiovascular disease, infection, malignant tumor, headache. |
| Vedolizumab                   | 300 mg                                                                            | 0, 2 and 6 weeks, then every 8 weeks | Nausea, headache, malaise, spondylarthrits, bronchitis, liver function injury, fever, fatigue, back pain, limb pain, rash, pruritus, progressive multifocal leukoencephalopathy, infusion related reactions and hypersensitivity reactions. |
| Anti-TNF                      |                                                                                   |                                    |                                                                                  |
| Infliximab                    | 5 mg/kg                                                                           | 0, 2 and 6 weeks, then every 8 weeks | (1) Acute infusion reactions: urticaria, fever, dyspnea, etc. (2) Delayed response: arthralgia, fever, rash, edema, and headache. |
| Adalimumab                    | Induction period of 4 weeks, subcutaneous immunization Standard dose: 20 mg/kg or 40 mg/kg every week. Low dose: 10 mg/kg or 20 mg/kg every week. | <40 kg: 0 week, 80 mg. 2 week, 40 mg, >40 kg: 0 week, 160 mg. 2 week, 80 mg. | (3) Infectious complications: urinary tract infection, pneumonia, cellulitis, mastitis, influenza and tuberculosis. (4) Cardiovascular system response. (5) Reactions: multiple sclerosis, paresthesia, and seizures. Malignant neoplasms and lupus-like syndrome. |
| Golimumab                     | 2 mg/kg                                                                           | 0, 4 weeks, then every 8 weeks      |                                                                                  |
| CTLA4 agonists                | Abatacept < 75 kg, 10 mg/kg ≥75 kg, 750 mg the maximum dose cannot exceed 1000 mg | 0, 2, and 4 weeks, then every 4 weeks | (1) Discoid lupus, cutaneous vasculitis, erythema nodosum, skin infections, skin tumors. (2) Conditional infections: pathogenic pneumonia, sepsis. (3) Hematological toxicity. (4) Pulmonary sarcoidosis. (5) Tuberculous uveitis, eye pigment layer inflammation. |
| Ipilimumab                    | 3 mg/kg                                                                           | Every 3 weeks                       | (1) Common adverse effects: insomnia, joint pain. (2) Serious adverse effects: oliguria, hematuria, diarrhea, stomachache, cough, chest pain or wheezing, fatigue, memory problems, hallucinations, seizures, or neck stiffness, diureses weight loss, sweat, constipation, depression. |
From limited evidence, dual biotherapy may be a safe option for patients with refractory IBD who have failed multiple biotherapies and for managing the extra-intestinal presentation of IBD (97). A cohort of refractory pediatric IBD reported the effectiveness and safety of dual biologics or a combination of biologics and JAK inhibitors (98). In a case series and review of the literature, eight children received a combination of infliximab and vedolizumab, and five children received a combination of infliximab and ustekinumab, which shows combining biological agents to be safe and beneficial in selected patients (99). However, larger studies are required to confirm the preliminary safety data that were observed.

Ruxolitinib, a selective JAK1/2 inhibitor, was found in a single-center retrospective study of patients with refractory VEO-IBD with AIP to be primarily used for dual therapy when complete remission was not achieved with primary therapy. All patients in this study showed clinical improvement and did not require complete parenteral nutrition or steroids. Other potential benefits of ruxolitinib included a lack of immunogenicity, a rapid onset of action, and a short half-life. In addition, ruxolitinib can be administered entirely with sufficient enteral absorption to achieve a clinical response in a cohort with severe intestinal disease. However, this study still has limitations and could not determine whether ruxolitinib will be effective or safe in general use (100).

**Exclusive Enteral Nutrition Therapy**

Exclusive enteral nutrition therapy (EEN) is the preferred treatment for European VEO-IBD patients. In a propensity score matching cohort analysis of children with Crohn's disease induced by total enteral nutritionor glucocorticoids (CSs) (101), EEN, and CSs were found to be equally effective in inducing remission. Through a central retrospective analysis, EEN was found to be more effective than CSs in improving nutritional status and growth recovery, with relatively few side effects. More importantly, EEN can achieve mucosal healing (MH), which is the target of CD treatment. When applied in an early stage, MH reduces the incidence of hospitalization, surgical resection, and fistula formation, providing a new pattern for the treatment of very early inflammatory bowel disease. Some data show that the intestinal flora, amino acids, and fecal metabolites of CD patients have significant changes before and after EEN treatment (102), providing a biochemical detection method for judging the efficacy of EEN.

**Hematopoietic Stem Cell Transplantation**

Due to events such as severe or opportunistic infections and malignancies associated with biologic methods, stem cell transplantation has entered clinical trials as a more permanent treatment for IBD. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established therapeutic option for VEO-IBD. In a retrospective investigation of autologous hematopoietic stem cell transplantation for CD, MSC therapy may be an alternative to endovascular and fistula treatment (103). In terms of IPEX and IL-10 signaling deficits, HSCT has been shown to improve colitis and gastrointestinal fistula (104, 105). VEO-IBD patients with IL-10R deficiency can also be cured by allo-HSCT (23, 106). However, 11 patients with transplanted IL-10 and IL-10R deficiency showed a very high frequency of primary graft rejection (3/11), and these data suggest that patients with either IL-10 or IL-10R deficiency need to have their transplant regimen adjusted to reduce the risk of rejection (105, 106). Therefore, the use of post-transplant cyclophosphamide and bone marrow transplantation with T cell-identical cells have been considered potential therapies for patients with IL-10R deficiency (107). Similarly, studies have shown that allogeneic hematopoietic stem cell transplantation can successfully treat XIAP-deficient idiopathic colitis with specific conditioning regimens (108). For patients with a refractory IBD phenotype and an increased risk of mortality due to XIAP deficiency, HSCT should be considered as early as possible, as it can address their risk of intestinal inflammation and the development of life-threatening hemophilic lymphocytosis (109). However, HSCT is not effective for all cases of VEO-IBD. IBD lacking NEMO or TTC7A cannot be improved after HSCT and it may even worsen (110, 111). Therefore, we believe that the application of therapeutic HSCT in certain conditions is promising, but it should always be personalized.

Bone marrow MSCs can promote wound healing and tissue regeneration by secreting TGF-β and fibroblast growth factor. This property offers a new approach to the treatment of CD with fistulae.

**Surgery**

Despite recent advances in treatments, surgery still plays an important role in the management of VEO-IBD. Although surgery cannot cure VEO-IBD, in some cases, it can help resolve acute complications and maintain remission, allowing disease-free intervals, and nutritional recovery (112), and has a huge impact on physical and mental development (113). The main indications for surgery in CD are unresponsive and refractory to maximum medical treatment, fistula, perforation, strictureing disease, and severe perianal disease. Meanwhile, acute indications for UC surgery also include toxic megacolon, which is rare in children. A systematic review noted that surgical rates for CD ranged from 10 to 72%, while colectomy rates for UC ranged from 0 to 50% (113). Minimally invasive surgery has also been used for the radical treatment of CD and UC since 2002. In recent years, robotic surgery, a single-hole approach and minimally invasive treatment of perianal fistula have been adopted (114).

**Other Treatments**

Two recent randomized controlled trials (RCTs) provided additional insight by suggesting that rebuilding the intestinal microbiota composition through fecal microflora transplantation (FMT) can improve UC activity in this patient subgroup (115, 116). Although a few nonrandomized control studies have been performed in older children (youngest child 7 years old) (117), the efficacy of FMT for VEO-IBD is unclear.

The use of immunosuppressive drugs in the treatment regimen increases the risk of infectious diseases and infection-related complications in children with IBD. Therefore,
vaccination to prevent related infections is an important aspect of long-term care of this disease.

CONCLUSION

Current studies show that the pathogenesis of VEO-IBD includes genetic factors, immune molecular factors, and changes in the intestinal environment. With research progress on the susceptibility genes of IBD, the localization of the susceptibility genes of IBD helps identify and distinguish the disease phenotype, track the clinical progress, and ultimately develop new targeted therapies. However, due to the lack of clinical follow-up data in VEO-IBD children, there are still great challenges in terms of the drug efficacy and the research and development (R&D) of new drugs. It is not enough to draw lessons from the adult treatment experience alone. In the future, rapid diagnosis and management of children should be carried out, diagnosis, and treatment criteria based on genetic abnormalities should be established, and a clinical database should be expanded. We need to establish control groups and explore the influence of environmental factors on the incidence, treatment and prognosis of VEO-IBD. Finally, a precision medicine model needs to be achieved, namely, individualized treatment for VEO-IBD children.

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