# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

## Very–Early-Onset Inflammatory Bowel Disease

Scott B. Snapper, MD, PhD
Wolpow Family Chair in IBD Treatment and Research
Director, Inflammatory Bowel Disease Center and Basic & Translational Research (Gastroenterology, Children's Hospital)
Director, Inflammatory Bowel Disease Research (Gastroenterology, Brigham and Women's Hospital)
Associate Professor of Medicine, Harvard Medical School
Boston, Massachusetts

**G&H** What is very–early-onset inflammatory bowel disease?

**SS** Many workshops have been held to develop definitions for pediatric inflammatory bowel disease (IBD). One important working group classified one subgroup of pediatric IBD patients to those presenting with symptoms at an age less than 10 years (known as A1a in the Paris classification) because of unique characteristics of these younger children. More recently, very–early-onset IBD (VEOIBD) has been defined as IBD that occurs in children less than 6 years of age. Within these patients is a subset with infantile IBD, which is defined as IBD that develops in children less than 2 years of age.

**G&H** How do VEOIBD and infantile IBD differ from IBD that occurs in adolescents or adults?

**SS** One difference is that IBD presenting at a very young age often behaves quite differently from the disease that develops in adolescents or adults. For example, it often appears that the disease is more commonly initially restricted to the colon in children instead of the small bowel, which is commonly involved in adolescent- and adult-onset IBD patients; thus, when children who are young develop IBD, oftentimes it only initially affects the colon.

Another difference is that IBD in very young children can be resistant to many of the standard medications for IBD. This is particularly true in patients with infantile IBD, but even children with VEOIBD are often resistant to standard medical therapy and surgical therapy. In up to approximately 25% of these patients, not only do they have IBD, but they also have an underlying immunodeficiency, which can also impact therapy. However, VEO-IBD patients have not been well studied, largely because of the rarity of this patient population, so there remains a need for further research in order to obtain a better sense of what they respond to and what they do not respond to.

A third distinction is that patients with VEOIBD often have a much stronger family history of the disease (ie, at least 1 first-degree relative with IBD). This is especially true in patients with infantile IBD. Many doctors believe that genetic susceptibility may play a more important role in VEOIBD, whereas adolescent- and adult-onset IBD may have a stronger environmental component.

**G&H** How common is VEOIBD as opposed to adult-onset IBD? Has the age of onset of IBD been changing recently?

**SS** This is a very important issue. Recent studies by Eric Benchimol and colleagues in Canada have suggested that the greatest change in the increase of IBD incidence has actually been occurring in younger children, those who are between the ages of 0 and 4 years as well as those between the ages of 5 and 9 years. Having said this, if pediatric IBD (ie, those with IBD who are less than 18 years of age) comprises approximately 20% to 25% of all IBD patients, likely 20% of that 25%, or somewhere around 5% of all IBD patients, are children less than 10 years of age

presenting with symptoms. Patients diagnosed less than 2 years likely represent less than 1% of all IBD patients, which indeed is a very small percentage. However, it is in the younger children where the incidence of IBD appears to be changing the greatest. The reason for this change in incidence is not well understood, but likely involves important environmental factors that may interact with genetic influences in ways that are not well understood.

**G&H** How do the causes of VEOIBD compare with those of adult-onset IBD?

**SS** This question raises one of the most exciting issues about VEOIBD, which is that by studying these cases, which are quite rare, we hope not only to be able to come up with novel therapies for these patients, but also to come up with therapies that will be applicable to patients with IBD in general. In some cases, infantile IBD or VEOIBD can be caused by a number of rare, single genetic mutations; for example, IBD can be caused by mutations in interleukin 10 (*IL-10*) or the IL-10 receptor (*IL-10R*), or mutations in *NCF2*, *XIAP*, *LRBA,* or *TTC7*, among many other genes. Alterations in some of these same genes have also been reported to be associated with increased risk of adolescent- or adult-onset IBD.

In the first example, some of the patients who present with severe IBD in the first month of life (often in association with folliculitis and sometimes arthritis) have been found to have mutations in *IL-10R*. IL-10 is a hormone, or cytokine, that is important for suppressing the immune system. This is especially important in the intestine, where there are a hundred trillion bacteria that are needed for gut health. These necessary bacteria residing in the intestine stimulate the immune system constantly and, if not kept in check by suppressive hormones such as IL-10, would lead to intestinal inflammation. Thus, if a patient does not have IL-10R, he or she cannot suppress the immune system in response to IL-10 and develops very severe IBD. It is quite easy to determine whether a patient has an abnormal IL-10R via a blood test. The remarkable thing is that if a patient is diagnosed with the absence of a functional IL-10R, a curative therapy (bone-marrow or stem-cell transplantation) can be used to treat the patient. Bone-marrow or stem-cell transplantation from a healthy donor works for these patients because the IL-10R defect largely affects blood (stem) cells that reside in the bone marrow.

Thus, we are hoping that for a number of disorders that present in very-early life, we can identify genetic causes that may lead to a very specific therapy. We hope that some of these therapies may work for IBD that presents even in older patients. Notably, large, international genetic studies for adult IBD have found that alterations in *IL-10,* as well as some other genes that cause VEOIBD, are associated with an increased risk of IBD that presents later in life. Therefore, research about the cause of VEOIBD is also important for all patients with IBD.

**G&H** How else can understanding VEOIBD lead to novel therapeutic approaches in both children and adults?

**SS** Several groups from Toronto, Paris, Utrecht, Boston, and Montreal discovered that a certain subset of patients presenting with infantile IBD and/or an immunodeficiency within the first months of life have a mutation of the *TTC7* gene. With a new technology (discovered by the laboratory of Dr Hans Clevers in Utrecht), a clinician can obtain a biopsy specimen and make a mini-intestine or mini-gut in a culture dish. One of the remarkable things about the discovery of the *TTC7* mutation in these patients is that when biopsy specimens were obtained from patients who had this genetic defect, their mini-guts grew inside-out, instead of the normal way. Remarkably, the groups in Paris and Utrecht found an agent that was able to switch the mini-gut from growing inside-out to the normal way. In the future, testing mini-guts generated from patient tissues that grow abnormally (ie, inside-out in the case of those patients with *TTC7* mutations) with thousands of compounds that are within the arsenal of material in pharmaceutical companies may be used to identify drugs that can lead to normal growth. It is these types of approaches, in which physician-scientists combine genetic studies and functional tests, that we are enthusiastic about the ability to find new therapies that not only will be valuable for the patient with VEOIBD, which is rare, but for patients with IBD in general.

**G&H** Are there any other examples?

**SS** Another example of identifying a genetic defect that led to a focused, personalized therapy involves the *NCF2* mutation. Dr Aleixo Muise from Toronto identified a patient with severe VEOIBD who, after genetic analysis, was identified to have a mutation in the *NCF2* gene. He was then able to tailor therapy for this patient, in this case with antibiotics, and the patient responded very well.

More recently is the discovery that mutations in *LRBA,* which is known to lead to common variable immunodeficiency and can present in young or older children with IBD, are associated with reduced surface expression of cytotoxic T-lymphocyte antigen-4 (CTLA4) on T cells. Treatment of these patients with abatacept (manufactured by Bristol-Myers Squibb), a CTLA4–immunoglobulin fusion drug, led to dramatic and sustained improvement in clinical symptoms.

**G&H** Has there been any research on the use of these new, tailored therapies for IBD, such as stem-cell transplantation?

**SS** As mentioned earlier, several groups have evaluated the use of stem-cell transplantation for patients who lack IL-10R. Christoph Klein's group in Munich first published this therapeutic approach in the *New England Journal of Medicine* and more recently in *Gastroenterology* on a larger experience of using stem-cell transplantation for patients with IL-10R deficiency. In this series of patients and in other recent studies, stem-cell transplantation has been shown to be extremely effective in patients with IL-10R deficiency.

It is also important to note that IL-10R–deficient patients are also at increased risk of developing lymphoma, so transplant is highly recommended. The exact basis for the development of lymphoma in these patients is not completely understood but may result from a critical role for IL-10 in the function of cytotoxic CD8 T cells, which are important in immune surveillance. There have been reports of a patient presenting with IBD during infancy and later with lymphoma development in adolescence where only after the lymphoma diagnosis was made was a diagnosis of IL-10R deficiency considered and confirmed. This patient responded well.

It should be noted that researchers, including some in Chicago and Seattle, have also looked at the possibility of using stem-cell transplantation for IBD in a more general way. However, at this time, the use of stem-cell transplantation for IBD should not be considered standard of care in any way and should only be performed in the setting of an approved clinical trial. More research needs to be performed in carefully selected patients because stem-cell transplantation is not without risk.

**G&H** How is VEOIBD usually treated then?

**SS** Currently, unless the patient clearly has one of the rare mutations mentioned above (which might lead to more of a precision medicine approach, including stem-cell transplantation, antibiotics, abatacept therapy, or other therapies), treatment for VEOIBD is the same as that given to adolescents and adults with IBD (eg, anti-inflammatory agents, immunomodulators, biologics, antibiotics, and surgical approaches).

*Dr Snapper has served on advisory boards for Pfizer, Merck, Janssen, Synlogic, Enterome, Hoffman-LaRoche, and AbbVie. His work is funded in part by grants from the NIH, CCFA, The Helmsley Charitable Trust, and the Wolpow Family Chair in IBD Treatment and Research at Boston Children's Hospital. Dr Snapper, Dr Aleixo Muise in Toronto, and Dr Christoph Klein in Munich are principal investigators of the Very–Early-Onset IBD Consortium—an international consortium that has 11 other founding investigators and over 250 partnering clinicians/scientists who are devoted to identifying the causes and cures of VEOIBD.*

## Suggested Reading


Benchimol EI, Mack DR, Nguyen GC, et al. Incidence, outcomes, and health services burden of very early onset inflammatory bowel disease. *Gastroenterology*. 2014;147(4):803-813.e7; quiz e14-e15.

Dhillon SS, Fattouh R, Elkadri A, et al. Variants in nicotinamide adenine dinucleotide phosphate oxidase complex components determine susceptibility to very early onset inflammatory bowel disease. *Gastroenterology*. 2014;147(3):680-689.e2.

Kotlarz D, Beier R, Murugan D, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology*. 2012;143(2):347-355.

Lo B, Zhang K, Lu W, et al. Autoimmune disease. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science.* 2015;349(6246):436-440.

Moran CJ, Klein C, Muise AM, Snapper SB. Very early-onset inflammatory bowel disease: gaining insight through focused discovery. *Inflamm Bowel Dis*. 2015;21(5):1166-1175.

Muise AM, Snapper SB, Kugathasan S. The age of gene discovery in very early onset inflammatory bowel disease. *Gastroenterology.* 2012;143(2):285-288.

Murugan D, Albert MH, Langemeier J, et al. Very early onset inflammatory bowel disease associated with aberrant trafficking of IL-10R1 and cure by T cell replete haploidentical bone marrow transplantation. *J Clin Immunol*. 2014;34(3):331-339.

Uhlig HH, Schwerd T, Koletzko S, et al; COLORS in IBD Study Group and NEOPICS. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology*. 2014;147(5):990-1007.e3.