ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Targeting Cytokines in Inflammatory Bowel Disease

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G&H How has the targeting of cytokines evolved in the treatment of inflammatory bowel disease?

MD The first biologic that was introduced in the concept of anticytokine therapy for inflammatory bowel disease (IBD) was infliximab, which is an anti–tumor necrosis factor (TNF) agent. TNF is a cytokine that is involved in most inflammatory pathways associated with chronic immune conditions as well as nonimmune conditions such as infection. It is an inflammatory response to the disruption caused by a trigger, antigen, virus, or, in the face of IBD, uncontrolled inflammation with an unknown etiology in a genetically susceptible person. Therefore, TNF is inherent to multiple immune diseases, rendering the discovery of an antibody against it a major discovery in the field.

Subsequently, adalimumab was introduced into IBD management, and it too focused on targeting TNF. One of the differences is that adalimumab is not delivered intravenously like infliximab, but subcutaneously, which involves self-administration as opposed to an infusion. However, it became clear that not all patients with IBD respond to blocking TNF, which means that there are additional cytokines that are important in propagating inflammation.

That led to the second major cytokines targeted, interleukin (IL)-12 and IL-23. Those are the cytokines that ustekinumab (Stelara, Janssen) targets. This agent is an antibody that targets the p40 subunit, which is inherent to both the IL-12 pathway as well as the IL-23 pathway. This mechanism was introduced in psoriasis before IBD. Patients with psoriasis, which has similar biologic mechanisms to IBD, responded to IL-12/IL-23 blockade, so ustekinumab was introduced in Crohn's disease and then several years later in ulcerative colitis.

Then, IBD again followed the lead of psoriasis. Blocking IL-23 appeared to have superior efficacy in psoriasis than blocking both IL-12 and IL-23. This led to the revolution of IL-23–only inhibitors, starting with risankizumab (Skyrizi, AbbVie), which was approved first in psoriasis in 2019 and then in Crohn's disease in 2022. IL-23 inhibitors under investigation include mirikizumab, which is waiting for approval in ulcerative colitis, and guselkumab, which is in the late phases of clinical trials in IBD. With this therapeutic approach, IBD treatment took a different path from targeting TNF, which is the effector phase, and looked to block cytokines like IL-23 that are involved earlier in the inflammatory cascade. An incredible article in *The New England Journal of Medicine* in 2021 showed the pathways around IL-23 relative to TNF and why it made sense to try to block

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IL-23 and not just TNF. The presumption was that blocking IL-23 may get not only closer to the beginning of the dysregulated, adaptive immune response, but also to the innate response, referring to what was happening directly to trigger the recruitment of inflammatory cells and cytokine production. Perhaps going upstream from TNF or a little closer to the inciting cascade would lead to improved safety and better efficacy. Essentially, IBD treatment has become even more specific in the targeting of cytokines and has been going beyond merely blocking TNF to get closer to the underlying biology of IBD and other immune-mediated inflammatory diseases.

G&H How have small molecules such as Janus kinase inhibitors been involved in cytokine pathways?

MD The world of therapeutics now tends to be divided into biologics vs small molecules. It is important to first highlight the difference between biologics and small molecules such as Janus kinase (JAK) inhibitors. Biologics are a type of medication derived from biologic sources, rather than artificially made. These are large proteins that are developed with the laser-focused mission to manage their specific pathway, both in the systemic circulation as well as in the lining of the intestine itself. This may help improve their effectiveness or reduce off-target effects over nonspecific treatments. Small molecules, on the other hand, are made from chemicals and target specific enzymes involved in inflammation. More specifically, they block signals transmitted by the JAK–signal transducer and activator of transcription (STAT), or JAK-STAT, pathway and not the cytokines directly. Many components of the immune system use this signaling pathway, and it is a known regulator of inflammation in a variety of diseases. The biologics to date have been anticytokine antibodies.

G&H How have other therapeutic approaches inhibited cytokine release?

MD An indirect way of minimizing cytokine release involves targeting lymphocyte trafficking. In this category is the biologic vedolizumab (Entyvio, Takeda), which was designed to be gut-specific, as opposed to more systemic anticytokine therapies such as anti-TNF and anti–IL-23 agents, which target inflammation beyond the gut. Vedolizumab blocks the ability of $\alpha 4\beta 7$ lymphocytes to bind to the signaling receptor in the lining of the blood vessel known as mucosal vascular addressin cell adhesion molecule 1 and blocks the lymphocytes from being transported into the mucosa to propagate the uncontrolled inflammatory response. At the time, this was a game-changing moment in the field, as the safety profile was very attractive to both clinicians and individuals with IBD.

The concept of lymphocyte inhibition continues with our new agents, sphingosine-1 phosphate (S1P) receptor modulators. One such agent (ozanimod [Zeposia, Bristol Myers Squibb]) is currently available for ulcerative colitis, and another (etrasimod) may be later this year. We can think about the difference between these types of therapies based on where the lymphocyte inhibition begins. In a sense, vedolizumab waited for the lymphocytes to be floating in the bloodstream before blocking them from the gut. S1P receptor modulators are fascinating because they go to the lymph node to specifically inhibit the release of lymphocytes that are selectively carrying the S1P receptor. This approach does not completely take all lymphocytes out of play; it is specific to S1P lymphocytes, which are known to be involved in inflammation. Thus, there are a number of different treatment approaches that impact, directly or indirectly, the most important problem in IBD, which is uncontrolled inflammation and cytokine release.

G&H How can safety risks and treatment benefits be weighed for these different approaches?

MD Drugs are not approved unless they are deemed to be effective and to meet the safety guidance of the US Food and Drug Administration (FDA). However, there may be warnings. For example, there are black box warnings with certain IBD therapies, like when an association was found between TNF blockers and lymphoma, infections, and tuberculosis. Similarly, in 2019, a study found an increased risk of blood clots and mortality associated with these blood clots in a high-risk group of rheumatoid arthritis patients taking the JAK inhibitor tofacitinib (Xeljanz, Pfizer), as compared with patients taking anti-TNF therapy. This led to an FDA boxed warning and the restriction of tofacitinib for IBD and non-IBD patients. However, this same level of risk has not been demonstrated in clinical trials or the real-world setting in patients with IBD.

It is important for providers to follow guidance and individualize treatment to the patient sitting in front of them, keeping in mind that particular factors increase the risk of certain safety events. Providers must always balance the risks of the therapies with the risks of uncontrolled and complicating disease. For example, IBD can result in such uncontrolled inflammation that a patient might need to remove their colon, which in itself carries risk, or Crohn's disease specifically can result in scarring owing to uncontrolled inflammation and/or the creation of fistulas, which can lead to infection in the entire abdomen

and a resultant ostomy bag, which can at times be devastating for a patient.

The need to have a risk-benefit discussion based on the label is particularly important in pediatric-onset IBD, as only 1 class of advanced therapy, targeting TNF, has been approved to date. The implications of a child not growing, losing their colon or a part of their bowel, having a complication, or needing chronic corticosteroid use all factor into the decision-making process. Luckily, outside of very early–onset IBD (eg, <6 years), data have suggested that children with IBD respond similarly to, if not better than, adults from an efficacy perspective to drugs that are not approved but used off-label. That is because children tend to be healthier than adults in general. For example, fewer children are smokers, have body mass index issues, are exposed to infections, and so on. Providers do not worry about cardiac effects or blood clots in children the same way they do for a 65-year-old smoker, for example. Providers weigh and personalize their decision-making and communicate with patients about safety, both from the 1-year clinical safety trial and real-world experiences. In fact, real-world experiences often help inform safety more than the label because the denominator of exposure exceeds the denominator of patients from a 1-year trial. In a trial of that length, adverse events that occur in fewer than 1 in 1000 individuals are not typically seen.

G&H How can providers choose the right cytokine or pathway to target?

MD Right now, the approach that providers tend to use often centers on familiarity and is not necessarily based on the latest science. Providers often rely on anti-TNF agents because those drugs have been available the longest and thus have the most data, and insurance companies want to use them before originator drugs because biosimilars are now available. In my experience, patients also tend to want a drug that has been available for a while.

However, the ultimate goal, which everyone is working toward, is for treatment to be more personalized, driven by an individual patient's biology, almost like what oncology has been able to do. Oncology takes the genetics of the tumor and matches that information to a drug protocol. A good deal of work is currently underway trying to quantify the biology of an individual patient, looking at their tissue. Researchers at Mount Sinai are looking at gene expression in the skin and in the gut to see whether that information can help us determine the predominate pathway for patients, so they can be started on a therapy that characterizes their biology. This makes sense as many drugs are approved for both psoriasis and IBD, and perhaps the skin can be used as a window into the gut.

Other, more indirect ways are also being studied to try to define what is happening in tissue noninvasively and deploy treatment based upon an individual patient's biology. I believe the most important biologic question is whether to use a TNF blocker or an IL-23 blocker first, or whether it is necessary to go beyond blocking those 2 targets and go straight to a JAK inhibitor as monotherapy or perhaps in combination with a safe anticytokine-based therapy. That is what is being worked toward for the future. We are moving in the right direction, and I am hopeful that in the next 3 to 5 years, there will be a tool or a way of differentiating which patients should receive which treatment first. The first drug usually has the best chance of working; therefore, it is important to make the right choice on the first try. If patients continue to have unchecked inflammation, it is known that, particularly in Crohn's disease, irreversible bowel wall damage sets in and lower efficacy is seen with subsequent medications introduced over time.

G&H Are there any other cytokines or pathways being studied that might be good targets for IBD treatment in the future?

MD TL1A is a new target that was developed by Prometheus Biosciences and has now been acquired by Merck. It involves blocking a novel target that is not only involved in traditional inflammatory response pathways but may have a role in the process and biology of fibrosis. Animal studies have shown that this molecule may reverse fibrosis, but human studies have not replicated this finding as of yet.

Disclosures

Dr Dubinsky has served as a consultant and advisor for AbbVie, Abivax, AstraZeneca, BMS, Eli Lilly, Janssen, Merck, Pfizer, Prometheus Biosciences, and Takeda.

Suggested Reading

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