ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Lymphocyte Trafficking in Inflammatory Bowel Disease

Brian Feagan, MD
Professor of Medicine
Western University
Alimentiv Inc
London, Ontario, Canada

G&H What is the current understanding of the role of lymphocyte trafficking in the pathogenesis of inflammatory bowel disease?

BF In the past, it was believed that lymphocytes played a primary role in the pathogenesis of inflammatory bowel disease (IBD). Today, theory regarding pathogenesis has evolved such that it is generally considered that the primary defect is at the mucosal interface between commensal bacteria and the innate immune system. However, once the pathologic process commences, mechanisms based on T cells, a lymphocyte subpopulation, are critical for perpetuating the disease. Evidence for this theoretical construct has accumulated from both animal and human studies in recent years, such that strong prima facie evidence, including clinical experience with vedolizumab (Entyvio, Takeda), supports the notion that T cells are important in pathogenesis. This monoclonal antibody directed against the α4β7 integrin blocks attachment of T cells to the vascular endothelium and subsequently interferes with trafficking from the gut vasculature into the tissue compartment. Animal data, empiric human data from early-phase clinical trials, and ultimately the phase 3 studies of vedolizumab that led to approval for multiple indications in IBD provided proof that interference with T-cell traffic was an effective therapy for both ulcerative colitis and Crohn's disease. This body of evidence also underscores the importance of T cells to human IBD pathogenesis. This redirected interest not only in T-cell trafficking but T-cell biology in general and identification of specific strategies for modulation of the adaptive immune response.

G&H How did IBD drugs first target T-cell trafficking?

BF This approach began with natalizumab (Tysabri, Biogen), a monoclonal antibody directed against α4, a subunit of an integrin that is present on a subpopulation of T cells primarily targeting trafficking to the gut. This approach was shown to be effective in Crohn's disease and led to approval of natalizumab for this indication as well as for multiple sclerosis. The drug was never approved in ulcerative colitis, and only a few early studies were conducted in that disease. However, in distinction to targeting α4β7, targeting α4 is not gut-specific, as it blocks a broad population of T cells, including those that are α4β1-positive, which represent the vast majority of T cells circulating in the systemic circulation. Unfortunately, targeting of α4, in distinction to α4β7, led to the unanticipated consequence of John Cunningham virus reactivation, which can cause progressive multifocal leukoencephalopathy (PML), an uncommon but serious brain infection. Although natalizumab is still used extensively to treat multiple sclerosis, development in IBD was curtailed because of this serious side effect.

This experience resulted in concerns that PML was a general phenomenon with T-cell trafficking inhibitors. This proved not to be the case because α4β7 inhibition via vedolizumab was highly specific for the gut and did not cause the same mechanistic problems as α4β1 inhibition. There have been multiple attempts to develop complementary or similar agents by targeting either β7 or the receptor for α4β7 on the endothelium of the gut postcapillary venules (mucosal vascular addressin cell adhesion molecule [MAdCAM]). α4β7 MAdCAM interactions drive the egress of gut-homing lymphocytes into the tissue and can be inhibited by targeting α4, α4β7, β7, or MAdCAM itself. Targeting α4β7 has proven far more successful than targeting β7 or MAdCAM for reasons that are still not completely clear. That body of evidence led to

increased interest in lymphocyte targeting in IBD therapeutics as well as further research in other fields (notably multiple sclerosis) that if there were specific mechanisms to govern the egress of lymphocytes into tissue, then perhaps there could also be very specific mechanisms that would facilitate their departure from tissue and recirculation back into central lymphoid organs.

G&H How did the concept of interference with sphingosine-1 phosphate receptors come into play?

BF The immune system is founded upon the circulation of T cells, which transit from central lymphoid organs such as the spleen and liver to peripheral lymph nodes and through mucosal surfaces. T cells continuously circulate between peripheral lymph nodes and central lymph nodes, trying to identify pathogens on the gut, respiratory epithelium, and the skin. If pathogens are identified, the T cells return to the central lymphoid organs, where they proliferate and subsequently recirculate to the location that the pathogen was originally identified. The mechanisms to get lymphocytes into intestinal tissue were already discussed. However, given the specificity of these processes, it is logical to assume that there is an equally sophisticated mechanism to allow the return of lymphocytes from the tissue compartment. That is how the concept of interference with sphingosine-1 phosphate (S1P) receptors came about. Such agents affect both T- and B-cell trafficking. Once the lymphocytes are in the tissues, they return to the central circulation through the lymphatics. This process is governed by a receptor gradient of S1P, a phospholipid present in the cell membranes of the lymphoid vessels. There is an S1P gradient from the interior of lymph nodes to their exterior. Lymphocytes follow that gradient from low S1P concentration to high concentration, allowing them to exit the lymphoid tissue, return to the central circulation, and ultimately recirculate. S1P receptor modulators, which might be more accurately described as agonists, interact with the S1P receptor on the surface of lymphocytes. This binding interaction internalizes the S1P receptor, which eliminates the ability of the lymphocytes to recognize the gradient and traps them in the peripheral lymphoid organs.

The consequences are quite opposite to those of interference with trafficking of lymphocytes into the tissue. Looking at peripheral lymphocyte counts in patients receiving natalizumab, the effects are not subtle. Following blockade of $\alpha 4\beta 1$, the peripheral lymphocyte count increases dramatically because that trafficking is blocked into the tissues in a large population of T cells. On the other hand, the effects of blockade with vedolizumab are minimal because less than 3% of peripheral lymphocytes are homing to the gut. In distinction to these observations, a decrease in peripheral blood lymphocyte counts is expected with S1P1 agonism because the cells are trapped in the periphery and cannot return to the central circulation. This mechanism thereby causes large decreases in lymphocyte counts.

This observation also underscores that the mechanism of action is less specific than with vedolizumab and more analogous to the broad trafficking disruption caused by natalizumab. Such a dramatic and perhaps nonspecific effect raises the issue of whether S1P1 receptor agonists might convey an important risk of PML similar to that observed with natalizumab. However, that has not proven to be the case based upon the extensive experience accumulated with these agents in the treatment of multiple sclerosis. There have been few reported cases of PML with S1P1 receptor agonists, likely because of a differential effect on the populations of lymphocytes affected. Recent data indicate that these drugs do not interfere with memory T cells, which is protective against a broad, immunosuppressive effect. In addition, the functional activity of the lymphocytes is likely not affected, and lymphocytes retain their functional capabilities despite being trapped in the tissue.

In addition, there are 5 classes of S1P receptors, which have different effects on the immune system and differential effects on other biological functions. For example, isotype 1 of the S1P1 receptor has cardiac conduction effects, and isotype 2 has effects on vascular permeability. Fingolimod, the prototypic drug used widely in multiple sclerosis, is a very broad-spectrum agent that interacts with all receptor isotypes. However, because this broad activity is undesirable, more selective inhibitors of S1P1 have been developed with the goal of reducing side effects. Specifically, the focus has been on targeting the isotypes relevant to immune functions: 1, 4, and 5. Ozanimod (Zeposia, Bristol Myers Squibb) was the initial member of this more selective class to be evaluated and approved for the treatment of ulcerative colitis, and then most recently etrasimod (Velsipity, Pfizer) has also become available.

G&H Might blocking the entrance for lymphocyte trafficking have any potential benefits over blocking the exit, or vice versa?

BF There has been speculation about the comparative efficacy of these therapeutic approaches and efficacy in patients who have failed the other mechanism of action. However, the currently available clinical data are very limited and insufficient to address these questions. There were a few patients included in the etrasimod program who had failed vedolizumab; however, the number was so small that it is difficult to make any definitive statements about potential efficacy in that population. Additional studies are needed.

G&H Could you discuss research examining the targeting of lymphocyte trafficking in specific IBD patient subgroups?

BF Most of the research has been conducted in patients with ulcerative colitis, for which both ozanimod and etrasimod have been approved for induction and maintenance therapy. The etrasimod program in particular was able to provide some novel information regarding 2 important patient subgroups. Traditionally, patients with ulcerative proctitis have been excluded from clinical trials based on the notion that these individuals have different clinical characteristics compared with those with more extensive forms of the disease and that the outcome measures might not be valid. There is also a concept that ulcerative proctitis is a more difficult condition to treat. The latter belief was, in my opinion, a bias resulting from the most-difficult proctitis patients being concentrated in tertiary care clinics.

The etrasimod program included a substantial number of patients who had ulcerative proctitis yet met the same inclusion criteria of the trial for those with more extensive colitis: a Mayo Clinic endoscopic subscore of 2 or 3 (meaning that they had active disease) and sufficient symptoms in bleeding and stool frequency. The study showed no substantial efficacy differences or placebo responses in patients with ulcerative proctitis relative to those with more extensive disease. This was an important finding that may change patient populations in future trials.

This study also evaluated a subclass of patients with milder disease than conventionally entered into phase 3 programs for approval of a new drug in ulcerative colitis. Etrasimod was also found to be effective in these patients. However, this conclusion was based upon a subgroup analysis, and etrasimod did not receive a label approval for these patients.

G&H Have there been any misconceptions or challenges with using this approach?

BF There have been important misconceptions regarding the difficulty of initiating therapy with these agents. Appropriate concerns exist about adverse effects related to nonimmune mechanisms, including interstitial lung disease, macular edema, and cardiac conduction defects, the last of which are related to interactions with the S1P1 isotype 1 receptor subtype. A monitoring electrocardiogram is required for detection of conduction abnormalities during the initiation of therapy. Patients with relevant cardiac disease should be evaluated by a cardiologist. Because of the risk of interstitial lung disease and macular edema, pulmonary function tests and ophthalmologic assessment should be considered in patients at risk. Liver enzyme monitoring is also required.

Although these requirements are a burden, it should be recognized that not many patients with ulcerative colitis will be ineligible for treatment with these agents. Fingolimod, which has a broader inhibition of the various receptor isotypes and more extensive monitoring requirements, has gained widespread acceptance by neurologists for treatment of multiple sclerosis. Although it might be perceived that the requirements for assessment and consideration of side effects indicate that these drugs are difficult to use and are potentially more toxic than others, this is not generally true and has not been a consideration in the neurology community. There is a learning curve, and, as with all drugs, it takes time for practitioners to become comfortable with new therapies.

G&H What further research is needed?

BF Translational medicine studies are required to understand the functional effects of the lymphocytes that are sequestered in the mesenteric lymph nodes. It would also be good to know which populations of patients are best treated with S1P receptor antagonists. There is a perception that these drugs should be used in patients with, say, milder disease rather than, say, other small molecules such as the Janus kinase (JAK) inhibitors tofacitinib (Xeljanz, Pfizer) and upadacitinib (Rinvoq, AbbVie). However, there is no direct evidence to support this concept. Additionally, it would be interesting to see trials initiated in early disease and in primary therapy. Whether these drugs should be combined with other agents is also a relevant issue. Oral anticytokine therapies are being developed. JAK inhibitors have broad-spectrum immunosuppression, and perhaps they are not the best agents to combine with an S1P1 receptor agonist; however, there will be other agents, such as oral anti–interleukin-23 inhibitors. Combining drugs in a single pill is an attractive concept.

Disclosures

Dr Feagan has been a scientific consultant to BMS, Pfizer, and Takeda.

Suggested Reading

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