ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Targeting Beta-7 Integrins for the Treatment of Inflammatory Bowel Disease

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G&H How and why did targeting beta-7 integrins become a therapeutic approach in the treatment of inflammatory bowel disease?

JR-N Lymphocytes that migrate to the intestine express surface integrins that are heterodimeric molecules, as they have 2 chains, an alpha chain and a beta chain. When an alpha-4 chain pairs with a beta-7 chain, a molecule binds to a ligand on the intestinal endothelium known as mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1). In an issue of the *European Journal of Immunology* in 1980, Dr Eugene Butcher, who is the father of this field, described the theory that cells that migrated to the gut specifically express certain integrins that allow them to recognize that particular environment. Years passed until the pharmaceutical industry started developing drugs against these integrins. The first drug that was approved was natalizumab (Tysabri, Biogen), which is still used for the treatment of Crohn's disease. An ulcerative colitis indication was never pursued. Natalizumab targets the alpha-4 chain in the alpha-4/beta-7 integrin as well as in the alpha-4/beta-1 integrin, which binds to vascular cell adhesion molecule 1 (Figure). Vedolizumab (Entyvio, Takeda), which targets a combinatorial epitope specific for the alpha-4/beta-7 integrin, was approved in 2014 for the treatment of both ulcerative colitis and Crohn's disease. Vedolizumab is currently in common use for these indications and is held in high esteem by inflammatory bowel disease (IBD) specialists because of its safety and because it acts through a different mode of action than cytokine blockade, a strategy commonly exemplified by tumor necrosis factor (TNF) blockade.

G&H Could you further explain the different modes of action for the IBD drugs that are currently available?

JR-N In IBD, there are many drugs, but when it comes to biologics, which are monoclonal antibodies, there are only 2 strategies. The first was to neutralize pro-inflammatory cytokines, the most important of which is TNF. Many drugs have been developed to block TNF. More recently, other cytokines have been targeted as well, including interleukin (IL)-12 and -23, such as with ustekinumab (Stelara, Janssen). There are now also IL-23–specific antibody blockades in the pipeline. The other strategy involves targeting lymphocyte traffic, which means interfering with inflammatory cells as they migrate into the intestine.

G&H Which IBD drugs in development target beta-7 integrins?

JR-N Of the drugs in development, etrolizumab (Roche), which targets the beta-7 subunit (shared by the alpha-4/beta-7 integrin and the alpha-E/beta-7 integrin), is at the most advanced stage. Phase 3 trial results are expected this fall. Ontamalimab (Shire) targets MAdCAM-1, the ligand for the alpha-4/beta-7 integrin in the intestine. This drug is currently in phase 3 development for both

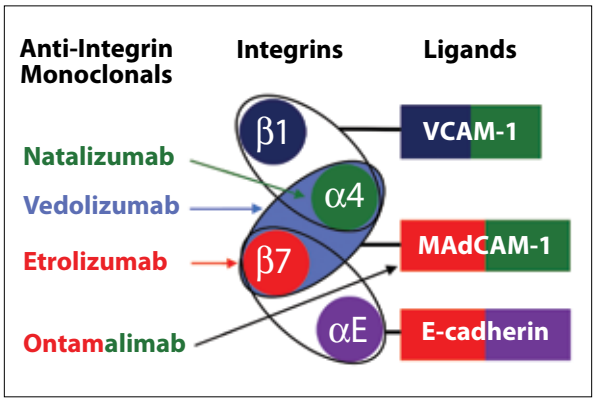

Figure. Anti-integrin antibodies target distinct integrins, their subunits, or their ligands.

MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1.

Crohn's disease and ulcerative colitis. There are also several small-molecule drugs in earlier stages of development.

G&H What are the most recent data on these drugs?

JR-N For etrolizumab, the most recent data that have been released are the phase 2 data published in *The Lancet* several years ago, which were promising. Remission was achieved in 21% of patients with ulcerative colitis who received 100 mg of etrolizumab compared to no patients in the placebo group. In addition, Crohn's Disease Activity Index remission was achieved at week 14 in 23% of patients with Crohn's disease who received 105 mg of etrolizumab, 29% of patients who received 210 mg, and 17% of patients who received placebo.

The most recent data on ontamalimab were presented several years ago at Digestive Disease Week. Ontamalimab did not show a signal for use in Crohn's disease patients. However, the drug seems to be promising for ulcerative colitis. Its ulcerative colitis data had an interesting bell-shaped curve; once maximum efficacy was reached, if more of the drug was given, it appeared to lose efficacy. However, the significance of this observation remains unclear.

G&H Does the targeting of beta-7 integrins appear to be more effective in certain patient subgroups?

JR-N Based on the data on vedolizumab published in 2013 in *The New England Journal of Medicine*, targeting the alpha-4/beta-7 integrin appears to be more efficacious in ulcerative colitis than in Crohn's disease. However, this is a complicated issue because Crohn's disease presents with various phenotypes (ileal, colonic, and ileocolonic).

G&H Why do some IBD patients not respond to the blockade of beta-7 integrins?

JR-N Little is known about why patients might not respond. There have been several publications, mostly of preclinical (ie, mouse) models, suggesting that proinflammatory lymphocytes can use the alpha-4/beta-1 integrin in place of the alpha-4/beta-7 integrin. This is likely the reason that natalizumab, which targets both of these integrins, had efficacy in Crohn's disease, which is the IBD that presents the most therapeutic challenges.

This theory might also explain the lack of efficacy that may occur in a significant number of IBD patients, including those with ulcerative colitis. Approximately 50% are primary nonresponders. However, as with any biologic, more patients lose efficacy later on as the immune system recognizes the drug and mounts an immune response against it. Patients can develop antidrug antibodies to all monoclonal antibody drugs, including those that are humanized or fully human, such as adalimumab.

G&H How safe are the drugs that use this therapeutic approach?

JR-N Other than natalizumab, the drugs that target beta-7 integrins have been proven to be extremely safe in general. Essentially, only mild symptoms, such as upper airway sinusitis and rhinitis, are seen. Vedolizumab, which targets only the alpha-4/beta-7 integrin, is very safe. From a basic science point of view, etrolizumab complicates matters by targeting the beta-7 subunit, which means that it actually targets 2 integrins: alpha-E/beta-7 and alpha-4/beta-7. By targeting the shared beta-7 subunit, etrolizumab may also have side effects involving the role of the alpha-E/beta-7 integrin, which is not fully understood. As with every drug, the more patients are exposed to the drug over time, the more likely adverse events may be seen.

G&H Should these drugs be avoided in any patients?

JR-N There is very little current use of natalizumab due to the possibility of progressive multifocal leukoencephalopathy (PML). This complication has been attributed to the lack of specificity of natalizumab, and it is not a concern with the other drugs in its class. One PML case was reported in a patient taking vedolizumab, but other immunosuppressives were also being taken at the same time, and it was not possible to determine whether the complication had been caused by vedolizumab. Most

likely, it was not the cause because the drug is being used widely in both the United States and Europe, and other cases of PML have not been reported.

G&H How should patients using this treatment approach be followed?

JR-N As with every biologic, the patient's trough level (ie, lowest drug level) should be monitored, especially when he or she is losing efficacy. The lowest drug level occurs right before the patient receives the next dose, and at this time, patients can also be tested for the presence of antidrug antibodies against the drug. This is how doctors monitor patients on vedolizumab, which is currently on the market, and I assume the same will be done with etrolizumab once it is approved.

G&H Are there any other benefits to targeting beta-7 integrins as a treatment approach?

JR-N Safety is probably the biggest benefit. There are also other indications that would potentially make sense for this treatment approach, but there have not yet been good supporting data. A number of patients who have ulcerative colitis also have primary sclerosing cholangitis, and it is thought that the cells that migrate to the liver to induce this process also use the alpha-4/beta-7 integrin. However, research in Europe has not found that this therapeutic approach is effective for primary sclerosing cholangitis. Another application of targeting beta-7 integrins could potentially be celiac disease, particularly in patients who have refractory celiac disease, for which removing gluten is not efficacious. The T cells that induce celiac disease also use the same integrins to migrate to the duodenum, so this application could potentially make sense conceptually. However, formal testing is needed. Currently, there are no indications for the targeting of beta-7 integrins other than ulcerative colitis and Crohn's disease.

G&H What are the next steps in research involving this therapeutic approach?

JR-N In my opinion, it would be beneficial if the pharmaceutical industry could develop small molecules that could be orally administered. One of the challenges of the medications that currently use this therapeutic mode of action is that they are parenterally administered. Patients have to go to the hospital to receive an infusion every 8 weeks, and there are associated costs, such as nursing and administration costs. Takeda is currently developing a pen to provide subcutaneous injection similar to adalimumab. Many patients prefer this route of administration because they can receive the medication at home.

Another advantage of developing a small-molecule drug is that small molecules do not have immunogenicity, which is the main challenge of biologics. Any drug that is a monoclonal antibody will eventually be recognized by the immune system; thus, there is always the possibility of losing response due to the immunogenicity of the drug. That would not happen with a small molecule.

An important issue for future research is where the targeting of beta-7 integrins should be positioned as a treatment approach for IBD patients. Currently, there are several anticytokine drugs, including anti-TNF drugs and anti–IL-12/-23 drugs (ustekinumab and more-specific anti–IL-23 drugs). There are also Janus kinase inhibitors, which are small molecules that target proinflammatory cytokines and are administered orally. Vedolizumab is currently on the market and etrolizumab will likely be by 2021. In what order should these therapies be implemented? In addition, what criteria should be used to make the decision of using either therapy? These are important questions that will need to be studied and answered.

Disclosures

Dr Rivera-Nieves has received research support through an Investigator-Initiated Sponsored Research Grant from Takeda Pharmaceuticals.

Suggested Reading

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