

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Anti-Adhesion Strategies for Inflammatory Bowel Disease

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G&H What does the term adhesion connote in inflammatory bowel disease?

BF Adhesion connotes the process by which white blood cells (WBCs) become attached to the linings of the blood vessels that service the gut. All WBCs have very specific means by which they adhere to the lining of blood vessels and then transport themselves across the endothelial lining into the tissue. All inflammation is governed by very specific cell-cell and protein-protein interactions.

G&H Do anti-adhesion strategies interrupt this process?

BF Yes. The hypothesis behind the development of anti-adhesion drugs is that if WBCs are not continuously reinforcing and augmenting inflammation in the tissues, then the balance will be shifted toward a repair process in the tissue.

G&H What are some of the specific anti-adhesion strategies for treating inflammatory bowel disease?

BF There is evidence that our conventional drugs, such as corticosteroids, prednisone, and the tumor necrosis factor (TNF) antagonists interfere with WBC trafficking. For example, TNF upregulates adhesion molecule expression on endothelial surfaces. Blockage of the mechanism is likely partially responsible for the efficacy of TNF antagonists.

More recently, increasingly selective approaches have been developed to interfere with leukocyte migration into tissues. Rather than having an indirect effect on adhesion molecule biology, researchers have developed specific monoclonal antibodies to directly target important molecules and thereby interfere with the adhesion process. One example is natalizumab, which was first developed as a treatment for multiple sclerosis.

G&H How does natalizumab work?

BF This antibody binds the α_4 -integrin on circulating lymphocytes. The integrin on lymphocytes are heterodimeric proteins, meaning they have two subunits, an α unit and a β unit. There are several types of β units, but the most common and important subunit combinations are α_4 - β_1 and α_4 - β_7 . Natalizumab blocks the interactions of both of these proteins. Large, well-controlled studies have demonstrated natalizumab to be effective in the treatment of Crohn's disease, and it is approved by the US Food and Drug Administration (FDA) for this indication.

Importantly, α_4 - β_1 interacts with vascular cellular adhesion molecule (VCAM), which is present on every vascular bed in the body. Thus, one would expect that natalizumab would have an effect on every inflammatory process in the body, not just those in the gut. This universality explains why this drug is effective for both multiple sclerosis and Crohn's disease. Conceptually, this broad-based approach might be associated with a greater possibility of adverse events.

G&H Have more selective antibodies been developed?

BF A more selective approach would involve inhibiting α_4 - β_7 , which interacts with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is present only in the gut. Vedolizumab, a monoclonal antibody directed against α_4 - β_7 , is currently in phase III clinical trials for the treatment of both ulcerative colitis and Crohn's disease.

This drug has already demonstrated promising activity in the treatment of ulcerative colitis, with results published in *The New England Journal of Medicine* in 2005.

Another agent in development is rhuMAb Beta7. This compound is not as selective as vedolizumab because β_7 is not specific to the gut alone. Also in early development is an agent that directly targets MAdCAM-1, the protein on the lining of the blood vessel that interacts with $\alpha_4\beta_7$.

G&H Do these various agents effectively diminish inflammation?

BF Natalizumab is very effective for both induction and maintenance of remission for patients with Crohn's disease. Unfortunately, the use of natalizumab has been limited due to a dangerous side effect: in approximately 1 in 1,000 patients treated with this agent, the JC virus, which is latent in the kidney cells of 50–60% of people, becomes active. In these patients, the virus becomes neurotropic and leads to progressive multifocal leukoencephalopathy (PML), a serious condition that may be fatal. Fear of this side effect has limited the use of the drug by gastroenterologists. Approximately 80,000 patients with multiple sclerosis are being treated with natalizumab worldwide, but very few patients with Crohn's disease are being treated with natalizumab.

G&H Why does natalizumab activate the JC virus?

BF This side effect may be due to the lack of specificity in targeting $\alpha_4\beta_1$ —VCAM. This interaction is not confined to the gut, and it appears that natalizumab is exerting some effect on antiviral T-cell surveillance in other tissues.

G&H Has this side effect been seen with other anti-adhesion drugs?

BF The newer compounds that are more selective do not interact with $\alpha_4\beta_1$ —VCAM. By targeting interactions present in the gut only, activation of a virus located in kidney cells is not likely to occur.

G&H Do you think that natalizumab is being underutilized due to concern about this virus?

BF Yes. There are patients for whom the burden of illness more than offsets the risk of developing PML. Experience in multiple sclerosis has shown us that there is not a huge risk of other opportunistic infections associated with this drug. Patients with multiple sclerosis being treated with natalizumab are being followed through an FDA-mandated registry, and the data accrued thus far indicate

that the risk of PML reaches its maximum level at 2 years, and that the risk remains constant at 1 in 1,000; it does not increase with time.

G&H Are strategies being investigated to prevent PML as a side effect of natalizumab?

BF Yes. Diagnostic tests for the JC virus may be developed so that clinicians can determine in advance whether natalizumab is safe to administer for a given patient. Similarly, it may be possible to monitor patients who are receiving natalizumab for JC virus activation. More effective treatments for PML are also being investigated.

G&H What other anti-adhesion strategies are currently being explored?

BF An oral drug that inhibits a chemokine is currently under investigation. Chemokines are messengers that enable WBCs to target the gut; they act like a guide to channel WBCs to a specific region. A small molecule inhibitor of a chemokine known as CCR9 recently completed a phase II/III clinical trial.

The potential advantage of this approach over monoclonal antibodies is that with small molecules there is no issue with sensitizing the patient. The human immune system is very good at recognizing foreign proteins and will develop antibodies against the antibodies being used as a drug. Sensitization is not a problem with small molecules.

G&H Do anti-adhesion drugs offer a benefit to patients with inflammatory bowel disease that other drugs do not?

BF Yes, potentially. The highly selective anti-adhesion drugs may be less toxic than TNF blockers and may potentially carry a lower risk of infection because of that. Because anti-adhesion drugs work through a different mechanism, they are an option for patients who have failed treatment with a TNF antagonist. Previously, primary or secondary failure of TNF antagonist therapy has presented a serious clinical problem because no effective treatment options existed.

With further study, these drugs may also be approved as first-line biologic therapies for high-risk patients.

G&H Is combination therapy using an anti-adhesion molecule plus conventional treatment an option?

BF This question is somewhat controversial, and there are not yet any data available on combination approaches.

Based upon experience in both rheumatoid arthritis and Crohn's disease, it is clear that foreign proteins are sensitizing; in approximately 10% of patients, anti-adhesion therapy must be stopped due to sensitization. Coadministration of an antimetabolite reduces the rate of sensitization. Evidence from the recent SONIC study indicates that combining an antimetabolite with a monoclonal antibody not only decreases sensitization but also improves efficacy.

However, the occurrence of PML has raised concerns that prior immunosuppression followed by an antimetabolite, or concomitant administration of these agents, could be a risk factor for activation of the JC virus. Because of this concern, some investigators believe that monotherapy is the best approach. There are no data on combination therapy as of now. A subgroup analysis from

the studies of vedolizumab should provide some useful insights on this issue.

Suggested Reading

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