

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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New Cytokine Targets in Inflammatory Bowel Disease

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G&H What role do cytokines play in inflammatory bowel disease?

TM Data from animal models convincingly show an association between elevated concentrations of cytokines in the gut wall and murine inflammatory bowel disease (IBD). If researchers knock out or overexpress certain cytokine genes, they can either prevent or cause IBD in mice and rats. Likewise, antibody-mediated neutralization of many different cytokines has been reported to ameliorate experimental IBD. In humans, it is clear that the levels of many different cytokines are elevated in the gut wall of patients with ulcerative colitis (UC) or Crohn's disease (CD). The success of anti-tumor necrosis factor α (anti-TNF α) therapy—as well as the limited success of other agents such as anti-interleukin (IL)-6—also indicates that cytokines are critically important in driving inflammation in human IBD.

G&H What is the advantage of cytokine inhibition as a treatment for IBD?

TM The advantage of cytokine inhibition is that if you can find the so-called “critical cytokine,” the one that is the master regulator of immune responses, then it may be possible to switch off inflammation without causing unwanted side effects. However, 1 of the challenges with

this approach is that immune-protective and inflammatory pathways overlap. Inflammation plays a major role in fighting infections, so meeting the needs for maintaining host protection against infection while dampening idiopathic inflammation is a major challenge when developing therapies that target cytokines.

G&H How has the development of anti-TNF α agents improved the treatment of IBD?

TM Anti-TNF α agents are powerful drugs that have significant side effects; for example, they make patients vulnerable to infections. However, they can also provide significant benefits for many patients whose disease does not respond to other therapies. Indeed, many patients have seen their lives transformed by anti-TNF α antibodies.

The other major conceptual advantage of these drugs is that they showed it was possible to intervene in a pathway that researchers had considered essential for health. Before the advent of anti-TNF α therapy, many researchers worried that this treatment would make people so immune-suppressed that they might get cancer, tuberculosis, and/or other serious infections. While people should not underestimate the risks of some of these drugs, hundreds of thousands of patients have been treated without serious adverse events, and that realization has been absolutely transformative in developing new therapies.

G&H What are some of the main disadvantages of anti-TNF α medications?

TM The risk of infection is significant, and vigilance is needed. In addition, a major disadvantage of anti-TNF α agents is that only about half of the people who receive these agents respond. Fortunately, clinicians are becoming more sophisticated in the ways in which they are using anti-TNF α agents; by using anti-TNF α agents in combination with other therapies such as azathioprine, additive effects are seen. Another problem with anti-TNF α agents is that some patients become unresponsive. In these cases, the drug is effective the first few times it is administered, but then it stops working. There are well-known effects related to the development of antibodies against the anti-TNF α antibody, which reduces efficacy, but personally I think a component of unresponsiveness is that treatment changes the pathways of cytokine-mediated damage in the tissues. For example, inflammation may go from being TNF α -driven to IL-6–driven.

G&H What other cytokines might be good targets for IBD treatment?

TM Investigators have recently examined the possibility of treating CD with an antibody that inhibits IL-12 and IL-23 p40. Theoretically, this antibody should diminish both Th1 and Th17 responses. However, results of these trials were quite disappointing, although there does appear to be efficacy in patients who are unresponsive to anti-TNF α antibodies. Similarly, studies of anti-interferon- γ antibodies in patients with CD were very disappointing. Anti-IL-17 has also been studied but did not appear to be effective. Studies using anti-IL-13 in patients with UC and anti-IL-21 in patients with CD have also been proposed.

Given the initial enthusiasm surrounding anti-TNF α agents, there was much hope that other cytokines might be even more effective, perhaps with less risk of infection. So far, that has not been the case, and I am not convinced that we will find any anti-cytokine therapy better than anti-TNF α antibodies.

G&H Which of the cytokine inhibitors currently being studied look most promising?

TM I think anti-IL-21 may be quite important, as IL-21 is involved in many different inflammatory pathways. There are much data showing that IL-21 is important in T-cell biology and IBD. Specifically, IL-21 is involved in maintaining T-cell survival and maintaining the production of cytokines, such as TNF α , IL-17, and interferon- γ .

However, IL-21 has deleterious effects in the intestine when it is produced in excess. For example, it causes the fibroblasts in the gut wall to start producing enzymes that cause ulcers. It also causes other cells to make chemokines, such as CCL20, which induce the migration of more T cells into the tissue to cause more damage.

G&H What possible side effects might be associated with an anti-IL-21 therapy?

TM There are some data suggesting that IL-21 is important for immunity to certain viruses—such as Epstein-Barr virus—which are often present, but are controlled in healthy individuals. Part of the control of these long-term viral infections may involve IL-21, so there is the possibility that neutralizing IL-21 may cause exacerbations of endogenous viruses. Also, IL-21 itself has been tested in patients with cancer because it causes apoptosis, so there is the possibility that neutralizing IL-21 may put patients at risk for developing cancer. Finally, IL-21 is made by cells called follicular helper T cells, which drive immunoglobulin (Ig)A responses in the gut, so targeting IL-21 may cause patients to become IgA-deficient. However, this is unlikely to be a problem, because many people are IgA-deficient, and they are largely well. Currently, these are all theoretical risks; we will not know if any of these issues are real concerns until anti-IL-21 is tested in patients.

G&H What further research is needed in this area?

TM Cytokines are made by inflammatory cells, and we are now getting much better at targeting these cells. The root of the problem in IBD is that T cells, macrophages, and neutrophils produce cytokines that damage the soft lining of the gut, so the best solution would be to kill or reprogram the T cells, rather than just dealing with the cytokines.

Retuning T cells and the immune system in general is the basis for trials of bone marrow transplantation in patients with CD. Bone marrow transplantation is not a practical treatment for CD because of the risks associated with the procedure, but these studies show that the key problems in this disease stem from the T cells and the macrophages in the gut wall. If we could deal with these cells more directly—by switching them off or altering their behavior—then I think it would be a more effective treatment strategy than targeting a single cytokine.

An alternative approach is to keep T cells out of the gut. Natalizumab (Tysabri, Biogen Idec/Elan Pharmaceuticals) is an antibody directed against the $\alpha 4$ -integrin. By binding to $\alpha 4\beta 1$ and $\alpha 4\beta 7$ on T cells, natalizumab

prevents the migration of T cells into inflamed gut, and it also disrupts costimulation. Traficet-EN (ChemoCentryx) is an orally available small molecule that blocks CCR9/CCL25 and also prevents T cells from moving into the gut.

Suggested Reading

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