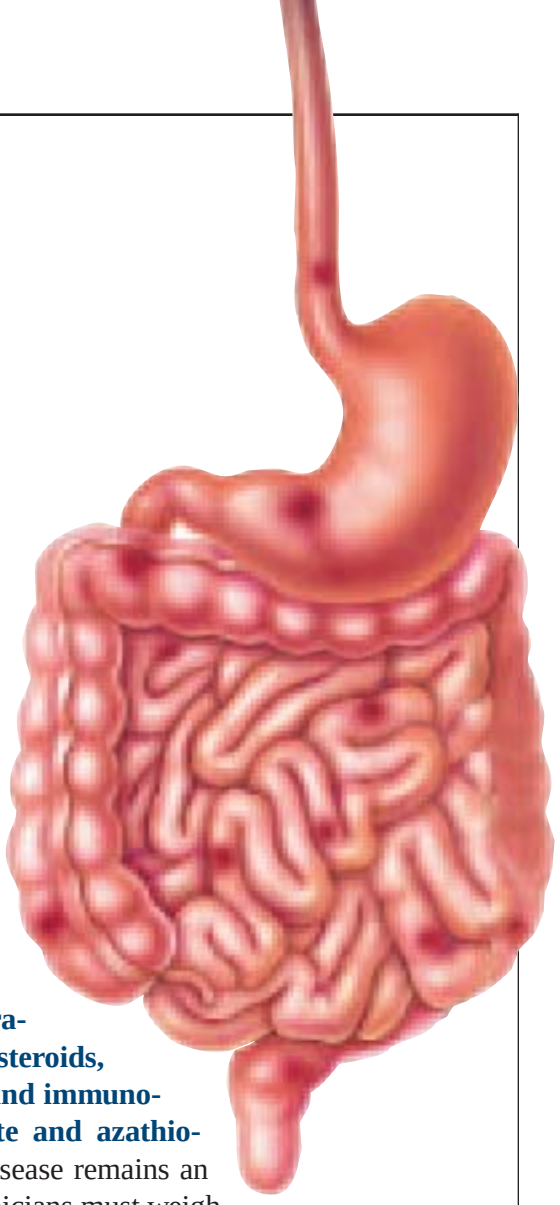
Biologic Therapies in Crohn's Disease:

The Next Generation



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Until recently, standard medical therapy for Crohn's disease consisted of steroids, 5-acetylsalicylic acid (ASA) preparations and immunosuppressive agents, including methotrexate and azathioprine. Despite these medications, Crohn's disease remains an illness characterized by chronic relapses. Clinicians must weigh the potentially toxic side effects of current anti-inflammatory drugs with their potential benefits. As we begin to understand the inflammatory pathways of Crohn's disease, new agents that more specifically act on these pathways are becoming available. The goal of these new agents is to be efficacious and have their selective activities lead to a more tolerable side-effect profile.

Which biological mediators are potential targets for Crohn's disease therapy?

The inflammation in Crohn's disease can be thought of as an imbalance between pro-inflammatory and anti-inflammatory cytokines. This is a cell-mediated or Th1 immunity pattern, mediated by cytokines, such as tumor necrosis factor α (TNF-α) and interferon-γ (IFN-γ).[1] Mucosal inflammation is probably triggered by an antigen, which has not yet been identified, but is likely a component of a ubiquitous group of gut bacterial flora. Macrophages present this antigen to CD4 + T cells, thereby stimulating the reactive T cells. In addition, macrophages also release cytokines, such as TNF-α and IL-12, which promote a T helper cell (Th)1 response. IL-12 promotes differentiation of undifferentiated Th0 T cells into Th1

cells. TNF-α acts to stimulate neutrophils and macrophages, as well as induce acute-phase reactants and proteases that contribute to tissue injury.[2]

Peripheral blood leukocytes are also recruited to participate in tissue inflammation. They migrate through vascular endothelium by adhering to intercellular adhesion molecules (ICAMs), such as ICAM-1.[2]

Macrophages also release IL-4, which promotes the Th2 pathway of chemical mediators. IL-10 is the predominant cytokine in this mechanism, acting to decrease production of many pro-inflammatory cytokines including IL-1, IL-2, IL-12, IFN-γ and TNF-α. Fibroblasts also release anti-inflammatory mediators, such as IL-11.[2]

Therapeutic manipulation of these biological mediators of inflammation includes antagonists to pro-inflammatory cytokines, such as TNF-α, or ICAM-1, as well as administration of the anti-inflammatory cytokines IL-10 and IL-11.

What is infliximab?

Infliximab is a chimeric monoclonal antibody that has been approved for specific indications in Crohn's disease. It targets TNF-α, binding to both soluble and membrane-bound TNF-α. Increased levels of TNF-α have been demonstrated in the bowel mucosa in Crohn's disease, as well as in the stool, where levels correlate with disease activity.[1,3] Infliximab may act by directly binding and inactivating TNF-α or by inducing apoptosis of cells bearing transmembrane TNF-α.[1] Monoclonal antibodies to other immune targets, such as the α4 adhesion molecule, are also showing promise in clinical trials.

Summary

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- The inflammation in Crohn's disease is an imbalance between pro-inflammatory and anti-inflammatory cytokines. This is a cell-mediated or Th1 immunity pattern, mediated by cytokines, such as tumor necrosis factor a (TNF-α) and interferon-g (IFN-γ).
- Infliximab may act by directly binding and inactivating TNF-α or by inducing apoptosis of cells bearing transmembrane TNF-α.
- Thalidomide is thought to decrease production of inflammatory cytokines including TNF-α and IL-12.
- IL-10. This acts to down-regulate Th1 activity, which is seen in Crohn's disease.

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How effective is infliximab?

Single doses of infliximab were shown to be effective in a 1997 double-blind, placebo-controlled trial. In patients with moderate to severe Crohn's, resistant to therapy with steroids, mesalamine and azathioprine, 65% of infliximab-treated patients showed a clinical response, as compared to 17% of those receiving placebo ($p < 0.001$). Several doses were used, with the best results seen with a 5 mg/kg intravenous dose (81% clinical response). Similarly, remission was attained in 33 patients receiving infliximab, as compared to only four receiving placebo. Results were long lasting, with 41% of treated patients still showing a clinical response 12 weeks after a single dose, compared to only 12% of placebo-treated patients.[4] A statistically significant improvement in endoscopic appearance, histologic inflammation, and serum C-reactive protein levels was also seen with infliximab treatment.[5]

In a 1999 trial, the patients who had initially responded to infliximab were randomized to placebo or infliximab every eight weeks for four treatments to determine the role of infliximab in maintenance therapy. Again, efficacy of infliximab was demonstrated, with 52.9% of treated patients in remission eight weeks after the last dose of infliximab *versus* 20% of those receiving placebo.[6] These results hold promise for the use of infliximab in maintenance therapy.

Fistulas are one of the most difficult manifestations of Crohn's disease to manage. Infliximab is one of the few agents proven to ameliorate fistulas in a randomized clinical trial. Fifty-five per cent of patients receiving 5 mg/kg of infliximab noted closure of all fistulas, as compared to only 13% of patients receiving placebo. This response was achieved in only 14 days, and was maintained for a median of three months after treatment.[7]

These results show promise for the use of infliximab in moderate to severe disease resistant to treatment, as well as for the treatment of fistulas, however, not all Crohn's patients respond to this drug. When non-responders were given a second, open-label dose of infliximab in the initial 1997 trial, they again responded no better than to placebo.[4] This lack of response may indicate heterogeneity in the inflammatory mediators of Crohn's disease among different patients.

To date, no randomized trials have looked at a benefit for infliximab in ulcerative colitis, but there is evidence from small, open-label studies that support its efficacy.[8] A randomized controlled trial of infliximab in ulcerative colitis is currently is under way.

Is infliximab safe?

Although side effects are infrequent, some important reactions occur. These include:

- ***Acute infusion reactions:*** Reactions are produced in 17% of infliximab treated patients, as compared to 7% of those with placebo.[9] Symptoms include headache, fever, chills, urticaria, chest pain and hypotension. Severe reactions

only occurred in 0.5% of patients, with less than 2% leading to discontinuation of the drug. These reactions often can be treated by slowing the infusion rate or administering dimenhydramine. Delayed infusion reactions, consisting of myalgia, arthralgia, fever, rash, facial edema and urticaria, after a two-year, drug-free interval were noted in 10 out of 40 patients in one study.[9] These symptoms occurred three to 12 days after infliximab administration, but most were seen after initial exposure to a form of infliximab that is no longer in use.

- ***Infections:*** There is no increased risk of generalized sepsis or severe infection with infliximab treatment. There is a risk of upper respiratory tract infection or urinary tract infection (seen in 26% of treated patients *versus* 16% with placebo).[9]

  In addition, FDA monitoring of infliximab's safety has revealed a risk of reactivating tuberculosis that is higher than the expected rate.[10] This may be due to a role for TNF-α in containing the disease. Currently, patients should be screened for latent tuberculosis before administering infliximab.

- ***Antibody formation:*** Infliximab is a chimeric antibody consisting of 25% murine and 75% human constituents. Thirteen per cent of patients receiving infliximab develop antibodies to it, likely due to its foreign antigen content.[9] The clinical relevance of these antibodies is unknown. CDP571, a genetically engineered human antibody to TNF-α contains only 5% murine residues and is less immunogenic than infliximab. A small clinical trial did indicate efficacy of CDP571 in Crohn's disease, and future evidence is awaited.[11]

  Autoantibodies (ANA) also are seen with infliximab administration. A total of 34% of patients demonstrated ANA formation, and 9% anti-dsDNA formation. Again, the significance of these antibodies is unclear, with only 0.39% of patients developing any symptoms of lupus. These symptoms included arthritis, pleuropericarditis and skin manifestations and resolved with appropriate treatment and discontinuation of infliximab.[9]

- ***Stricture formation:*** Strictures do not respond to infliximab therapy readily. In one trial, development of a new stricture occurred, as well as progression from an ulcerated stenosis to a non-ulcerated stricture.[5] Symptomatic stenosis or stricture is an exclusion criteria in most clinical trials of infliximab therapy.

- ***Lymphoma:*** In a retrospective review of the 771 patients who have received infliximab in various clinical trials, six have developed lymphoproliferative disorders.[12] Neither of the two cases described in Crohn's disease patients can be definitively linked to infliximab. In one case, the lymphoma was diagnosed only two weeks after infliximab administration, making a causal link unlikely. In the other, there had been previous administration of an immunosuppressive drug that could also have predisposed to lymphoma.

  Reporting of adverse effects will continue as infliximab becomes more widely used, and these results will need to be followed carefully.

What does this therapy cost?

A 100 mg vial of infliximab costs $1,150. At 5 mg/kg, a 70 kg male would require $4,025 worth of treatment for each dose of infliximab. This is currently paid for on a case-by-case basis in hospital, and it remains to be seen whether private insurance will cover the cost of biologic therapy as an outpatient.

Are there other biological therapies around the corner?

Thalidomide. Thalidomide is thought to decrease production of inflammatory cytokines including TNF-α and IL-12. Small pilot studies have shown efficacy with clinical responses, ranging from 56% to 58% for luminal disease and 69% for fistula closure, with remission in 17% to 41% of patients.[13,14] In a cohort of 12 patients, there was a decrease in steroid dosage by at least 50% in all patients.[13] Thalidomide was well tolerated in these patients, with the most common side effect being sedation. A transient neuropathy was also noted in a minority of patients, which improved after drug withdrawal. Of course, thalidomide is a well known teratogen and could not be offered to women of child-bearing age. For this reason, it is unlikely that thalidomide will be used in the therapy of Crohn's disease in the foreseeable future. Modifications of the molecule, or use of a non-teratogenic isomer may be investigated in the future.

IL-10. This acts to down-regulate Th1 activity, which is seen in Crohn's disease, and mice that are deficient in IL-10 develop a colitis similar to that seen in Crohn's.[15] Several investigators have attempted treatment with recombinant IL-10 in resistant Crohn's disease. An initial pilot study of 46 patients showed a remission rate of 50% in IL-10 treated patients, as compared with 23% in the

placebo group, but the study was not designed to detect differences in clinical responses.[16] A larger trial of 95 patients treated for 28 days showed a remission in 23.5% in the IL-10 group with a 0% remission in the placebo group.[17] In both of these trials, the drug was well tolerated, but there was a dose-related anemia and thrombocytopenia, which did not result in clinically significant complications. In contrast, a trial of 329 patients showed no significant difference in remission between IL-10 and placebo.[18] No current studies of IL-10 in the treatment of Crohn's disease are being performed.

IL-11. This anti-inflammatory cytokine also has been investigated for use in Crohn's disease. In a dose-finding study, it was shown to elicit a response in 42% of patients, as compared to a 7% response to placebo.[19] It was well-tolerated, but did show a dose-related thrombocytosis, with a 37% increase in platelet count at a dose of 16 µg/kg/week. There were no thrombotic complications associated with this laboratory abnormality. Again, further investigation is warranted in this area.

ICAM-1. This adhesion molecule plays a role in the transit of neutrophils through vascular endothelium. Research into ISIS 2302 (Alicaforsen), an antisense oligonucleotide to ICAM-1, showed promising results in a group of 20 patients with active Crohn's disease.[20] Remission was attained in 47% of the experimental group and only 20% of the placebo group, with significantly lower steroid doses needed in the treatment group. Other than a transient elevation in the partial thromboplastin time (PTT), the study drug was well tolerated. A recent, large clinical trial showed a dose response with the highest doses resulting in significant improvement in Crohn's disease activity index scores.[21] A higher-dosed study (phase IIb) is currently ongoing in North America.

Etanercept. This is a genetically engineered fusion protein, consisting of two chains of recombinant tumor necrosis factor receptor fused to the Fc domain of human immunoglobulin G (IgG)1. It has been useful in treating rheumatoid arthritis, and since it acts by inactivating TNF, it was hoped it would prove efficacious in Crohn's disease as well. Unlike infliximab, it has no murine residues, so it may be less immunogenic. Etanercept failed to show any benefit over placebo in a randomized, placebo-controlled trial.[22] This may be because the dose used in rheumatoid arthritis is not adequate for use in Crohn's, or perhaps etanercept is not highly bioavailable to the gut mucosa. At this point, etanercept is not in clinical use for Crohn's disease.

How can I integrate these therapies into my practice?

Infliximab has been shown to be effective in moderate to severe Crohn's disease and in treating fistulas. Its efficacy has been demonstrated to as long as 44 weeks after an initial dose, and it can be used to achieve, as well as maintain, a clinical response or remission.[6] At this point, infliximab would not be considered a first-line treatment for Crohn's disease, but could be considered in a patient who is not responding to appropriate therapy including steroids, 5-ASA and immunomodulators, such as azathioprine.[23] Further follow-up is needed to determine any long-term side effects that may be related to infliximab therapy.

The other biologic targets mentioned previously are not yet suitable for clinical use, but remain potential areas of research. As we discover more about the pathogenesis of inflammation in Crohn's disease, we are identifying a large number of new potential targets for therapeutic manipulation as well. CME

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