The Use of Biologic Therapy in the Treatment of Crohn’s Disease

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Introduction
Significant changes have been made in the approach to the treatment of inflammatory bowel disease (IBD) in recent years. With these advances, the goals of medical therapy have expanded beyond inducing and maintaining symptomatic relief to include averting complications of the disease. Treatment success is now being defined to include the avoidance of hospitalization, surgery, and corticosteroid use.

Although immunosuppressive therapy with thiopurines and methotrexate effectively maintains remission of symptoms and makes it possible to discontinue corticosteroids, these agents have not shown the ability to reduce hospitalization or surgery. There is growing evidence that biologic therapy can reduce hospitalizations and the need for surgery in patients with moderate to severe Crohn’s disease (CD). Given the evolving landscape of biologic therapy, physicians are now faced with difficult decisions regarding when to administer biologic therapy and to whom, and which biologic agent to use.

The armamentarium of biologic treatments for CD has grown from a single agent given as a single dose for active disease to 4 FDA-approved agents that can be used for both induction and maintenance, and thus far, biologics are the only class that has proved effective for these 2 uses. Currently, 3 tumor necrosis factor-alpha antagonists (anti-TNF agents) are approved by the FDA for CD: infliximab (Remicade, Centocor), adalimumab (Humira, Abbott), and certolizumab (Cimzia, UCB) (Figure 1). Dosing information for these agents is summarized in the Table.

Initiating Anti-TNF Therapy
The first evidence that anti-TNF therapy is effective at treating CD was published by van Dullemen and colleagues. When anti-TNF therapy was first used in CD, it was given as a last line of therapy for patients with disease refractory to conventional immunomodulator therapy. Increasingly, interest has been growing in the use of anti-TNF therapy at earlier phases of CD, based on evidence that this may alter the natural history of CD.

The concepts regarding the administration of conventional immunosuppression before anti-TNF therapy (step up) or early intervention with anti-TNF therapy (top down) in the treatment of CD are still evolving. Definitive evidence is still lacking to support either as the preferred approach to initiating therapy.

D’Haens and colleagues conducted the only controlled study comparing conventional immunosuppression at induction (initial therapy with corticosteroids and azathioprine if patients experienced symptoms following steroid taper) with early combined intervention (azathioprine and infliximab as induction therapy followed by infliximab as needed). Patients in the early combined intervention group were significantly more likely to be in corticosteroid-free remission without surgical resection than the conventional group (Figure 2).

However, this study was not blinded, and subjects in the conventional therapy arm were not simultaneously treated with immunosuppression at induction. As a result, it is still unclear if the earlier use of conventional immunosuppression would be equivalent to early combined therapy, negating the need for the early use of anti-TNF therapy. It should also be noted that the patients in this study received infliximab as needed, not as scheduled maintenance therapy. It is possible that scheduled maintenance with infliximab would further improve the outcomes in the early combined intervention group. Finally, no significant differences were found in the safety of the 2 regimens, suggesting that a concern for safety is not a reason to withhold the early use of anti-TNF therapy. Until definitive data indicating that one approach is superior to the other with regard to safety and efficacy are available, the choice of early anti-TNF use or anti-TNF use after conventional immunosuppression will be based on physician preference and the prescribing guidelines of individual insurance providers.

Clinical Response
Once anti-TNF therapy has been initiated, roughly 40% to 80% of patients respond. The response typically begins within 2 to 8 weeks. No current studies have specifically evaluated the continuation of therapy in patients who have not responded to the initial induction regimen, but it has been assumed that these patients are unlikely to respond to maintenance therapy. Given the cost and possible risk associated with this class of drugs, if no response is seen after the induction regimen, therapy should be discontinued.

Maintaining Response
In general, when a patient shows a clinical response to induction therapy, it is advisable to continue with a maintenance regimen. All currently approved anti-TNF therapies have been shown to be superior to placebo at maintaining long-term response and remission. Furthermore, antibodies to the specific anti-TNF therapy being used are more likely to develop in a patient receiving episodic therapy. Adverse reactions to the medications, a shortened response, and loss of the response are also more likely to occur in a patient who has received episodic therapy. Unless a patient has an adverse reaction or loses the clinical response to therapy, maintenance therapy should be encouraged and episodic therapy avoided if possible.

Concomitant Immunosuppression
The concomitant use of immunosuppression has been shown to reduce the risk for antibody formation during anti-TNF therapy. However, it has not...
been shown to have any clinically significant effect on patient outcomes. Concern has been raised regarding the concomitant use of immunosuppressant because cases have been reported of hepatosplenic T-cell lymphoma in young patients receiving combined therapy with infliximab and azathioprine or 6-mercaptopurine (6-MP). 25

The combination of methotrexate and infliximab has been shown to be effective in fistulizing CD.27 Recently, infliximab as monotherapy was shown to be as efficacious as the combination of methotrexate and infliximab in CD.28 Although there were no safety concerns in this trial, this regimen cannot be recommended for all patients starting biologic therapy, given the lack of improved efficacy.

The addition of conventional immunosuppressants when a biologic-naive patient starts anti-TNF therapy is not generally recommended. Certain categories of patients, such as those who have lost a previous response to biologic therapy, may benefit, but this has not been studied.

Choosing an Anti-TNF Agent
Of the 3 anti-TNF agents that the FDA has approved for CD, certolizumab is the most recent to have received FDA approval. Certolizumab is different from infliximab and adalimumab in that it is a pegylated antibody-binding fragment (Fab) of an immunoglobulin G (IgG) anti-body and does not contain a crystallizable fragment (Fc) component.29 In contrast, both adalimumab and infliximab are whole IgG antibodies and contain the Fc portion.20 It is not clear if the regulation and lack of the Fc portion affect the efficacy or safety of certolizumab.29 The drug has been shown to be effective in all groups of patients who have been studied. These include but are not limited to biological-naive patients, those with a lost response or intolerance of other biologics, those with normal or elevated levels of C-reactive protein, and patients with all anatomic distributions of disease.

No studies have directly compared the safety or efficacy of these agents, and it is unlikely that directly comparative studies will be conducted in the near future. All 3 agents have been shown to be effective at rapidly reducing symptoms in patients with active CD.30-32 In addition, scheduled maintenance therapy is superior to placebo for sustaining response and remission in those patients who have responded to initial therapy.

Given the lack of comparative data and in view of the fact that all of the current anti-TNF therapies appear to be similar in regard to safety and efficacy, a physician’s choice of which anti-TNF therapy to prescribe should be based on the direct cost to the patient and the patient’s preferred mechanism of delivery (infusion versus subcutaneous injection).

Conclusion
Available therapies for CD are expanding rapidly. In contrast to conventional immunosuppression, current evidence suggests that biologic therapy will significantly reduce the most severe complications of disease. Although this evidence is encouraging, no evidence is yet available to support the early use of biologics in all patients. The choice of when to use a biologic is the physician’s and is based on an evaluation of the individual patient. We now have 3 anti-TNF therapies available, so physicians need to be aware of the differences in cost to the patient and the patient’s preferred mechanism of delivery. A multitude of questions regarding biologic therapy remain unanswered, but physicians should understand that these therapies are effective and in general safe to use in patients with CD.

References


Table. Anti-TNF Biologic Agents: Dosing Considerations29-31

<table>
<thead>
<tr>
<th>Dosing Route</th>
<th>Adalimumab</th>
<th>Certolizumab</th>
<th>Infliximab</th>
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<td>Interval between doses, wk</td>
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Figs. 2. Early combined immunosuppression vs conventional management.9 100

Preparation of Patients With No Response, %

Early combined immunosuppression

Conventional management

P=0.031

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