Optimizing Infliximab Treatment of Crohn’s Disease Using New Laboratory Methods

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Abstract:

Infliximab (IFX) is an effective Anti-TNFα agent approved for the treatment of moderate to severe Crohn’s disease. Combination of IFX with azathioprine (AZA) promotes greater response rates in Crohn’s patients and is preferred over monotherapy with IFX or AZA. In this article we discuss the risks and benefits of combination therapy with IFX and AZA, as well as the use of new laboratory tests to guide the treatment of Crohn’s patients with loss of response to IFX.

Introduction:

In 1998, the introduction of Infliximab Remicade (Centocor Ortho Biotech) for the treatment of Crohn’s disease revolutionized the management of this chronic and progressive disorder. At the time of initial FDA approval, IFX was routinely administered in a dosing schedule of 5-10 mg/kg at time 0, 2, and 6 weeks, i.e., “3 and out,” with IFX retreatment considered for relapse of the disease.3,4 This practice of sporadic dosing lead to a “hectic” pattern of disease remission, relapse and the frequent (37-61%) development of human anti-chimeric antibodies (HACA) that bind to and neutralize IFX or cause infusion reactions.5 Ultimately, a schedule of indefinite, serial infusions has become the standard IFX dosing regimen to maintain remission of the disease. Unfortunately, serial and sustained dosing of IFX does not prevent the development of HACAs and the associated loss of response to IFX is estimated to be ~10% per year.6,7 Pretreatment with hydrocortisone before IFX infusions and concomitant immunosuppressive therapy have been shown to be effective in reducing HACA formation and preserving IFX efficacy.4,8,9,10,11

The importance of co-administration of immunosuppressive therapy with IFX has been highlighted in the recent SONIC Trial.12 These investigators randomized 508 biologic and immunomodulator naive Crohn’s disease patients with brief duration of disease (mean 2.3 years) into three treatment groups: Azathioprine (AZA) at 2.5 mg/kg, IFX at 5 mg/kg (T 0, 2, 6, then every 8 wk) or the combination of IFX plus AZA. The results of the SONIC Trial clearly showed combination therapy (IFX plus AZA) to be superior to monotherapy with either agent for maintenance of Crohn’s disease remission and endoscopic healing. (Table 1). Furthermore, overall infection rates were lower in the combination group, primarily due to a decreased number of gastrointestinal infections. Infusion reactions to IFX were much less common in the combination group vs. IFX or AZA monotherapy, (5% vs. 16.6% and 5.6%, respectively). Measurements of antibodies to IFX (ATI or HACA) and trough levels of IFX were inversely related to response rates. (Table 1). Not surprisingly, the difference in the detection of antibodies to infliximab (ATI’s) among the combination group (0.9%) and the IFX monotherapy (14.6%) was 13.7% which is the approximate difference in the 26-wk remission rates for the two groups (56.8% vs. 44.4%).
The conclusion of the SONIC trial is powerful and simple: patients with moderate-to-severe Crohn’s disease who are treated with IFX plus AZA are more likely to have a steroid-free clinical remission than those receiving IFX or AZA monotherapy. One of the likely mechanisms for greater clinical success with combination therapy (IFX plus AZA) is the prevention of ATI formation. This finding has led many clinicians to conclude that combination therapy (IFX plus AZA) should be the standard when considering initiating IFX treatment for Crohn’s disease.

The enthusiasm for combination IFX plus AZA treatment of Crohn’s disease has been tempered by the increased risk for infection and malignancy associated with combination therapy.14,15 The unique association of hepatosplenic T-cell lymphoma (HSTCL) among Crohn’s patients that have received thiopurine analogues (azathioprine and 6-mercaptopurine) and/or IFX or adalimumab (ADA) has prompted the FDA to mandate a black-box warning concerning the potential for developing HSTCL.16,17 This risk is greatest for men younger than 35 yrs and has prompted many clinicians to consider an alternate treatment pathway for this group.17 Some have substituted Methotrexate (MTX) for AZA as mono or dual therapy with IFX.18,19 Others have looked toward monotherapy with either of the two other Anti-TNFα therapies approved for treatment of Crohn’s disease [ADA or certolizumab (CTZ), Cimzia certolizumab], that are suggested to be less immunogenic than IFX.20,21

The long experience with IFX treatment of Crohn’s disease has taught us that 40% of patients will lose response to IFX over time.6,7 In the past, lack of clinically available assays to measure HACA and IFX concentrations, led to the common practice of empiric IFX dose escalation in the attempt to recapture Crohn’s patients with loss of response. “Blind” escalation of IFX dosing was associated with unpredictable response, increased risk of immune suppression, and significant healthcare costs. Afif, et al, have recently conducted a retrospective review of their collective five year experience at the Mayo Clinic measuring HACA and IFX concentrations among inflammatory bowel disease (IBD) patients.22 The primary indication for measuring HACA and IFX in these patients was loss of or incomplete response to IFX (71%). Treatment decisions for IBD patients with loss of response to IFX were guided by IFX concentrations [Table 2], HACA status, the clinical response of IFX dose escalation, and results of switching to a different Anti-TNFα (ADA or CTZ).

**Table 1. Summary of Sonic Trial 26 wk results. Adapted from Colombel JF, et al. NEJM. 2010;362:1383-95.**

<table>
<thead>
<tr>
<th>N=508</th>
<th>26 wk remission</th>
<th>26 wk healing</th>
<th>Infection rate</th>
<th>ATI</th>
<th>Trough [IFXμg/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combo (IFX + AZA)</td>
<td>56.8%</td>
<td>43.9%</td>
<td>3.9%</td>
<td>0.9%</td>
<td>3.5</td>
</tr>
<tr>
<td>IFX + Placebo</td>
<td>44.4%</td>
<td>30.1%</td>
<td>4.9%</td>
<td>14%</td>
<td>1.6</td>
</tr>
<tr>
<td>AZA + Placebo</td>
<td>30.0%</td>
<td>16.5%</td>
<td>5.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Clinical Implication of IFX Levels. Adapted from Afif W, et al. Am J Gastroenterol. 2010;105:1133-1139.**

<table>
<thead>
<tr>
<th>IFX Levels</th>
<th>Timing of Measurements</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 mcg/ml</td>
<td>4 wk post infusion</td>
<td>Sub therapeutic</td>
</tr>
<tr>
<td>&gt; 12 mcg/ml</td>
<td>4 wk post infusion</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>&gt; 1.4 mcg/ml</td>
<td>Pre-infusion (dosing trough)</td>
<td>Therapeutic</td>
</tr>
<tr>
<td>undetectable</td>
<td>Pre-infusion (dosing trough)</td>
<td>Sub therapeutic</td>
</tr>
</tbody>
</table>
Results of the Afif, et al, study indicate that IFX concentrations and HACA status impacts treatment decisions in over 70% of IBD patients.22 Based on their findings, we suggest the following algorithm for management of IBD patients with IFX loss of response. (Figure 1). For IBD patients with IFX loss of response that are HACA (+), changing to a different Anti-TNFα (ADA or CTZ) has a 92% probability of favorable clinical response, while only 17% of these patients have a favorable response to increasing the dose of IFX. IBD patients that fail adequate IFX therapy (HACA negative and therapeutic IFX concentrations), should be evaluated carefully for active IBD, since it is more common that alternative etiologies (IBS, infectious enteritis, C. difficile, etc) are responsible for symptoms. True IFX failure (confirmed IBD activity with HACA negative & therapeutic IFX concentrations) often portends that the entire class of Anti-TNFα agents will be ineffective, and other therapies such as methotrexate, natalizumab and even surgery should be investigated.

Conclusions:

The introduction of Anti-TNFα agents has been a major advance in the treatment of Crohn’s disease. Experience, knowledge and development of new laboratory tests that detect Anti-TNFα Antibodies and trough drug levels should now be part of our “Best Practice” model in guiding therapy for Crohn’s patients with a loss of response. Presently we have three Anti-TNFα agents (IFX, ADA, and CTZ) for the treatment of Crohn’s disease. All of these Anti-TNFα agents are foreign proteins susceptible to the development of neutralizing antibodies.22 Clinical gastroenterologists must start to utilize HACA and IFX tests to guide management of IBD. Also, they should encourage the development of commercially available tests for ADA & CTZ antibodies and blood concentrations to guide the safe and effective use of these agents.

**Figure 1.** Algorithm for Management of IBD patients with loss of response to IFX. Abbreviations: Endoscopy (Endo), Radiography (RAD). (adapted from Afif w, et al. AM J Gastroenterol. 2010;105:1133-1139).22
References:


