Ulcerative colitis (UC) is a lifelong disorder caused by a complex interaction between the host immune system, gut microbiota, and the environment.\(^1\) The mucosa of the rectum and colon is the target of this disease and inflammation is most intense where gut bacterial concentrations are greatest.\(^2\) Initially, the distribution of UC is seen in just the rectum (proctitis, 30%), and/or more extensive involvement of colitis to the level of the splenic flexure (30%), and/or colitis extending beyond the splenic flexure (30%) of which 20% includes pan-colitis, \textit{Figure 1}. Over a lifetime of disease, pan-colonic extension is seen in ~50% of all UC cases.\(^1,3,4,5\)

Ulcerative colitis has an undulating pattern of disease activity, with 50% of all cases of UC estimated to be in remission at any moment in time.\(^1\) Although the inflammation of active UC is usually responsive to anti-inflammatory drugs to include: 5-ASA, corticosteroids, immunomodulators, in some cases it does not. In fact, 1/3rd of UC patients require colectomy in their lifetime, because of the development of cancer/dysplasia or colitis refractory to medical therapy.\(^6\) Although surgery is considered a cure for UC, it is still associated with significant morbidity to include pouchitis (10% first year and up to 40% lifetime),\(^7,8\) impotence in males (10%),\(^8,9\) decreased fecundity in females (20-37%).\(^9\)

Corticosteroids are effective in 50% of UC patients, while fewer than 20% will have no response to therapy.\(^10,11\) Responders to corticosteroids can be expected to remain in long term remission 50% of the time. Of those that relapse approximately 40-60% cases are responsive to immunomodulator therapy with azathioprine (AZA) or 6-mercaptopurine (6-MP).\(^12,13\) This leaves a substantial number of UC patients with medically refractory disease, and in need of a surgical solution or more effective medical treatment. Increased TNF from mucosal macrophages isolated from IBD lesions and increased TNF...
concentrations found in blood, mucosal tissue and stool of patients with UC has led to the consideration of Anti-TNF-α in the treatment of UC. The Active Ulcerative Colitis Trials (ACT-1 and ACT-2) were the first large, randomized, placebo controlled trials that firmly established the efficacy of Anti-TNF-α (Infliximab, IFX Janssen Biotech, Inc. Horsham, PA 19044 ) in the treatment of moderate to severe UC, Table 1.  

A long-term, open label extension trial of the study subjects included in the ACT-1 and -2 studies, showed that IFX was well tolerated and provided durable benefit for upto 3 additional years of treatment. However, 31% of these IFX responders (54-wk ACT-1 and 30-wk ACT-2) had to discontinue IFX due to adverse events (11%), lack of efficacy (5%), colectomy (0.4%) or other reasons (15%) during the extension phase. Enthusiasm for the use of IFX in the treatment of moderate to severe UC has also been tempered by the frequent development of neutralizing antibodies to IFX (ATI). Lastly, primary lack of response to IFX and the need for intravenous IFX administration, have contributed to a need to evaluate other less antigenic Anti-TNF agents that can be administered more conveniently by a subcutaneously route.

Adalimumab (Humira, Abbott Laboratories, North Chicago, IL) is a recombinant human IgG1 monoclonal antibody specific for human TNF that can be administered sub cutaneously. Humira is created using phage display technology resulting in antibody with human-derived heavy and light chain variable regions and human IgG1:k constant regions. Preliminary studies evaluating the efficacy of ADA in the treatment of UC patients failing IFX have shown promising benefit. In an open label study of ADA (160/80/40 mg EOW) in patients with UC that had prior loss of response (LOR) to or intolerance to IFX, the 8 week clinical remission and response rates were seen in 5 and 25% of patients, respectively. The healing rates were 30% among both remitters and responders receiving ADA. At week 24, remission and response rates were 25% and 50% respectively. Equally important was, ADA treatment allowed 58% of patients on corticosteroids to taper or discontinue them completely. The results of two recent phase 3 clinical drug trials have conclusively shown ADA to be effective in the treatment of UC. The study results led to the recent FDA approval of ADA (Humira) to control ulcerative colitis when immunosuppressant medicines like corticosteroids, azathioprine, and 6-mercaptopurine have not worked.


**Table 1. Results of the Active Ulcerative Colitis Trials 1 and 2.** Summary of results expressed as Percentage of Remission and Healing at 8, 30, and 54 wks. for Infliximab (IFX, 5 mg/kg) vs. Placebo (PBO).

<table>
<thead>
<tr>
<th></th>
<th>8 wk.</th>
<th></th>
<th>30 wk.</th>
<th></th>
<th>54 wk.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Remission</td>
<td>Healing</td>
<td>Remission</td>
<td>Healing</td>
<td>Remission</td>
</tr>
<tr>
<td>ACT1</td>
<td>39%</td>
<td>15%</td>
<td>62%</td>
<td>16%</td>
<td>50%</td>
</tr>
<tr>
<td>ACT2</td>
<td>34%</td>
<td>6%</td>
<td>60%</td>
<td>31%</td>
<td>26%</td>
</tr>
</tbody>
</table>

**Abbreviations: ACT (Active Ulcerative Colitis Trials 1 and 2), IFX (infliximab, 5 mg/kg), PBO (Placebo).**
immunomodulator therapy. In this study, participants had to exhibit moderate to severe UC as defined by complete Mayo Score of 6-12 points, Figure 2 and 3.

<table>
<thead>
<tr>
<th>“Full” Mayo Score</th>
<th>Variable</th>
<th>0 Points</th>
<th>1 Points</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel movement (BM) frequency</td>
<td>Normal</td>
<td>1-2 BM &gt; nl</td>
<td>3-4 BM &gt; nl</td>
<td>≥ 5 BM &gt; nl</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>None</td>
<td>Streaks on stool &lt; 50% BM’s</td>
<td>Obvious blood with most BM’s</td>
<td>Blood alone</td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Normal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Physician Global Assessment (PGA)</td>
<td>Normal</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** “Full” Mayo Score includes symptoms (number of bowel movements), endoscopic findings, and physician global assessment (PGA) to define severity of ulcerative colitis. The full Mayo Score ranges from 0 to 12: Mild 3-5 points, Moderate 6-10 points, Severe 11-12 points. Remission defined as Mayo Score < 2 points and Response defined as a decrease in Mayo Score > 3 points and 30% from baseline and decrease in rectal bleeding sub score > 1 point or absolute rectal bleeding sub score of 0 or 1.

The study subjects in ULTRA-1 were randomized to placebo or one of two ADA treatment arms (160/80/40/40mg or 80/40/40/40mg) administered subcutaneously at time – 0, then every 2 weeks. The study results shows that ADA 160/80/40/40 mg is twice as effective as placebo in achieving 8 week remission rates among patients with moderate to severe UC (18.5% vs. 9.2%, respectively, P = 0.031). The ADA induction dosage of 80/40/40/40 mg was not effective for the treatment of moderate to severe UC compared to placebo (10% vs. 9.2%, p = NS). Secondary end points, evaluated by Reinisch, et al, included mucosal healing, rectal bleeding, Physician Global Assessment (PGA), and stool frequency, Table 2. Although, numerical improvement was seen for all secondary endpoints for the ADA 160/80 mg group over placebo, only improvements in rectal bleeding and PGA score achieved statistical significance.

Both of ADA induction doses (ADA 160/80/40/40mg and 80/40/40/40mg) appeared to exhibit acceptable short term safety. There was no significant difference between ADA (160/80mg or 80/40mg) vs. Placebo for any adverse events (AE): malignancy, injection reaction, opportunistic infection, CHF, demyelination or Lupus-like reactions. Serious AE’s occurred
in 7.6%, 3.8% and 4% of patients in the placebo, ADA 80/40/40mg and ADA 160/80/40mg groups respectively. Two malignancies were seen in the placebo group, none in the ADA treatment groups.

The results of the ULTRA-1 study, by Reinisch, et al, are weakened by several important inconsistencies in scientific methodology. First, exclusion of important demographic information; second dramatic variance in study results by regional study sites and lastly, after initiation of ULTRA-1 study, the investigators made an interim change in study design to include an ADA 80/40 treatment arm (Request of European Regulatory Authorities – Amendment 3). In ULTRA-1, there was an inexplicably high placebo response rate among study participant enrolled in the Canada and Eastern Europe study groups. The placebo response from these two study regions (54 and 58%, respectively) equaled or exceeded ADA treatment response for all 4 regions (Canada 50%, E. Europe 55%, US/PR 58%, and W. Europe 52%). Smoking history has a known inverse association with UC disease activity. In ULTRA-1, smoking history (never, active, &/or discontinued) was not include in the demographic data. The variance in smoking rates and smoking cessation programs is likely to be an important regional study group variable!

The sub analysis of the ULTRA-1 data set identified several additional important findings. Study participant weighing > 82 Kg, exhibiting extensive colitis and/or high CRP > 10, all predicted non-remitter status. These findings suggest subgroups of UC patients that may the need greater immune suppression, hence a higher induction dosage of ADA for patients weighing > 82 Kg or exhibiting more extensive colitis or inflammation manifest by CRP > 10. Further prospective study of different ADA induction doses is clearly warranted.

**Ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA 2)**

The second phase 3 study of ADA in the long term maintenance treatment of moderate to severe UC (ULTRA-2) was conducted by Sandborn and colleagues. All of the study patients had moderate to severe UC as defined by Mayo Score (6-12 points). All patients were receiving concurrent oral corticosteroids, azathioprine or 6-mercaptopurine. The study included UC patients previously treated with TNF-α (40% of all subjects), and randomization was stratified by prior TNF-α use. Mayo scores were used to assess disease activity, Figures 2 & 3, throughout the study. Remission was defined as a Mayo Score < 2, and no individual score > 1. Evidence of remission at weeks 8 and 52, were the co-primary study end-points and both were achieved.

ULTRA-2 study results showed ADA remission rate was 16.5% at 8 wk. and 17.3% at 52 wk., vs. Placebo remission rate of 9.3% at 8 wk. and 8.5% at 52 wk., respectively (p=0.019 and p=0.004). Secondary end-points of clinical response and mucosal healing also achieved statistical significance for both weeks 8 and 52, Figure 4 & 5.

### Table 2. ULTRA-1, Secondary Study End-Points

<table>
<thead>
<tr>
<th>Secondary End-Points</th>
<th>PBO vs. ADA 160/80/40</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Healing (score &lt; 1)</td>
<td>41.5% vs. 46.9%</td>
<td>P = NS</td>
</tr>
<tr>
<td>Rectal Bleeding</td>
<td>66.2% vs. 77.7%</td>
<td>P = 0.038</td>
</tr>
<tr>
<td>(score &lt; 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGA (score &lt; 1)</td>
<td>46.9% vs. 60%</td>
<td>P = 0.035</td>
</tr>
<tr>
<td>Stool Frequency (score &lt; 1)</td>
<td>37.7% vs. 48.5%</td>
<td>P = NS</td>
</tr>
</tbody>
</table>

PBO (placebo), ADA (Adalimumab), PGA (Physician Global Assessment)
The ULTRA-2 study did not reveal any new safety concerns. There were no significant differences between ADA vs. Placebo for any AE’s: malignancy, injection reaction, opportunistic infection, CHF, demyelination or Lupus-like reactions. Two patients experienced malignancy and were in the ADA group (one squamous cell carcinoma and one gastric cancer). There were no cases of tuberculosis, lymphoma, or demyelinating disease reported in this study.

Sub-analysis of ULTRA-2, provides some additional insights about ADA treatment of moderate to severe UC failing conventional therapy. Trough ADA concentrations were obtained periodically throughout the study. A trough cut off value of ADA concentration > 10 was seen for UC remitters, see Table 3.

In the ULTRA-2 study, antibodies to ADA were detected in 2.9% (7 of 245) of patients in the ADA group; all patients positive for antibodies to ADA received ADA-mono therapy. Although the rate of developing ADA antibodies (2.9% at 1 year) with ADA-mono therapy in ULTRA-2 was far less that that witness with IFX-mono therapy in the Sonic

Table 3. ULTRA-2 Median Trough ADA Concentrations Obtained Over Time by Remission Status.
trial (14.6% at 6 month), both are higher than seen with ADA-combination in ULTRA-2 (0% at 1 year) and IFX-azathioprine combination seen in Sonic trial (0.9% at 1 yr.). The potential benefit of Anti-TNF combination with immunomodulator to prevent development of neutralizing antibodies for both ADA and IFX deserves further study. Any benefit derived from Anti-TNF combination, must be weighed against any potential increased risk for cancer, infection and other adverse events. Further study on the benefit of Anti-TNF/immunomodulator combination therapy will need to be explored, now that Anti-TNF drug concentrations and neutralizing antibodies are available and capable of guiding treatment decisions.  

Unlike the ACT 1 and 2 Trials (IFX), the ULTRA-2 Trial (ADA) permitted the enrollment of Anti-TNF experienced UC patients (40% of study patients). Results of the ULTRA-2 study indicate that Anti-TNF experienced patients were less likely to experience remission with ADA, than Anti-TNF naïve patients, 9.2% remission vs. 21.3%. Unfortunately, Sandborn, et al, did not provide information on the IFX antibody status and trough drug levels among the patients included in the ULTRA-2 Trial. Today, determination of Anti-TNF trough concentrations and detection of neutralizing antibodies are routinely used to guide decisions concerning dose escalation vs. switch to another Anti-TNF within class or switch to another class of biologic agent. However, these results do suggest the need for additional study of Anti-TNF experienced patients before routinely switching to another Anti-TNF agent (IFX or ADA).

There is much to be further learned by the ULTRA-2 sub analysis. The ULTRA-2 study design, allowed both ADA and placebo non-responders to switch into open label ADA 40mg every other week (EOW) and then escalate into ADA 40 mg every week (EW) for non- or incomplete response. The longitudinal results from this cohort, will further our understanding of the potential value of ADA dose-escalation, for UC non-responders.

Comparison of Infliximab and Adalimumab in the Treatment of Moderate-Severe UC (ACT 1 and 2 vs. ULTRA 1 and 2) 

Direct comparisons between the IFX and ADA Phase 3 Trials in the treatment of UC are not appropriate for many reasons, but study results for ACT-1/2 and ULTRA-1/2 are summarized in Table 4. First, the ULTRA studies were conducted a decade later than ACT. Study participants in the ULTRA trial were failing corticosteroid, immunomodulator therapy and 40% were TNF-α experience (LOR or intolerant to IFX). The ACT1/2 Trials (IFX) did not allow patients with inadequate response to leave the blinded trial and receive open-label therapy, while ULTRA-2 permitted any patient with relapse or failure to receive open label ADA. Lastly, the Mayo Scores for ULTRA and ACT were calculated differently. In the ULTRA-1 and -2 studies, the Mayo Score was calculated based on the worst score from the last 3 days for stool frequency and rectal bleeding, while in the ACT-1 and -2 studies, the Mayo Score was derived from the average score for stool frequency and rectal bleeding from the last 3 days.

Table 4. Comparison of Remission and Healing by IFX and ADA Reported in ACT-1/2 and ULTRA-1/2.
Golimumab [(GOL), Simponi, Janssen Biotech, Inc. Horsham, PA] is a human IgG1 Anti-TNF monoclonal antibody, which has a higher affinity to soluble TNF-α than either IFX or ADA. Golimumab is currently approved for use in RA in conjunction with methotrexate. A Phase III multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of two subcutaneous induction doses of GOL in patients with moderate to severe ulcerative colitis: PURSUIT SC, was recently presented at Digestive Disease week.

A total of 774 patients were enrolled in the PURSUIT Study and all were Anti-TNF naïve. Patients were randomized to placebo or two induction doses of GOL 200/100 or 400/200 mg given subcutaneously at time 0 and 2 weeks. The primary study end point was clinical response at 6 weeks defined as a decrease in the Mayo score of at least 30% or 3 points. Secondary end points at 6 weeks included clinical remission, mucosal healing and change in quality of life. Both primary and secondary end points for treatment of moderate to severe UC were achieved and met statistical significance, but the data has not been published. Golimumab is a new human IgG1 and appears to be a promising new choice in the treatment of moderate to severe UC. We await further peer review of GOL studies in the treatment of IBD.

Conclusions:

There are now two Anti-TNF-α agents (IFX and ADA) available for the treatment of moderate to severe UC failing conventional treatment with 5-ASA, corticosteroids and immunomodulators. Clearly, both IFX and ADA have been shown to be effective in achieving two very stiff primary end points – disease remission and mucosal healing in these UC patients. It is important to point out that ADA has not been prospectively studied in patients with SEVERE UC refractory to high dose intravenous steroids. Only, intravenous cyclosporine, IFX or surgery have been shown to be effective in these very ill patients. Until prospective studies determine the effectiveness of ADA in such patients, ADA should NOT be substituted for either CYA or IFX in these severely ill UC patients.

Further study is still needed to guide clinicians on individualizing the induction dose of Anti-TNF. Higher induction doses may be needed for patients weighting over 82 Kg or those with more extensive or severe inflammation (CRP >10). Maintenance Anti-TNF therapy should utilize drug trough levels to guide dose adjustments. Lastly, measurement of Anti-TNF neutralizing antibodies should be routinely done in patients with LOR, to guide changes in biologic agents within or outside the Anti-TNF class.
References:


