Beyond Infliximab: Other Anti-TNF Therapies for Ulcerative Colitis

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The era of biologic therapy for inflammatory bowel disease (IBD) was launched in 1998 with the Food and Drug Administration's (FDA) approval of infliximab (IFX), a chimeric monoclonal antibody to tumor necrosis factor-alpha (TNF-α), for Crohn's disease (CD) [1]. However, it was not until 2005, after the results of several open-label clinical studies [2–5] and of the ACT1 and ACT2 trials [6] of IFX for treatment of moderate to severe ulcerative colitis (UC), that this agent was approved for therapy of UC. In a recent meta-analysis, it was estimated that the number of patients with UC needed to treat with IFX to achieve one remission was only four [7]. However, as experience with using anti-TNF-α agents in CD has shown, the development of loss of response or intolerance to an initial anti-TNF-α agent, partly due to immunogenic effects, is a real problem and having other choices for blocking TNF-α is advantageous [8–10]. Since 2012, the FDA has approved two other anti-TNF-α antibodies, adalimumab and golimumab, for the treatment of UC. In this chapter, we will review the evidence supporting the use of these agents for UC therapy.

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Adalimumab for Ulcerative Colitis

Adalimumab (Humira, Abbott Laboratories, Abbott Park, IL) (ADA) is a fully humanized recombinant monoclonal antibody (human IgG1 heavy chain and kappa light chain variable regions) with specific and high-affinity binding to soluble and transmembrane forms of TNF-α. Clinical trials demonstrated that ADA was effective in inducing and maintaining remission in CD including in patients who were naïve to IFX or had previously responded to IFX and then lost response or became intolerant [11–18]. The FDA had previously approved ADA to treat rheumatoid arthritis (2002), psoriatic arthritis (2005), ankylosing spondylitis (2006), CD (2007), plaque psoriasis (2008), and juvenile idiopathic arthritis (2008) and then approved it for the treatment of UC in September 2012.

Initial descriptions of efficacy of ADA for UC came from case reports and small open-label trials in UC patients who had previously been exposed to IFX [19–21]. In an open-label 4-week clinical trial of ten patients with mild to moderate UC who had lost response to or become intolerant of IFX [19], four patients (40 %) benefited from subsequent ADA therapy (a loading dose of 160 mg ADA subcutaneously at week 0 followed by 80 mg at week 2) with one achieving clinical remission and three having clinical improvement at week 4. Among the six patients who did not respond, two underwent colectomy. In another small, single center, open-label trial of 13 patients with mild to moderate UC who had lost response to or become intolerant of IFX [22], long-term treatment with ADA (median 42 weeks; starting with ADA 160 mg subcutaneously at week 0, 80 mg at week 2, and then 40 mg every other week) was well tolerated with no serious toxicities and was effective in maintaining clinical remission in a subgroup of UC patients,

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potentially avoiding colectomy in about half of the patients. Finally, Afif et al. [20] conducted a 24-week open-label clinical trial of ADA 160 mg on week 0, 80 mg on week 2, then 40 mg every other week starting week 4 in 20 patients with moderate to severe UC including 13 patients who had lost response or developed intolerance to IFX. Disease activity was assessed using the Mayo score. At week 8, clinical response (defined as decrease in Mayo score of >30 % from baseline and a decrease of ≥3 points plus a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1) was 25 %, clinical remission (defined as Mayo score ≤2 with no individual score >1) was 5 %, and mucosal healing (defined as decrease of the Mayo endoscopy subscore from 2 or 3 to 0 or 1) was 30 %. At week 24, based on a partial Mayo score, 50 % had clinical response and 25 % were in clinical remission. The authors concluded that ADA was well tolerated and provided a clinically beneficial option for UC patients who had lost response to or could not tolerate IFX [20]. However, although these early studies suggested efficacy of ADA in patients with mild to moderate UC who had lost response or become intolerant to IFX, results needed to be interpreted with caution due to factors such as non-blinding/open-label dosing, no comparison groups, and small sample sizes.

The first randomized, placebo-controlled trial of ADA in UC was named ULTRA1 [23] and aimed to assess the efficacy and safety of ADA in anti-TNF naïve patients with moderately to severely active UC. In this 8-week trial, 390 adult patients with moderate to severe UC as defined by a Mayo score of ≥6 points and an endoscopic subscore of 2–3 points despite treatment with corticosteroids and/or immunomodulators were randomized to one of three arms: (1) ADA 160/80 (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6), (2) ADA 80/40 (80 mg at week 0, 40 mg at weeks 2, 4, and 6), or (3) placebo. It is important to note that the study was originally designed to compare only the ADA 160/80 and placebo groups, but after initiation of the study and recruitment of the first 186 subjects, the study design was amended to include the ADA 80/40 group as required by European regulatory agencies. The primary endpoint of clinical remission at week 8 as defined by a Mayo score ≤2 with no individual subscore >1, ranked secondary endpoints, and safety of treatment were assessed. At week 8, 9.2 % of those in the placebo group had achieved clinical remission as compared to 18.5 % of patients in the ADA 160/80 group ($p = 0.03$) and 10.0 % in the ADA 80/40 group ($p = 0.83$). Serious adverse effects occurred in 7.6, 3.8, and 4.0 % of patients in the placebo, ADA 80/40, and ADA 160/80 groups respectively, but these differences were not statistically significant. A total of two malignancies occurred, both in placebo-treated patients (one basal cell carcinoma and one breast cancer). One opportunistic infection (esophageal candidiasis) occurred in the ADA 160/80 group. There were no cases of tuberculosis or death. For the secondary endpoints including clinical response, mucosal healing, rectal bleeding, physician global assessment, and stool frequency, there were minimal statistically significant differences due to unusually high response rates in the placebo group. Interestingly, however, there were marked regional differences in these placebo response rates at week 8, reaching 54 % in Canada and 57 % in Eastern Europe compared to 31 % in the United States/Puerto Rico and 31 % in Western Europe.

The dosing of ADA used in the ULTRA1 trial was based on the ADA doses known to be safe and effective in CD [14, 15, 18]. Based on subgroup analyses of body weight (<82 kg vs. ≥82 kg) and CRP, the authors suggested that UC patients may require a higher dose of ADA to induce remission compared to CD patients [23]. In addition, on analysis of sequential partial Mayo score data, the authors made an observation that plateau efficacy may not have been reached at week 8, indicating that a longer exposure of ADA may be required to induce remission in UC patients.

Subsequently, a long-term 52-week randomized placebo-controlled trial named ULTRA2 [24] was conducted to assess if ADA 160/80 (160 mg at week 0, 80 mg at week 2, and then 40 mg every other week) could induce and maintain clinical remission in 494 adults with moderate to severe UC. Patients in this trial had active disease despite treatment with corticosteroids and/or 6-mercaptopurine or azathioprine. Of note 40 % of subjects had previously received anti-TNF treatment. The two co-primary endpoints were clinical remission at week 8 and clinical remission at week 52 defined as a Mayo score of 2 or less with no subscore greater than 1. At week 8, 16.5 % in the ADA group versus 9.3 % in the placebo group had achieved clinical remission ($p = 0.02$), and at week 52, the corresponding numbers were 17.3 % for ADA versus 8.5 % for placebo ($p = 0.004$). In terms of secondary endpoints, clinical response rates at week 52 were 30.2 % in the ADA group compared to 18.3 % in the placebo group ($p = 0.002$) while mucosal healing rates at week 52 were 25.0 % in the ADA group and 15.4 % in the placebo group ($p = 0.009$). In a subgroup analysis, patients with prior anti-TNF exposure had twofold lower remission rates compared to the anti-TNF naïve group: 9.2 % at week 8 and 10.2 % at week 52 for prior anti-TNF exposure compared to 21.3 % at week 8 and 22 % at week 52. The remission rates in the anti-TNF naïve group are comparable to the effects reported with IFX in patients with UC who were naïve to anti-TNF therapy (Table 16.1).

ADA treatment was generally well tolerated and the overall safety profile was comparable with placebo. Malignancies occurred in two ADA-treated patients (one skin squamous cell carcinoma and one gastric cancer) compared to none in the placebo group. There was no significant difference in serious adverse events between the ADA- (12.3 %) and placebo-treated (12.1 %) groups. Greater proportions of reported injection site reactions (12.1 % in ADA group vs. 3.8 % in placebo group, $p < 0.001$) and hematological-related adverse events (1.9 % in ADA group vs. 0 % in placebo group, $p = 0.03$) were observed in ADA-treated patients. The development of antibodies to ADA was detected in 2.9 % (7 of 245) of patients in the ADA 160/80 treatment

Table 16.1 Comparisons of efficacy of IFX (infliximab), ADA (adalimumab), and GLM (golimumab) treatments in moderate-to-severe UC

	ACT1/ACT2			ULTRA1/ULTRA2			PURSUIT-SC			
Clinical trials	Placebo ($n=121/123$)	IFX 5 mg/kg ($n=121/121$)	IFX 10 mg/kg ($n=122/120$)	Placebo ($n=130/246$)	ADA 80/40 ($n=130/–$)	ADA 160/80 ($n=130/248$)	Placebo ($n=331$)	GLM 100/50 ($n=72$)	GLM 200/100 ($n=331$)	GLM 400/200 ($n=331$)
Study design	*ACT1*: moderate-to-severe active UC despite concurrent CS alone or CS+AZA/6-MP; randomized to placebo or IFX (5 or 10 mg/kg) at week 0, 2, and 6 then every 8 week through week 46 *ACT2*: moderate-to-severe active UC despite concurrent CS alone or CS+AZA/6-MP and 5-ASA; randomized to placebo or IFX (5 or 10 mg/kg) at week 0, 2, and 6 then every 8 week through week 22			*ULTRA1*: moderate-to-severe active UC despite CS and/or AZA/6-MP; anti-TNF naïve; randomized to placebo or ADA (80/40: 80 mg at week 0, 40 mg at week 2, 4 and 6; 160/80: 160 mg at week 0, 80 mg at week 2, 40 mg at week 4 and 6) through week 8 *ULTRA2*: moderate-to-severe active UC with concurrent CS and/or AZA/MP; 40 % had previous treatment of anti-TNF; randomized to placebo or ADA (160 mg at week 0, 80 mg at week 2, 40 mg every other week) through week 52			*Pursuit-SC induction*: moderate-to-severe active UC despite CS and/or AZA/6-MP, or CS dependent; anti-TNF naïve; randomized to placebo or GLM (100/50: 100 mg at week 0, 50 mg at week 2; 200/100: 200 mg at week 0, 100 mg at week 2; 400/200: 400 mg at week 0, 200 mg at week2) through week 6 *Pursuit-SC maintenance*: patients who responded to induction therapy with GLM were randomized to placebo, GLM 50 mg, GLM 100 mg every 4 weeks through week 52			
Clinical response										
Week 8[a]	37.2 %/29.3 %	69.4 %/64.5 %	61.5 %/69.2 %	44.6 %/34.6 %	52.5 %/–	54.6 %/50.4 %	29.7 %	–	51.8 %	55.0 %
Week 54[b]	19.8 %/–	45.5 %/–	44.3 %/–	–/18.3 %	–/–	–/30.2 %	31 %	47 %	51 %	–
Clinical remission										
Week 8[a]	14.9 %/5.7 %	38.8 %/33.9 %	32.0 %/27.5 %	9.2 %/9.3 %	10.0 %/–	18.5 %/16.5 %	6.3 %	–	18.7 %	17.8 %
Week 54[b]	16.5 %/–	34.7 %/–	34.4 %/–	–/8.5 %	–/–	–/17.3 %	15 %	24 %	29 %	–
Mucosal healing										
Week 8[a]	33.9 %/30.9 %	62.0 %/60.3 %	59.0 %/61.7 %	41.5 %/31.7 %	37.7 %/–	46.9 %/41.1 %	28.5 %	–	43.2 %	45.3 %
Week 54[b]	18.2 %/–	45.5 %/–	46.7 %/–	–/15.4 %	–/–	–/25 %	27 %	42 %	44 %	–
Adverse event										
Any AE (%)	103 (85.1)/90 (73.2)	106 (87.6)/99 (81.8)	111 (91.0)/96 (80.0)	108 (48.4)/218 (83.8)	70 (53.8)/–	112 (50.2)/213 (82.9)	126 (38.3 %)/103 (66.0 %)	34 (47.9 %)/112 (72.7 %)	124 (37.5 %)/113 (73.4)	129(38.9 %)/–
Any serious AE (%)	31 (25.6)/24 (19.5)	26 (21.5)/13 (10.7)	29 (23.8)/11 (9.2)	17 (7.6)/32 (12.3)	5 (3.8 %)/–	9 (4.0 %)/31 (12.1)	20 (6.1 %)/12 (7.7 %)	2 (2.8 %)/13 (8.4 %)	9 (2.7 %)/22 (14.3 %)	5 (1.5 %)/–
Serious infection (%)	5 (4.1)/1 (0.8)	3 (2.5)/2 (1.7)	8 (6.6)/3 (2.5)	3 (1.3)/5 (1.9)	2 (1.5)/–	0 (0)/4 (1.6)	6 (1.8 %)/3 (1.9 %)	0 (0.0 %)/5 (3.2 %)	1 (0.3 %)/5 (3.2 %)	3 (0.9 %)/–
Malignancies (%)	0 (0)/1 (0.3)	2 (0.6)/1 (0.3)	1 (0.3)/0 (0)	2 (0.9)/0 (0)	0 (0)/–	0 (0)/2 (0.8)	–/1 (0.4 %)	–/0 (0 %)	–/1 (0.3 %)	–/–

[a]Week 6 for PURSUIT-SC induction trial
[b]Week 52 for ULTRA1/2 trials; *CS* corticosteroids, *AZA* azathioprine, *6-MP* 6-mercaptopurine

group; all seven patients had received ADA monotherapy. Similar to reports with other anti-TNF antibodies, the development of anti-ADA antibodies was lower in patients receiving combination therapy with ADA and an immunosuppressive agent [25]. Serum trough ADA concentrations for remitters were numerically higher than those for non-remitters throughout the duration of the study. This correlation is consistent with observations in other studies [26].

Of note, in the ULTRA2 trial, greater proportions of ADA-treated patients achieved almost all secondary endpoints at week 8 (clinical response, mucosal healing, physician global assessment, rectal bleeding subscore, corticosteroid-free remission, IBDQ score). This is in contrast to the ULTRA1 trial in which only rectal bleeding and physician global assessment subscores were significantly better in ADA-treated patients. This discrepancy might be due to the relatively high placebo response rates observed in ULTRA1 as noted above. In summary, evidence from these trials demonstrates that ADA is effective in inducing and maintaining clinical remission and clinical response in patients with moderate to severe UC failing conventional treatment with corticosteroids and/or immunomodulators.

Golimumab (SIMPONI) for UC

Golimumab (GLM) is a human IgG1κ monoclonal antibody specific for human TNF-α which was genetically engineered using mice immunized with human TNF. It was approved by the FDA in May 2013 for the induction and maintenance of clinical response and remission in UC as well as for improving endoscopic mucosal appearance during induction therapy. The approved dosing is induction with a 200 mg subcutaneous injection at week 0 followed by a 100 mg injection at week 2 and then maintenance therapy dosed at 100 mg every 4 weeks.

A combined phase 2 and phase 3 placebo-controlled randomized trial [27] called the "PURSUIT-SC" trial was conducted to assess the dosing and dose-response relationship of GLM and to evaluate the safety and efficacy of GLM induction therapy in patients with moderate to severe UC. Patients included in this study had active UC with failure to respond to or inability to tolerate treatment with oral mesalamine, oral corticosteroids, 6-mercaptopurine, and/or azathioprine, or were corticosteroid dependent; all patients were naïve to anti-TNF therapy. In the phase 2 portion of the study, 169 patients were randomized and an additional 122 patients were enrolled while the phase 2 data were analyzed. Based on findings of a trend to a dose-response relationship and a correlation between higher GLM serum concentrations and clinical response parameters, the phase 3 portion of this study randomized 774 patients to treatment at weeks 0 and 2 with placebo ($n=258$), GLM 200/100 ($n=258$, 200 mg at week 0 and 100 mg at week 2), or GLM 400/200 ($n=258$, 400 mg at week 0 and 200 mg at week 2). The primary endpoint was clinical response at week 6, defined as a decrease in Mayo score of both ≥30 % and ≥3 points along with an improvement in the rectal bleeding subscore. Secondary endpoints included clinical remission, mucosal healing, and change from baseline IBDQ. At week 6, patients who received GLM did significantly better than placebo-treated patients in terms of clinical response rates (51.8 % in GLM 200/100 and 55.0 % in GLM 400/200 vs. 29.7 % in placebo; $p<0.0001$ for both GLM group comparisons to placebo), clinical remission rates (18.7 % in GLM 200/100 and 17.8 % in GLM 400/200 vs. 6.3 % in placebo, $p<0.0001$ for both GLM group comparisons to placebo), mucosal healing rates (43.2 % in GLM 200/100 vs. 28.5 % in placebo, $p=0.0005$; 45.3 % in GLM 400/200 vs. 28.5 % in placebo, $p<0.0001$), and improvement in IBDQ scores from baseline (27.4 points in GLM 200/100 and 27.0 points in GLM 400/200 vs. 14.6 points in placebo; $p<0.0001$ for both GLM group comparisons to placebo). Similar to the phase 2 findings, there was a correlation between higher serum GLM concentrations and clinical response parameters.

Among all treated patients in the phase 2 and 3 studies, adverse events occurred in 39.1 % of the GLM groups compared to 38.2 % in the placebo group; serious adverse events occurred in 3.0 % of the GLM groups and 6.1 % of the placebo group. One death and one case of demyelination occurred, both in patients from the GLM 400/200 group.

A follow-up phase 3 placebo-controlled, randomized, double blind, withdrawal study called "PURSUIT-M" [28] was conducted to evaluate the safety and efficacy of subcutaneous (SC) GLM maintenance therapy among moderate to severe active UC patients who had responded to GLM induction therapy. Four hundred and sixty-four patients who had responded to induction therapy with either intravenous or subcutaneous GLM were randomized to receive placebo, GLM 50 mg, or GLM 100 mg at week 0 and then every 4 weeks through week 52. The primary endpoint was clinical response maintained through week 54 as assessed by partial Mayo scores every 4 weeks and full Mayo scores at weeks 30 and 54. Secondary endpoints included clinical remission at both weeks 30 and 54, mucosal healing at both weeks 30 and 54, maintenance of clinical remission among those who entered the study in remission, and corticosteroid-free clinical remission among those who were on steroids at baseline. The primary endpoint was achieved in 31.4 % of placebo-treated patients, 47.1 % of GLM 50 mg treated patients ($p=0.01$ vs. placebo), and 50.6 % of GLM 100 mg treated patients ($p<0.001$ vs. placebo). Clinical remission at both week 30 and week 54 was 15.4 % for placebo, 23.5 % for GLM 50 mg ($p=0.09$ vs. placebo), and 28.6 % for GLM 100 mg ($p=0.003$ vs. placebo), while mucosal healing at both week 30 and week 54 was 26.9 % for placebo, 43.5 % for 41.8 % for GLM 50 mg ($p=0.01$ vs. placebo), and GLM 100 mg ($p=0.001$ vs. placebo). Among patients who were in clinical remission at baseline of the PURSUIT-M study, greater proportions of those treated with GLM maintained clin-

ical remission (40.4 % of GLM 100 mg and 36.5 % of GLM 50 mg) compared to those treated with placebo (24.1 %), but these differences did not reach statistical significance. Among patients who were on corticosteroids at baseline of the PURSUIT-M study, there were no significant differences between groups in achieving corticosteroid-free clinical remission at week 54.

Through week 54, the proportions of any adverse event were 66.0, 72.7, and 73.4 % and of serious adverse events 7.7, 8.4, and 14.3 % in the placebo, GLM 50 mg, and GLM 100 mg groups respectively. There were four cases of active TB among patients from India, Poland, and South Africa, all of whom were on GLM. Three deaths occurred through week 54, all in the GLM 100 mg group, and another 6 deaths were reported after week 54, 1 from the placebo group and 5 from the GLM groups. Malignancy rates were 0.4, 0.0, and 0.3 % in placebo, GLM 50 mg, and GLM 100 mg, respectively. The authors concluded that the safety of GLM in UC was similar to GLM experience in other labeled rheumatological indications and with other anti-TNFs.

Certolizumab (Cimzia) for UC

Certolizumab pegol is a humanized monoclonal antibody Fab fragment linked to polyethylene glycol, which increases its plasma half-life and reduces the requirement for frequent dosing. Based on in vitro studies [29], certolizumab pegol has higher binding affinity for TNF than ADA or IFX and does not activate complement pathway, cell- or antibody-mediated cytotoxicity, or apoptosis due to lack of the Fc portion of the immunoglobulin molecule. Certolizumab pegol was approved by the FDA in 2008 for the treatment and maintenance of response in adults with moderate to severe CD. The use of certolizumab pegol for moderate to severe UC is currently under study in a phase 2 clinical trial [30].

Positioning Adalimumab, Golimumab, and Infliximab Use in Ulcerative Colitis

Table 16.1 shows side-by-side comparisons of study design and results for the IFX (ACT1/2), ADA (ULTRA1/2), and GLM (PURSUIT-SC/PURSUIT-M) in UC trials. On initial review, IFX appears to have higher rates of clinical response, clinical remission, and mucosal healing compared to the other two agents. Although these agents have the same mechanism of action, one can theorize whether factors such as intravenous versus subcutaneous administration or higher dose requirements play more of a role in UC as compared to CD. However, because there are no head-to-head trials, one cannot directly compare these response rates between IFX, ADA, and GLM. In addition, although the study designs are similar for the three agents, there are some differences that may partially explain different results between trials. For example, the ULTRA2 trial included subjects who had received prior anti-TNF therapy whereas this was an exclusion factor for all the other studies. In that trial, patients with prior anti-TNF exposure had much lower response, remission, and mucosal healing rates compared to the anti-TNF naïve group so this had an effect on overall response/remission rates. Also, in the ULTRA1 and ULTRA2 trials, there was a suggestion that higher doses of ADA may be needed in UC compared to CD. In the PURSUIT-M study, there was a more stringent definition for the primary endpoint of clinical response through week 54, with a requirement that patients needed to be in continuous clinical response through week 54 with assessments every 4 weeks. Finally, when reviewing Table 16.1, one of the most notable differences between study agents is in clinical remission rates. At week 6/8, remission rates for IFX 5 mg/kg were 39 % as compared to 17–19 % for ADA 160/80 and 19 % for GLM 200/100. Interestingly, however, the numbers for the placebo groups were also very different with placebo remission rates of 15 % in the IFX study as compared to 9 % for the ADA study and 6 % for the GLM study. Such variability could be due to factors such as differences in patient characteristics across studies or to systematic differences in assessment and scoring of the measures used to assess remission. This latter point is highlighted by the findings from a mesalamine study that interobserver differences in endoscopic assessment in UC trials can affect study results [31]. For future studies, centralized review of endoscopic images in UC trials will likely play an important role.

Conclusion

After the FDA approval of IFX for the treatment of UC in 2005, there was a 7-year time interval during which it was the only anti-TNF agent approved for UC therapy. However, between September 2012 and May 2013, both ADA and GLM were approved for UC therapy, thus currently providing clinicians with 3 options for anti-TNF therapy in UC. At this point, choosing between these agents should depend on factors such as patient preference for intravenous versus subcutaneous administration, physician experience in prescribing each of the agents, and medical insurance coverage for formulary drugs.

However, similar to the experience and the learning curve with anti-TNF agents in CD, many questions remain. Chief among these are the role of top-down therapy in UC, whether concomitant immune modulators should be added when starting anti-TNF therapy, and determining the effectiveness of a second or third anti-TNF agent after loss of response or intolerance of a first or second course of anti-TNF therapy. In addition, although there is some information for IFX, assessment of outcomes such as rates of hospitalization and colectomy and long-term sustainability of response and remission for IFX, ADA, and GLM are needed.

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