

Chapter 2

Antitumor Necrosis Factor Agents in Ulcerative Colitis

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Introduction

Ulcerative colitis (UC) is an autoimmune inflammatory bowel disease (IBD) that results in ulceration of the colonic mucosa, resulting in symptoms that classically include abdominal pain, diarrhea, and hematochezia. UC has a relapsing, remitting natural history, and active UC increases the risk of stricture formation, dysplasia, colorectal cancer, and a poor quality of life when disease is not adequately controlled. While the majority of UC patients are managed with medical therapies, 20–30% of UC patients undergo colectomy for medically refractory disease [1, 2]. Treatment paradigms for UC are based on disease severity and the extent of disease involvement. Biologic therapies, including those that antagonize tumor necrosis factor alpha (anti-TNF α), are indicated to treat moderately to severely active UC. These therapies are frequently prescribed in combination with other medications with the goal of steroid-free clinical and endoscopic remission. Anti-TNF α therapies currently approved for the treatment of UC include infliximab (Remicade®), adalimumab (Humira®), and golimumab (Simponi®). Biosimilars are now available and FDA approved, and biologics with an alternative mechanism of action are available; however neither of these will be discussed in this chapter.

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Currently, biologic therapies including anti-TNF α agents, utilized with or without concomitant immunomodulators, are considered the most effective medical therapies for moderately to severely active UC. Clinical trials support the efficacy of anti-TNF α therapies, suggesting that approximately two thirds of patients achieve clinical response after treatment with the first anti-TNF α medication, one third attain clinical remission, and one third are refractory or intolerant to the medication [3]. Anti-TNF α therapies are generally well tolerated, but potential adverse effects include injection site and infusion reactions, infection, autoimmunity, neutropenia, cutaneous reactions, malignancy, and worsening of existing demyelinating disease or heart failure. This chapter will review the use of anti-TNF α therapies in UC including the indication, goals of therapy, and the safety and efficacy for individual agents. Also discussed will be the treatment of older adults, general monitoring for safety and efficacy, factors that influence choice of anti-TNF α agent, information regarding switching agents, and important topics for patient education.

Indication for Use of TNF α Therapy in Ulcerative Colitis

Approach to therapy in UC is based on the endoscopic extent and clinical severity of disease presentation. Endoscopic extent can include disease limited to the rectum (ulcerative proctitis), involvement of the entire colon (pan-colitis), or any extent between. Severity can be categorized as mild, moderate, severe, or fulminant and guides therapeutic intervention [4]. Anti-TNF α agents are reserved for those patients refractory to first-line therapies (discussed in another chapter) or who are systemically ill. Patients with mildly to moderately active extensive colitis who are steroid refractory and steroid dependent and/or those who have failed adequate mesalamine or thiopurine therapy are candidates for anti-TNF α therapy. If patients respond to the anti-TNF α induction regimen, then maintenance therapy with that agent is indicated to maintain remission. Anti-TNF α therapies are contraindicated for patients with active infection, untreated latent tuberculosis, moderate-to-severe congestive heart failure, demyelinating disorders, or malignancies.

Goals of TNF α Therapy

Goals of UC therapy include (1) inducing and maintaining steroid-free remission, (2) preventing disease-related complications, and (3) improving quality of life and minimizing adverse events [5]. However, goals in the treatment of UC have evolved

in recent years. While resolution of patient symptoms was historically utilized as a primary goal of therapy, recent studies suggest that achieving endoscopic or mucosal improvement is associated with higher rates of sustained clinical remission, corticosteroid-free clinical remission, decreased hospitalization, and improved quality of life [6–9]. A systematic review and meta-analysis suggests that mucosal healing is associated with higher rates of clinical remission, colectomy avoidance, sustained mucosal healing, and likely corticosteroid-free clinical remission [10]. While mucosal healing is considered an important goal of therapy for UC, the definition of this outcome is not standardized.

Anti-TNF α Agents

Introduction

TNF α , a key pro-inflammatory cytokine in the pathogenesis of Crohn's disease, is also found in increased concentrations in the blood, colonic tissue, and stool of patients with UC [11–13]. The mechanism of action for anti-TNF α agents is to bind free and membrane-bound TNF α , which prevents TNF α from binding to its receptor sites and neutralizes its biological activity. Three anti-TNF α agents to date have been studied for the induction and maintenance of clinical remission in UC (Tables 2.1 and 2.2). One of these agents, infliximab, is administered intravenously (IV), while adalimumab and golimumab are administered as subcutaneous (SC) injections. There are currently no head-to-head studies comparing the safety and efficacy of these agents; however, placebo-controlled trials have evaluated each therapy individually.

Infliximab

Induction and Maintenance Clinical Trials

Infliximab is an IV-administered, chimeric monoclonal antibody against TNF α for the treatment of UC, as well as rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease [14]. In the UC population, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) found patients with moderately to severely active UC who received infliximab were more likely to have a clinical response than those receiving placebo. Each study was a double-blind, placebo-controlled trial evaluating infliximab at a dose of 5–10 mg/kg of body

Table 2.1 Summary of efficacy for induction and maintenance clinical trials of anti-TNF α medications in UC

Anti-TNF α medication	Authors, date	Study summary	Study population, sample size	Dosing information	Clinical response	Clinical remission and mucosal improvement
Infliximab	Rutgeerts et al. [15]	Induction (ACT 1)	364 TNF-naïve patients with moderate-to-severe active UC	Placebo or infliximab 5 mg/kg or 10 mg/kg IV at weeks 0, 2, and 6 and then every 8 weeks through week 46	Clinical response at week 8 occurred in 69% of patients on 5 mg/kg, 61% of patients on 10 mg/kg, and 37% of patients on placebo ($P < 0.001$ for both comparisons with placebo)	Clinical remission at week 8 occurred in 38.8% of patients on 5 mg/kg, 32% of patients on 10 mg/kg, and 14.9% of patients on placebo ($P < 0.001$, $P = 0.002$, respectively) Mucosal improvement at weeks 8, 30, and 54 occurred in significantly more patients in the infliximab groups than in the placebo groups ($P < 0.001$ for all comparisons)
		Induction (ACT 2)	364 TNF-naïve patients with moderate-to-severe active UC	Placebo or infliximab 5 mg/kg or 10 mg/kg IV at weeks 0, 2, and 6 and then every 8 weeks through week 22	Clinical response at week 8 occurred in 64% of patients on 5 mg/kg, 69% of patients on 10 mg/kg, and 29% of patients on placebo ($P < 0.001$ for both comparisons with placebo)	Clinical remission at week 8 occurred in 33.9% of patients on 5 mg/kg, 27.5% of 10 mg/kg, and 5.7% of patients on placebo ($P < 0.001$ for both comparisons to placebo) Mucosal improvement at weeks 8 and 30 occurred in significantly more patients in the infliximab groups than in the placebo groups ($P \leq 0.009$ for all comparisons)

Adalimumab	Reinisch et al. [18]	Induction (ULTRA-1)	576 patients with moderate-to-severe UC despite corticosteroids or immunosuppressants Study protocol amended and led to two analyses (ITT-A3, $N = 390$ and ITT-E, $N = 576$) ^a	Randomized 1:1:1 to 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA160/80), 80 mg at week 0, 40 mg at weeks 2, 4, and 6 (ADA80/40), or placebo	Clinical response at week 8 achieved in 54.6% of the ADA160/80 group, 51.5% of the ADA80/40 group, and 44.6% of the placebo group	Clinical remission at week 8 achieved in 18.5% of patients in the ADA160/80 group ($P = 0.031$), 10.0% in the ADA80/40 group ($P = 0.833$), and 9.2% in the placebo group Mucosal improvement occurred in 46.9% of the ADA160/80 group, 37.7% of the ADA80/40 group, and 41.5% of the placebo group
	Sandborn et al. [19]	Maintenance (ULTRA-2)	494 patients with moderate-to-severe UC who received concurrent treatment with oral corticosteroids or immunosuppressants, 40% of study population had prior TNF exposure	Adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo	Clinical response at week 8 occurred in 50.4% of adalimumab-treated patients and 34.6% of placebo-treated patients ($P < 0.001$) Clinical response at week 52 occurred in 30.2% of adalimumab-treated patients and 18.3% of placebo-treated patients ($P < 0.002$)	Overall clinical remission at week 8 achieved in 16.5% of adalimumab-treated patients and 9.3% of placebo-treated patients ($P = 0.19$) Overall clinical remission at week 52 achieved in 17.3% of adalimumab-treated patients and 8.5% of placebo patients ($P = 0.004$) Mucosal improvement at week 8 achieved in 41.1% and 31.7%, respectively, for adalimumab and placebo groups ($P = 0.032$). Mucosal improvements at week 52 were 25.0% and 15.4%, respectively, for adalimumab and placebo groups ($P = 0.009$)

(continued)

Table 2.1 (continued)

Anti-TNF α medication	Authors, date	Study summary	Study population, sample size	Dosing information	Clinical response	Clinical remission and mucosal improvement
Golimumab	Sandborn et al. [28]	Induction with SC golimumab (PURSUIT-SC)	761 patients	Randomized to placebo, 200/100 mg, and 400/200 mg at weeks 0 and 2	Rates of clinical response at week 6 were 30.3%, 51.0%, and 54.9% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively (both, $P \leq 0.0001$)	Rates of clinical remission at week 6 were 6.4%, 17.8%, and 17.9% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively (both, $P < 0.0001$) Rates of mucosal improvement were 28.7%, 42.3%, and 45.1% for placebo, 200/100 mg, and 400/200 mg golimumab groups, respectively ($P = 0.0014$, $P < 0.0001$, respectively)
	Sandborn et al. [29]	Maintenance (PURSUIT-SC maintenance)	464 patients who responded to induction therapy with golimumab	Randomized to placebo, 50 mg, or 100 mg golimumab every 4 weeks	Clinical response maintained through week 54 in 31.2%, 47.0%, and 49.7% of patients receiving placebo, 50 mg, and 100 mg golimumab, respectively ($P = 0.010$ and $P < 0.001$, respectively)	Rates for clinical remission and mucosal improvement at weeks 30 and 54 were 15.6% and 26.6% for placebo, 23.2% and 41.7% for golimumab 50 mg, and 27.8% and 42.4% for golimumab 100 mg ($P = 0.004$, $P = 0.002$, respectively)

^aClinical response, clinical remission, and mucosal improvement results are all for the ITT-A3 treatment group, which were patients in the amended study protocol

Table 2.2 Summary of FDA-approved induction and maintenance dosing for anti-TNF α medications for UC

Anti-TNF α medication	Induction dosing	Maintenance dosing
Infliximab	5 mg/kg IV weeks 0, 2, and 6	5–10 mg/kg IV q 8 weeks
Adalimumab	160 mg SC day 1 and 80 mg SC day 15 -OR- 80 mg SC day 1, day 2, and day 15	Day 29 initiate 40 mg SC q 2 weeks
Golimumab	200 mg SC day 1 and 100 mg SC day 15	100 mg SC q 4 weeks

weight or placebo administered at weeks 0, 2, and 6 and then every 8 weeks through week 22 in ACT 2 and week 46 in ACT 1 [15]. TNF α -naïve patients with active moderate-to-severe UC who had failed or were intolerant to conventional therapies were included. Concomitant medication remained stable throughout each study, except for corticosteroid therapy, which was tapered after week 8. The primary endpoint of each trial was clinical response at week 8.

In ACT 1, 69.4% of patients receiving 5 mg/kg (84 of 121) and 61.5% of patients receiving 10 mg/kg (75 of 122) had a clinical response at week 8, compared with 37.2% of patients receiving placebo (45 of 121, $P < 0.001$ for both comparisons). In ACT 2, 64.5% of patients receiving 5 mg/kg (78 of 121) and 69.2% of patients receiving 10 mg/kg (83 of 120) had a clinical response at week 8, compared with 29.3% of patients receiving placebo (36 of 123, $P < 0.001$ for both comparisons). Clinical remission and mucosal improvement occurred in a higher proportion of patients treated with infliximab compared with placebo in both ACT 1 and ACT 2 trials at weeks 8, 30, and 54 and weeks 8 and 30, respectively ($P \leq 0.009$ for all comparisons). Incidence of infliximab antibody formation at week 54 in ACT 1 was 6.1% (14 of 229 patients) and 6.4% (12 of 188 patients) at week 30 in ACT 2. In ACT 1, infusion reactions occurred in 10.7% (13 patients) in placebo group, 9.9% (12 patients) of 5 mg/kg group, and 12.3% (15 patients) of 10 mg/kg group ($P = 1.00$). In ACT 2, incidence of infusion reactions was 8.1% (10 patients) in placebo group, 11.6% (14 patients) in the 5 mg/kg group, and 11.7% (14 patients) of the 10 mg/kg group ($P = 0.37$). At week 54 in ACT 1, 35.4% of patients with anti-infliximab antibodies had an infusion reaction compared with 9.8% of patients with negative or inconclusive antibody testing (5 of 14 and 21 of 215, respectively). At week 30 in ACT 2, 50% of patients with anti-infliximab antibodies had an infusion reaction compared with 9.7% of patients with inconclusive or lack of antibodies (6 of 12 and 17 of 176, respectively), suggesting that patients with positive tests for antibodies were more likely to develop infusion reactions than those without antibodies. Infliximab was generally well tolerated, and incidence of adverse events and infections was similar for both patients treated with drug and placebo.

Long-Term Safety and Efficacy

Long-term infliximab maintenance therapy for UC was evaluated during the ACT 1 and ACT 2 extension studies, in which patients who achieved a benefit from infliximab continued to receive up to three additional years of therapy [16]. Of

484 infliximab-treated patients in ACT 1 and ACT 2, 229 patients continued to receive infliximab in the extension studies. Of the 229 patients in the infliximab group, 70 (30.6%) discontinued infusions: 24 (10.5%) due to an adverse event, 11 (4.8%) due to lack of efficacy, 1 (0.4%) required colectomy, and 34 (14.8%) for other reasons. The primary intent of the efficacy analysis was to evaluate maintenance of efficacy. At week 0 of the extension study, 42.4% (97 of 229 patients) had no disease activity, and at week 152, 54.6% (125 of 229 patients) had no disease activity. For patients with mild or no disease activity, the proportion was 76.9% (176 of 229 patients) at week 0 and 89.5% (205 of 229 patients) at week 152. Based on these results from the intention-to-treat analysis, efficacy was maintained in both subgroups. Of note, patients who discontinued the study due to trial termination or for other reasons had the last available observation carried forward.

Safety was reported as events per 100 patient-years, for any patient who received at least one infusion of infliximab ($N = 230$), with a mean treatment duration of 1.99 years in the extension studies. Overall rates of adverse events were 506 per 100 patient-years, and infliximab was discontinued secondary to an adverse event at a rate of 4.63 patients per 100 patient-years of therapy. Infusion reactions occurred at a rate of 7.25 patients per 100 patient-years (36 of 230 patients). Only three patients experienced serious infusion reactions. Five malignancies were diagnosed during the extension studies, including adenocarcinoma of the lung, breast cancer, prostate cancer, basal cell carcinoma, and skin cancer of the nose and forearm (1.01 patients per 100 patient-years of therapy). No new or unexpected safety data compared to previous data on safety of infliximab was reported during the extension studies.

Adalimumab

Induction and Maintenance Clinical Trials

Adalimumab is a SC-administered, recombinant human antibody against TNF α approved for the treatment of UC, in addition to rheumatoid arthritis, juvenile idiopathic arthritis, hidradenitis suppurativa, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and Crohn's disease [17]. The first trial to evaluate the safety and efficacy of adalimumab in UC was the Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab (ULTRA 1). This 8-week, multicenter, randomized, double-blind, placebo-controlled study assessed adalimumab for the induction of clinical remission in anti-TNF α -naïve patients with moderate-to-severe UC despite concurrent therapy with corticosteroids and/or immunomodulators [18]. A second multicenter, randomized, double-blind, placebo-controlled clinical trial, ULTRA 2, was performed to further evaluate the efficacy and safety of adalimumab in patients with moderate-to-severe UC and gather long-term data [19].

The ULTRA 1 study protocol originally included one adalimumab group of patients receiving adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA160/80), and placebo. However, the study protocol was amended to include a second induction group of adalimumab 80 mg at week 0 and 40 mg at weeks 2, 4, and 6 (ADA80/40). Patients in the study continued to receive adalimumab 40 mg SC every 2 weeks through week 52 in an open-label phase. There were two intention-to-treat analyses, one including patients under the amended study protocol (ITT-A3, $N = 390$) and a second intention-to-treat population including all patients under the original protocol and amendments (ITT-E, $N = 575$). In the ITT-A3 population, 18.5% of patients in the ADA160/80 arm, 10% of patients in the ADA80/40 arm, and 9.2% of patients in placebo arm achieved primary efficacy endpoint of clinical remission at week 8 ($P = 0.031$, $P = 0.833$ versus placebo, respectively). Adalimumab treatment was generally well tolerated at both induction doses, and overall safety profile was comparable to placebo. The findings of ULTRA 1 trial demonstrated that ADA160/80 was safe and effective for induction of remission of moderate-to-severe UC.

The ULTRA 2 trial randomized 494 patients with moderate-to-severe active UC despite concurrent corticosteroid and/or immunomodulator therapy to adalimumab or placebo. Unlike ULTRA 1, prior treatment with infliximab was allowed if it had been discontinued due to loss of response or drug intolerance for greater than 8 weeks, and approximately 40% of the total study population had prior infliximab exposure. Patients were randomized 1:1 to ADA160/80 or placebo after stratification by prior anti-TNF α exposure. The primary efficacy endpoint was rate of clinical remission at weeks 8 and 52. At week 8, 16.5% of patients treated with adalimumab achieved clinical remission compared with 9.3% receiving placebo ($P = 0.019$). Similarly, at week 52 patients treated with adalimumab achieved a significantly higher rate of clinical remission (17.3% versus 8.5%, $P = 0.004$). At week 52, both anti-TNF α -naïve and experienced patients achieved clinical remission at significantly higher rates compared with placebo arms (22% versus 12.4%, $P = 0.029$ and 10.2% versus 3%, $P = 0.039$, respectively). Whereas, at week 8 only patients who were anti-TNF α naïve had a statistically significant rate of clinical remission compared with placebo group (21.3% versus 11%, $P = 0.017$). In secondary endpoint analyses, significantly more patients treated with adalimumab compared with placebo achieved clinical response at week 8 (50.4% versus 34.6%, $P < 0.001$) and week 52 (30.2% versus 18.3%, $P = 0.002$). Adalimumab-treated patients also achieved mucosal improvement more often than placebo-treated patients (week 8, 41.1% versus 31.7%, $P = 0.032$, and week 52, 25% versus 15.4%, $P = 0.009$). Overall, adalimumab treatment had a similar safety profile to placebo.

The ULTRA 2 trial was designed to permit patients with inadequate response to initial treatment to switch to open-label adalimumab 40 mg every other week at week 12 or later and weekly adalimumab 40 mg for patients who continued to demonstrate inadequate response. After week 12, 31.7% (39 of 123) of week 8 responders and 61.6% (77 of 125) of week 8 nonresponders switched to open-label adalimumab. Furthermore, 16.3% (20 of 123) and 38.4% (48 of 125) escalated to weekly adalimumab for responders and nonresponders, respectively [20]. Remission,

response, and mucosal improvement rates at week 52 for prior week 8 responders were 20%, 45%, and 45%, respectively, compared with 2.1%, 25%, and 29.2%, respectively, for prior week 8 nonresponders. These results indicate that escalation to weekly adalimumab dosing may be beneficial for both patients who initially respond to induction dosing and then lose response, as well as patients who are primary nonresponders. Weekly dosing was not associated with a greater risk of adverse events.

Long-Term Safety and Efficacy

Efficacy and safety data for long-term use of adalimumab was reported for patients enrolled in the ULTRA 1 and 2 trials. Colombel et al. evaluated 600 of the 1094 patients enrolled in ULTRA 1 and 2 who received at least one dose of adalimumab (ADA Randomized Set) and found that 199 patients remained on adalimumab at week 208 [21]. Long-term remission rates and mucosal improvement rates over time were analyzed using nonresponder imputation (NRI), whereby patients with missing data were assumed not to have achieved the endpoint. For the ADA Randomized Set, rate of remission per partial Mayo score was 24.7% (148 of 600 (NRI)), and mucosal improvement was 27.7% (166 of 600 (NRI)) at year 4. Authors also evaluated the maintenance efficacy of adalimumab through week 156, for 588 patients who enrolled in the open-label extension, ULTRA 3, from ULTRA 1 and 2 (ADA Extension Set). Three hundred and sixty patients remained on adalimumab through week 156 in ULTRA 3. Long-term remission with mucosal improvement per partial Mayo score was 63.6% (NRI) at week 156 (of 242 patients who entered in remission) and 59.9% (NRI) at week 144 (of 409 patients who entered with mucosal improvement).

Safety data was reported for patients receiving at least one dose of adalimumab in ULTRA 1, 2, and 3 ($N = 1010$ patients or 2338 patient-years of exposure). Rates of serious adverse events per 100 patient-years of exposure were similar to or lower than that observed in prior studies. The overall rate was 30.7 events per 100 patient-years for week 52 of ADA 160/80/40 compared with a rate of 17.7 events per 100 patient-years for all ADA. During the ULTRA 3 study, three events of B-cell lymphoma occurred; however all patients had prior or current thiopurine use. Serious adverse events included, but were not limited to, two cases of cytomegalovirus colitis, one serious tuberculosis infection, one cardiorespiratory arrest, and one right ventricular failure. No new or unexpected safety data compared to previous data on safety of adalimumab was reported during the extension studies.

Golimumab

Induction and Maintenance Clinical Trials

Golimumab is a fully humanized, SC-administered antibody against TNF α that is approved for the treatment of UC and also for rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis [22–27]. In the UC population, the Program of

Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) study evaluated the safety and efficacy of induction therapy with SC golimumab [28]. This multicenter, randomized, double-blind, placebo-controlled trial concluded that induction with SC golimumab 200/100 mg and 400/200 mg at weeks 0 and 2 was effective in inducing clinical response, clinical remission, and mucosal improvement in patients with moderately to severely active UC. The study also found that induction therapy was well tolerated with a safety profile consistent with other anti-TNF α therapies.

Specifically, this integrated phase 2 and 3 clinical trial enrolled patients with moderate-to-severe UC who were intolerant or refractory to oral 5-aminosalicylates, oral corticosteroids, azathioprine, and/or 6-mercaptopurine but naïve to anti-TNF α antagonists. In the phase 2 dose-finding portion of the trial, 169 subjects were randomized 1:1:1:1 to SC placebo or golimumab 100/50 mg, 200/100 mg, or 400/200 mg at weeks 0 and 2. In the phase 3 study, 774 subjects were randomized 1:1:1 to receive SC placebo, golimumab 200/100 mg, or 400/200 mg at weeks 0 and 2. At week 6, 51.0% and 54.9% of the golimumab 200/100 mg and 400/200 mg patients were in clinical response, compared to 30.3% of placebo patients. This result was statistically significant and met the primary endpoint of the study ($P < 0.0001$). Additionally, significantly more patients on golimumab 200/100 mg or 400/200 mg reached clinical remission as compared to placebo (17.8%, 17.9%, and 6.4% respectively, $P < 0.0001$). Significantly more patients on golimumab 200/100 mg or 400/200 mg also attained mucosal improvement. 42.3% on golimumab 200/100 mg ($P < 0.0014$), 45.1% on golimumab 400/200 mg ($P < 0.0001$), and 28.7% on placebo had mucosal improvement. Golimumab was generally well tolerated with an adverse event profile similar to placebo. Serious adverse events and serious infections were rare [28].

One thousand, two hundred and twenty eight patients completing one of two induction studies were then enrolled in a phase 3, multicenter, placebo-controlled, double-blind, and randomized-withdrawal study to evaluate SC golimumab maintenance therapy [29]. Patients received either golimumab 50 mg and 100 mg or placebo every 4 weeks through week 52. Results of the primary analysis population ($N = 456$) showed that significantly more patients treated with golimumab 100 mg or 50 mg maintained clinical response as compared to placebo (49.7%, 47.0%, 31.2%; $P < 0.001$ and $P = 0.010$, respectively); thus the study achieved the primary endpoint. For clinical response through week 52, the numbers needed to treat were 5 and 6, respectively, for the 100 mg and 50 mg golimumab groups. Significantly more patients on golimumab 100 mg were in clinical remission at weeks 30 and 54 compared to placebo (27.8%, 15.6%, respectively, $P = 0.004$). Clinical remission rates in the golimumab 50 mg SC group were numerically superior, but not statistically significant. The number needed to treat to attain clinical remission for the 100 mg group was 8. Analysis suggests that the incidence of anti-golimumab antibody formation is 2.9% after 54 weeks of therapy; subgroup analysis revealed those receiving concomitant immunomodulators had a 1.1% (4 of 362) incidence of anti-drug antibody formation compared to 3.8% (28 of 741) of those receiving golimumab alone [29]. The overall safety profile in the maintenance clinical trial was consistent with the known safety profile of golimumab and included increased risk of rare serious infections, tuberculosis, malignancies, and antidrug antibodies [29].

Long-Term Safety and Efficacy Data

Authors published long-term safety and efficacy data on SC golimumab in 2016 [30]. 1240 anti-TNF α -naïve patients with moderate-to-severe UC from the phase 3 PURSUIT maintenance study were randomized to receive placebo or golimumab 50, 100, or 200 mg for 52 weeks in the maintenance study and then continued to receive treatment in the long-term extension study through week 104 [30]. At week 104 researchers noted that 86% of included patients had inactive or mildly active disease activity. Additionally, of the 174 patients who were corticosteroid-free at week 54, 88.5% remained corticosteroid-free at week 104.

For patients receiving at least one dose of golimumab (1664.0 patient-years), the safety profile was similar to that observed in earlier studies. Rates of serious adverse events per 100 patient-years of exposure were similar for exposure through weeks 54 and 104 (19.65% and 11.10%, respectively), as were adverse events that lead to discontinuation of golimumab (12.72% and 5.98%, respectively). Authors reported that tuberculosis, opportunistic infection, and malignancy rates were low; during the trial two nonmelanoma skin cancers, one metastatic colon cancer, and two deaths (biventricular heart dysfunction, sepsis) occurred between weeks 54 and 104 [30].

Treating Adults Over the Age of 60 with Anti-TNF α Therapy

In the United States, an estimated 10–15% of IBD patients are newly diagnosed after the age of 60, with an incidence of 6–8/100,000/year [31]. Additionally, aging patients who have been diagnosed earlier in life add to the growing population of older adults with IBD. While limited data exists to evaluate safety and efficacy of anti-TNF α biologics in older adults, the indication to use anti-TNF α medications in older populations is similar to that of younger patients [32]. Nonetheless, treatment decisions for older adults with UC are complicated by the lack of trials evaluating safety and efficacy of medications in this population. Additionally, older adults have a higher incidence of comorbid diseases and polypharmacy, complicating therapy. Furthermore, physiologic changes associated with aging increase the risk of morbidity and mortality; one study reports that 25% of IBD hospitalizations are for patients over the age of 65 [33].

Few studies have evaluated the safety and efficacy of anti-TNF α therapy in adults over the age of 65; in fact older adults are routinely excluded from clinical trial enrollment [5, 34]. In 2011, a retrospective study evaluated an Italian cohort of 95 IBD patients over the age of 65 of whom 78 patients (36 with UC and 58 with Crohn's disease) were treated with anti-TNF α agents with or without concomitant immunomodulators. Retrospective evaluation revealed 22 of 37 (59%) UC patients and 38 of 58 (65%) CD patients achieved clinical remission. Of patients receiving anti-TNF α therapy, 11% developed severe infections, 3% developed neoplasms, and 10% died, as compared to matched controls of whom 0.5% reported severe

infections, 2% developed neoplasms, and 2% died [33]. Although results suggest higher risk in older populations, the retrospective study design limited comparability, and patients treated with anti-TNF α therapy may have had more severe disease than the control group which may have significantly biased outcomes.

Another observational and retrospective study in 2015 compared 66 IBD patients over the age of 65 receiving anti-TNF α therapy, 112 IBD patients under the age of 65 receiving anti-TNF α therapy, and 61 anti-TNF α -naïve patients. Authors reported an increased risk of serious adverse events in the greater-than-65 anti-TNF-treated cohort as compared to those under the age of 65 treated with anti-TNF α therapy (RR = 4.7; $P < 0.001$). This risk was also higher as compared to those greater than 65 not treated with anti-TNF α therapies (RR = 3.09; $P = 0.0008$) [35]. Authors also reported that patients greater than 65 years old had significantly lower clinical response after 10 weeks of anti-TNF α therapy, as compared to patients less than 65 treated with anti-TNF α therapies; however, no difference in clinical response was noted between the groups after 6 months of therapy. Importantly, this assessment was limited by retrospective study design, and clinical response was based on clinical assessment only, not endoscopic evaluation [35].

Another consideration relevant to older populations with IBD treated with anti-TNF α therapies is the known risks of complications and adverse events. For example, anti-TNF α agents are contraindicated in moderate-to-severe New York Heart Association class III or IV heart failure [36], a comorbidity more common in older populations. Additionally, an increased risk of melanoma and nonmelanoma skin cancers has been associated with IBD. This will be discussed further in another chapter, but given the increased risk in older populations, appropriate screening is warranted [37]. Furthermore, the risk of lymphoproliferative disorders in the IBD population is thought to be similar to or slightly higher than the general population; however thiopurine therapy is associated with a four- to sixfold increased relative risk. The absolute risk is higher in adults over the age of 70 as compared to younger patients, with the absolute risk thought to be 1 in 4000–5000 for patients aged 20–29 and 1 in 300–400 in those over 70 [38]. While we feel that this risk is not an absolute contraindication to utilizing thiopurine therapy in conjunction with anti-TNF α therapy, this increased risk should be considered in this specific population. The true risk associated with anti-TNF α monotherapy is unclear as many patients treated with anti-TNF therapy are treated concomitantly with immunomodulators; this will be discussed further in a subsequent chapter.

While consideration should be given to potentially higher risk of complications, older adults with UC may present with severe disease, and, when indicated, these patients should be offered the most effective therapy, including anti-TNF α agents when appropriate. The assessment of risk in this population should compare the alternative therapies available including other classes of biologics, the inherent risk of patients being on steroids, and the risk of surgery which is also higher in the elderly population. Without the benefit of prospective controlled trials in this population, given a potential for higher rates of complications, it is important to try and reduce complications. Currently guidelines for any patient on anti-TNF α therapy, much less those at highest risk, include evaluation prior to initiation of therapy for

any infections or comorbid illness that would preclude use of anti-TNF α therapy. Additionally, guidelines recommend appropriate preventative care with immunizations and cancer screening when indicated. Evaluation of comorbid illness and performing appropriate immunizations and cancer screening are even more critical in older patients, as they appear to have the highest absolute risk for adverse events when on anti-TNF α therapy.

General Monitoring for Safety and Efficacy of Anti-TNF α Agents

Prior to initiation of anti-TNF α therapy, patients with UC should be screened for contraindications to therapy including tuberculosis, hepatitis B virus, and active infection. Other relative and absolute contraindications to therapy, including history of heart failure, demyelinating disease, the presence of current malignancy, and recent receipt of live vaccines, should be considered. Patients should be monitored throughout the therapy for signs and symptoms of infection, heart failure, hypersensitivity reaction, lupus-like syndrome, and malignancy. Safety laboratory monitoring at baseline and throughout treatment should include complete blood count and liver tests [39]. Therapeutic efficacy is generally evaluated with clinical assessment of symptomatic improvement, ability of patients to taper off of corticosteroids, and laboratory and endoscopic measures of improvement. Therapeutic drug monitoring is discussed in detail in a subsequent chapter.

Choice of Anti-TNF α Agent to Treat UC

The safety and efficacy of anti-TNF α therapies to treat moderately to severely active UC are in general similar among different agents. While each agent has been evaluated individually in double-blind, placebo-controlled clinical trials, no head-to-head studies comparing agents are currently available. However, without the benefit of head-to-head trials, when considering which anti-TNF α medication to utilize, factors that may influence the choice of therapy include the route of administration, the setting in which medications are administered, and cost [40].

Patient preference should be considered as therapies offer different routes of administration, either subcutaneous injection or intravenous infusion [40]. Also, maintenance dosing schedules vary, with infliximab typically administered intravenously every 8 weeks, adalimumab administered subcutaneously every 2 weeks, and golimumab administered subcutaneously every 4 weeks. Patient lifestyle is important to consider as the route or timing of doses may impact patient preference regarding therapy. For example, patients who live far from an infusion center or who have difficulty scheduling infusion appointments during clinic hours may prefer injectable agents that can be self-administered at home, while others may prefer the

infrequency of every 2 months of intravenous dosing. Furthermore ease of intravenous access is important to consider as patients with difficult IV access may prefer subcutaneous administration. Discomfort with self-injection may be a factor for other patients. Additionally, access to refrigeration is often required to store injectable medications, while intravenous medications are maintained at a clinical site and do not require patient storage of medications.

The location of administration may also impact choice of therapy. Intravenous medications are administered by a healthcare professional either in an infusion center or in the patient's home, which may be desirable for patients who prefer the presence of healthcare professionals during medication administration or in those who have difficulty adhering to a self-administered medication schedule. Additionally, intravenous administration facilitates laboratory monitoring without the need for additional clinic visits to arrange for ongoing blood draws.

Finally, given the expense of anti-TNF α therapies, insurance coverage often influences choice of first-line therapy in the absence of compelling indications for a particular therapy. Often this will be the primary factor regarding the choice of anti-TNF α therapy for patients. Without head-to-head trials, there is not compelling data to select a specific anti-TNF α therapy over another based on safety or efficacy.

Switching Anti-TNF α Therapies

Discontinuation of one anti-TNF α therapy and initiation of a subsequent anti-TNF α therapy may occur in the case of primary or secondary nonresponse to the previous agent, inadequate response, allergic reaction, patient nonadherence, or other interruption to therapy. Studies have suggested that response and remission rates are highest after treatment with the first therapy and lower with the second and third medication; however it appears that the reason for discontinuation of prior anti-TNF α therapies is a predictor of response to subsequent therapies. In general for patients who have responded to a specific anti-TNF α therapy, we do not advise "switching" to another anti-TNF α therapy, unless the patient loses response or has an adverse reaction.

In anti-TNF α -naïve patient populations, an estimated two thirds of patients with IBD have clinical response to the first anti-TNF α medication, one third achieve clinical remission, and one third are either intolerant or refractory to the medication [3]. Patients who do not respond to therapy are classified into primary nonresponders (those with no significant response to therapy), secondary nonresponders (those who initially respond to therapy and then subsequently lose response), and patients who are intolerant to the medication.

The response rate of patients treated with a second anti-TNF α therapy appears dependent on the reason for discontinuation of the first medication. A systematic review and meta-analysis suggest that of 61% of patients intolerant to the first anti-TNF α therapy, 45% of secondary nonresponders and 30% of primary nonresponders achieved remission with a second anti-TNF α agent [3]. However, response and

remission rates varied widely in retrospective studies, and currently only one placebo-controlled trial has evaluated the efficacy of a second anti-TNF α therapy in a Crohn's disease population [41]. In this study 301 patients who failed treatment with infliximab were randomized to receive induction with adalimumab or placebo. Twenty-one percent of adalimumab patients and 7% of placebo patients achieved remission after 4 weeks of treatment ($P < 0.001$). Statistically more adalimumab patients also achieved clinical response as compared to placebo (52%, 34%, respectively, $P < 0.001$). This suggests that patients with inadequate response or intolerance to infliximab can achieve remission with adalimumab, a second anti-TNF α medication [41].

Limited studies have evaluated the efficacy of treatment of IBD with a third anti-TNF α medication after failure of two previous anti-TNF α therapies, and the majority of the available data is in the Crohn's disease population [42]. One retrospective study evaluated 67 patients with Crohn's disease who were treated with a third anti-TNF α medication after intolerance or failure of two prior anti-TNF α therapies. This small retrospective study suggests that at weeks 6 and 20, 61% and 51% of patients, respectively, reported clinical response; however significant limitations of the study include small sample size, retrospective design, and lack of standardization of the definition of failure of prior anti-TNF α therapies [42, 43]. Another small retrospective study evaluating 63 patients with IBD treated with a third anti-TNF α therapy reports that 75% of patients achieved clinical response after 3 months of therapy, with 36% achieving remission [42, 44].

Patient Education

Patient education regarding anti-TNF α therapy is important for patient-centered shared decision-making to inform patients of the risks and benefits of therapy and to improve adherence. Education should include a discussion of goals of therapy, risk of adverse reactions, and the safety and efficacy monitoring plan. Patients should be instructed to notify healthcare professionals with signs or symptoms of infection or other adverse events. Patients should also be informed of the importance of contacting their healthcare team if they have planned surgery, as medication adjustment may be indicated. They should also inform their healthcare team if they are pregnant or considering conceiving, to discuss the role of therapy in pregnancy.

The importance of adherence to anti-TNF α medications to induce and maintain remission should be emphasized. Adherence is imperative to maintain response and to decrease the risk of developing antidrug antibodies that are associated with loss of response and increased risk of adverse reactions. Current treatment paradigms strongly encourage adherence to maintenance therapy to control active disease; the consequence of stopping therapy is discussed in a subsequent chapter.

Importantly, patients on immunosuppressant medications including anti-TNF α therapies should discuss age-appropriate healthcare maintenance recommendations

with their providers to consider the role of vaccines to reduce the risk of preventable illnesses [45, 46]. Patients should also be advised that receiving live vaccines while on immunosuppressant therapy is contraindicated. Age- and sex-appropriate cancer screening should be discussed. Additionally, patients should be informed about logistical issues related to insurance coverage of anti-TNF α therapies, including the need to notify healthcare providers about insurance changes to facilitate approval of medical therapy and to prevent dosing delays.

Conclusion

For those patients who have failed first-line therapy for UC, anti-TNF α agents can be utilized to induce and maintain remission. For the population that has failed first-line therapy, anti-TNF α therapy has been the most well-studied class of biologic therapy and has been proven to be relatively safe and effective for the treatment of UC. For those patients who initiate anti-TNF α therapy, prescribers should understand that the goals of therapy include improving the patient's quality of life and symptoms. However, other goals including achieving steroid-free remission, avoidance of hospitalization and complications from UC, and achieving improvement in the severity of disease based on endoscopic evaluation are of equal importance.

Currently there are three FDA-approved anti-TNF α therapies in the United States. This includes infliximab, adalimumab, and golimumab. In general, the safety profile and efficacy of the three available therapies are similar. There are no head-to-head trials to definitively show if one anti-TNF α therapy is superior to the others. The primary risks associated with anti-TNF α therapy are risk of infection, adverse reaction to the medication (infusion reaction or injection site reaction), and, while uncommon, an association with the development of other autoimmune reactions (lupus-like reaction, psoriasiform rash).

While therapy is generally tolerated very well, all patients and in particular adults over the age of 60 should be monitored carefully for signs of adverse reactions to the medication itself, infection, and malignancy. The primary contraindications to initiation of anti-TNF α therapy include evidence of active infection (e.g., tuberculosis, opportunistic infections, or hepatitis B), history of class III or IV heart failure, known demyelinating disease, known hypersensitivity reactions, or the presence of malignancy.

The initial choice of a specific anti-TNF α therapy, as there is no evidence that one is superior to another, has been primarily based on insurance authorization, patient's preference for infusion versus injection, and patient's out-of-pocket cost for any given therapy. For those patients with poor intravenous access, while infliximab is not contraindicated, adalimumab or golimumab may be a preferential first-line choice as they do not require intravenous access.

In general we do not recommend switching one anti-TNF α therapy to another for convenience or insurance factors. However, for those patients who have had intolerance or loss of response to a previous anti-TNF α therapy, it is reasonable to consider

trying a second anti-TNF α agent. We do not advocate switching unless the patient has lost response or been intolerant to a specific anti-TNF α therapy because this will increase the risk of the development of antibodies to the previous anti-TNF α therapy. Additionally, it has been shown that those patients started on a second anti-TNF α therapy generally have a lower response and remission rate compared to the first anti-TNF α agent. The utilization of concomitant immune suppression with anti-TNF α therapy will be discussed in detail in another chapter. However, in general we recommend that the majority of patients, unless there is intolerance or contraindication, should be on concomitant immune suppression when on an anti-TNF α therapy.

Patient education regarding the risks and benefits of anti-TNF α therapy is critical. It is also extremely important for patients to understand that interruption of therapy can result in antibody formation and loss of response. Therefore, adherence is an essential issue with regard to the long-term maintenance with anti-TNF α therapy.

In summary, for UC patients who have failed first-line therapy, anti-TNF α therapy can be utilized for the induction and maintenance of remission. Anti-TNF α therapy is relatively safe and effective for the treatment of UC provided patients are selected to ensure there are no treatment contraindications and that all patients are monitored carefully.

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