Update on the Management of Ulcerative Colitis

Sahar Taba Taba Vakili[1], Mohammad Taher[2], and Nasser Ebrahimi Daryani[3]

[1] *Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[2] *Department of Internal Medicine, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Gastroenterology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- The present treatment goals for inflammatory bowel diseases (IBD) especially ulcerative colitis (UC) include rapid induction of clinical remission, steroid-free maintenance of clinical remission, mucosal healing and improvement of quality of life in UC patients. Immunomodulators have been reserved for steroid-dependent or steroid- refractory UC patients. Among these agents, azathioprine/6-mercaptopurine should be used for maintenance of remission in quiescent UC. Calcineurin inhibitors can be prescribed as a short-term rescue therapy in steroid- refractory UC patients, but the long term efficacy of these agents remains unclear. According to retrospective studies, methotraxate is not recommended for inducing and maintaining remission in UC. Novel biological therapies targeting different specific immunological pathways continue to be developed and introduced for a variety of clinical scenarios in IBD. Infliximab is currently used for induction and maintenance therapy in patients who have moderately to severely active UC with an inadequate response to conventional agents such as aminosalicylates, corticosteroids, or immunomodulators. Other anti-TNF agents and biologic therapies are undergoing evaluation in clinical trials for their efficacy in IBD. Most patients who start biologics should continue treatment for the foreseeable future and potential consequences of discontinuation should be discussed with individual patients. Currently, data do not exist to administer biologics as first-line therapy in UC. Emerging data suggest that biologics may have the potential to prevent complications and limit disease progression. If such benefits are proven, biologics may be used in the future to modulate subclinical inflammation and to prevent the development of clinical disease.

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Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) confined to the large intestine and has an incidence rate of 2-7 per 100,000 in the United States. However, the incidence and prevalence rate of IBD in Iran is not clear (1,2). This disease has common complex and multifactorial pathogenesis. It is currently accepted that genetic, environmental and immunological factors contribute to development of IBD. The treatment goals for IBDs especially UC are to induce and maintain remission of symptoms and mucosal inflammation. Therapy for mild to moderate disease comprises oral and topical mesalamine and topical corticosteroids; therapy for moderate to severe disease is composed of systemic corticosteroids and immunosuppressives (azathioprine, 6-Mercaptopurine), reserving biologics for patients who have failed these agents (3,4).

The principles of treatment include:

i. Maximizing the use of medications with a more favorable side effect profile (mesalamine and topical corticosteroids)
ii. Minimizing the use of medications with a less favorable side effect profile by limiting the duration of treatment (corticosteroids)
iii. Acceptance of surgical resection as a highly effective and curative treatment with low morbidity
iv. Reservation of immunosuppressive and biologic medications for patients who fail other treatments (5).

In best circumstances, 66% of patients will achieve clinical remission with medical therapy, and 80% of the treated ones maintain remission. Up to 15% of UC patients will have severe colitis and are less likely to respond to first-line conventional therapy. About 30-40% will not respond to corticosteroid therapy and will need urgent colectomy (6). Iranian gastroenterologists frequently encounter patients who do not respond to conventional treatments as expected and suffer from the

Corresponding Author: Sahar Taba Taba Vakili
Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 21 88098176, 912 1342888, Fax: +98 21 88799840, E-mail: saharvakili63@gmail.com

disabling course of the disease and drug complications (1). Here, we present a thoroughly updated review of the available and best treatments in the literature for UC.

Immunomodulators

Asathioprine (AZA) and 6-mercaptopurine (6-MP)

Approximately 10-20% of UC patients become steroid-dependent usually one year after initial response to steroids (7). The thiopurine derivates, azathioprine and its metabolite 6- mercaptopurine have been proven to be effective in steroid–dependent or steroid–refractory UC patients. These drugs are usually used as steroid sparing agents for long–term management of UC. (8) Other indications of thiopurines for UC patients include:

- Patients with severe relapses
- Patients who need ≥2 courses of steroid within a 12 months period
- Patients with relapses when the dose of steroid is < 15 mg
- Patients with relapses <3 months of discontinuing steroids (9).

Data supporting the use of AZA/6-MP in UC patients are limited (10). Ardizzone *et al*. randomized 72 steroid–dependent UC patients to 5-ASA or AZA groups. Tapering doses of steroid were allowed to be continued. This study demonstrated that significantly more patients in the AZA group compared with 5-ASA group achieved clinical remission and discontinued steroid therapy, both in the intent- to-treat (AZA vs 5-ASA: 53% vs 21%) and per-protocol (58% vs 21%) analysis (11).

There are several non-controlled studies assessing the efficacy of AZA/6-MP in UC patients. The mean efficacy of AZA / 6-MP in UC patients was 65% (95% CI, 62-67%) from the non-controlled studies. AZA was more effective in the cases than 6-MP. (66% vs 61%) The mean efficacy rate of AZA/6-MP in steroid – resistant patients was 66% (95% CI, 59-73%), while this rate was 71% (95% CI, 66-77%) in steroid – dependent patients (the difference was not significant statistically). The efficacy rate of AZA/6-MP for the induction of remission of UC was less than the efficacy rate of the drug for the maintenance of remission (65% vs 76%; *P*=0.03). Comparing AZA with placebo or 5-aminosalicylate for the induction of remission in UC patients did not show statistically significant benefit of AZA over placebo (OR= 1.59, 95% CI, 0.59-4.29)(12). Generally, thiopurines should not be used for induction of remission in active UC patients. (13) Comparing AZA/6-MP with placebo or 5- ASA for the maintenance of remission in UC, demonstrated a benefit of AZA (OR=2.56; 95% CI, 1.51-4.34) with statistically significant results (12).

A recent systematic review compared AZA with placebo for maintenance of remission in quiescent UC and demonstrated a significant decrease in the relapse rate in the AZA group compared with placebo, with an NNT of 4 (14).

In a recent study, AZA was found to be similarly effective for both UC and Crohn's disease (CD) patients. (49% for CD and 42% for UC patients) (15) Generally, it seems that AZA is at least as effective in UC as in CD patients. The recommended dose of azathioprine is 1.5-2.5 mg/kg/day and of 6-MP is 1-1.5 mg/kg/day (16). Some potential side effects of AZA/6-MP are bone marrow suppression, impairment of liver function tests, pancreatitis, fever, skin rash, opportunistic infections and lymphoma. Bone marrow suppression (commonly leuckopenia) and liver function test alteration correlate with the level of 6-thioguanine (6-TG) and 6-methylmercaptopurine (6-MMP), respectively. These metabolites are produced by thiopurine s-methyltransferase (TPMT) enzyme (17).

About 0.3% of the general population has low or absent TPMT enzyme activity and should not take AZA/6-MP. However, 11% of the general population have intermediate enzyme activity and can receive a low dose of AZA/6-MP. Bone marrow suppression due to an increased 6-TG level obligate to reduce AZA/6-MP dose (17).

6-TG and 6-MMP level measurement cannot replace complete blood count (CBC) and liver function test to assess the side effects of AZA/6-MP. These laboratory assessment should be done weekly or biweekly during the first month of therapy (17). Recently, multidrug resistance protein 4 (MRP 4) polymorphism has been detected to be responsible for AZA/6-MP induced leukopenia, particularly in Japanese patients (18). In a study upon 130 IBD patients taken AZA/6-MP, the WBC count was significantly lower in patients with the MRP 4 variant alone (n=26) compared with patients with a wild allelotype (n=74) (*P*=0.014) (16). The risk of lymphoma is also increased in IBD patients who are taken AZA/6-MP, particularly in serologic Ebstein Bar Virus (EBV) positive patients (19).

Calcineurin inhibitors

Cyclosporine A (CsA)

Cyclosporine is a fungal cacineurin inhibitor which was isolated from a fungus (*Tolypocladium inflatum*) and can prevent the transcription of mRNA encoding

interleukine-2, thus CsA interferes with mucosal inflammation (20). Approximately 25% of fulminant UC patients are steroid-refractory which is defined as the loss of response to five-to-seven days treatment with IV steroid (21). Several uncontrolled (22,23) and controlled trials (24) have shown the efficacy of CsA as a short-term " rescue therapy" in steroid-refractory UC patients.

A randomized controlled trial established that there was more responders among patients who received IV cyclosporine compared with those received IV steroid (25). As a summary, intravenous cyclosporine (4mg/kg) is an effective treatment to prevent emergency surgeries in patients with fulminant UC (26). To reduce the adverse effects of CsA, the initial dose should be minimal. A recent study showed that prescription of 2 mg/kg/day of CsA is sufficient to induce remission in fulminant UC patients. This study also indicated that blood levels of CsA between 150-250 ng/ml is enough to induce remission (27). Despite the proven short-term efficacy of CsA at inducing remission in acute severe UC, the long-term efficacy of CsA remains unset. (28) Thus, as a maintenance therapy, CsA is used as a bridge to AZA/ 6-MP. (29) In patients with steroid-refractory fulminant UC, the CsA initiated concurrently with AZA/ 6-MP; then steroids can be tapered rapidly and CsA discontinued, at which time the AZA/6-MP can be used as maintenance therapy (21). In fact, the remission rate was increased by using AZA / 6-MP following IV CsA (30).

In one additional study upon 41 UC patients, the efficacy of CsA was evaluated at short-term and midterm (2 weeks and 1 year after CsA administration, respectively) and also long-term (at the end of the observation period) time points. The short-term response rate was 71% and the midterm relapse-free survival rate was 51%. Administration of AZA after CsA therapy significantly reduced the relapse rate (72.5% vs 26.7%, P=0.0237) and also the colectomy rate at 1 year (66.7% vs 30.5%, P=0.0309). Among patients who respond to CsA, AZA naive patients had a significantly less likelihood of colectomy than those who receive AZA prior to CsA treatment (31).

Before administration of CsA, CMV infection should be assessed by CMV Ag, PCR and etc. if CMV infection is suspected, reduction of the prednisolone dose and prescription of ganciclovir are recommended. Furthermore, in patients who receive CsA and steroid concomitantly, pneumocyctitis carinii infection prophylaxis with oral trimethoprim-sulfamethoxasole or inhaled pentamidine should be considered. During infusion therapy with CsA, its plasma levels should be monitored carefully (21). According to some guidelines closely monitoring of renal function is also recommended in patients receiving CsA (32).

Potential side effects of CsA include nephrotoxicity, hypertension, seizure, opportunistic infections, peripheral neuropathy, anaphylaxis, colonic perforation, increased postoperative mortality, hirsutism and headache (33). Predisposing factors of seizure in patients who treated with CsA include hypocholestrolemia, hypomagnesemia, hypertension and high plasma level of CsA (34).

Tacrolimus (FK506)

Tacrolimus is a macrolide isolated from *Streptomyces tsukubaenesis* has similar pharmacologic mechanism to CsA, but its immunosuppressive effects are greater than those of CsA (35).

Fellerman *et al.* reported that 47% UC patients who were refractory to steroid and AZA / 6-MP responded to oral (0.1-0.2 mg/kg/day) and/or intravenous (0.01-0.02 mg/kg/day) tacrolimus (36).

The first RCT evaluating the effect of tacrolimus in UC patients was published by Ogata et al. In this trial oral tacrolimus (randomized to either 5-10 or 10-15 ng/ml trough level) was compared with placebo in 63 patients with steroid-refractory or steroid-dependent UC. After 2 weeks of administration of tacrolimus, the clinical remission rates in the high-trough, low trough and placebo groups were 68.4%, 38.1% and 10%, respectively (37).

A recently published review of controlled trials demonstrated that patients receiving tacrolimus in the high plasma concentration group were significantly more likely to achieve clinical remission than patients receiving placebo (OR=8.66, 95% CI, 1.79-42) (38). Although several studies have demonstrated the short-term efficacy of tacrolimus in refractory UC, but data supporting its long-term effects are scarce. A long-term study upon 40 UC patients reported that 77.5% of patients who were treated with tacrolimus avoided colectomy within a mean follow-up period of 39 months (39). A recent study reported that 62% of UC patients who were in clinical remission with tacrolimus treatment within 30 days did not require colectomy after 65 months (40). Tacrolimus therapy is associated with several side effects such as tremor, renal dysfunction, opportunistic infections, gastrointestinal discomfort and diabetes mellitus (37). Thus, monitoring of renal function and tacrolimus level should be performed at least once or twice a month (41).

Methotrexate (MTX)

Methotroxate which was initially introduced in 1948 for the treatment of leukemia, has also been used to treat

other diseases such as Wegener's granulomatosis, rheumatoid arthritis and psoriasis. The efficacy of MTX has been proven in adults with steroid-dependent Crohn's disease who are refractory or intolerant to thiopurines (42).

The first study by Kozarek *et al.* demonstrated that 5 of 7 patients with UC who were treated with MTX (25 mg/week intramuscularly) achieved successful induction of remission (43). In a prospective open labeled study, patients with steroid-dependent UC and CD were assigned to either 6-MP (1 mg/kg/day), MTX (15 mg/po/week) or 5-ASA (3 gr/day) groups. Concomitantly prednisolone (20 mg/day) were prescribed to patients in all groups. The remission rates after 30 weeks of treatment were 78.6% for 6-MP, 58.3% for MTX and 25% for 5-ASA. (P<0.05) After 106 weeks of treatment, only one of 7 patients on MTX remained in remission compared to 7 of 11 in the 6-MP group and none in the 5-ASA group (44).

One additional study evaluated the short- and long-term efficacy of MTX therapy (12.5 mg i.m/week) in ten steroid-dependent UC patients who were intolerant or resistant to thiopurine therapy. Clinical remission was achieved in 100% of patients after 6 months of therapy, 6/10 of patients had complete endoscopic and histological remission. After a follow up period of 2 years, all patients in clinical remission remained without change and 2/4 patients with incomplete remission had relapsed (45). There are several retrospective studies which assess the efficacy of MTX therapy in UC patients. Washed et al reported a clinical response rate of 68% in UC patients who were treated with MTX. Furthermore, MTX had a steroid- sparing effect in these patients (46).

The results of retrospective studies on MTX therapy in UC patients are heterogenous and based on these evidences, MTX is not recommended for inducing and maintaining remission in UC (13).

The most common side effects of MTX include nausea, anorexia, stomatitis, diarrhea, hepatotoxicity, bone marrow suppression and hypersensitivity pneumonitis and opportunistic infections (47). MTX is contraindicated during pregnancy. Impairment of liver function tests is frequently observed in patients who receive MTX, but cirrhosis or liver fibrosis is a rare complication of MTX therapy. Predisposing factors for MTX hepatotoxicity include alcohol consumption, obesity, diabetes mellitus and viral hepatitis (48).

Mycophenolate mofetil (MMF)

Mycophenolate mofetil, an ester prodrug of mycophenolic acid, has been proven to be efficacious in allograft transplant recipients and in patients with disease such as psoriasis and lupus nephritis (49).

MMF administration in patients with IBD is indicated in those who are steroid-dependent, refractory or in intolerant of more traditional therapies (50). There is not any randomized, placebo-controlled trial of MMF in IBD patients.

In a large cohort study, 70 refractory IBD patients (51 had CD and 19 had UC) treated with MMF and steroid-free remission rate of 24.3% was reported. The efficacy of MMF in ulcerative colitis (32% achieving remission) was better than this treatment for Crohn's disease (22% achieving remission) (51) These results were similar to remission rate of 38% reported by Orth *et al.* in another cohort study (52).

In another prospective study, the short and long-term efficacy of MMF in steroid-dependent or steroid-refractory and AZA / 6-MP intolerant IBD patients (total of 14 patients; 9 had CD and 5 had UC) was evaluated. The patients were followed for more than a year. Two-thirds of the patients had failed anti-TNF therapy, suggesting a more difficult to treat population of patients compared to other studies. After 8 weeks of therapy, the response rate of 71% was achieved. After 12 months of therapy, 57.1% of all patients remained in remission (53).

According to those limited evidences, MMF can be efficacious and well tolerated in refractory IBD patients who are intolerant to AZA/6-MP, but larger, randomized, double-blind studies to further define the role of MMF in IBD treatment are needed.

Some potential side effects of MMF which are observed in approximately 20-30% of IBD patients in cohort studies, include nonspecific malaise, mood disorders such as depression, arthralgia, skin rash, pancreatitis, diarrhea, alteration of liver function tests and alopecia (51).

Biologic therapies

Biological therapies were introduced into the United States, and subsequently the world market, for the treatment of CD in 1998 and eventually for the treatment of UC. These therapies have been incorporated into the recent guidelines for therapy of UC by the American College of Gastroenterology (ACG) (11). Biologics, produced by biotechnology, are type of treatment aimed at various stages of the inflammatory process. Basic directions of biological therapy involve neutralization of proinflammatory cytokines, use of anti-inflammatory cytokines and inhibition of neutrophil adhesion (54).

Initially, biologics targeting tumor necrosis factor- α (TNF α) were approved for patients with persisting signs

and symptoms of disease refractory to conventional agents, and they have proved to have a dramatic impact in achieving new therapeutic goals. Novel biological therapies targeting different specific immunological pathways continue to be developed and introduced for a variety of clinical scenarios in IBD (55).

Biological agents licensed for IBD treatment

Infliximab

In 2006, FDA approved infliximab for induction and maintenance therapy in patients who have moderately to severely active UC with an inadequate response to conventional agents. Infliximab (Remicade, Centocor, Malvern, Philadelphia, PA), is a 149,100-d chimeric, mouse–human, IgG1 monoclonal anti-TNFa antibody which consists of human constant and murine variable regions.(1, 5) Infliximab is used for induction of response in adults and children who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators. Besides it can induce emission in outpatients with moderately to severely active disease. Its role in acute severe (fulminant) UC is not yet proven, but it has shown some promising effects in alleviating extra intestinal manifestations of UC such as Spondyloarthropathy and Pyoderma gangrenosum (1,56).

The drug is administered in 5 mg/kg doses by 2‑hour intravenous infusion. Induction therapy in 3 doses is recommended, following the algorithm of week 0, 2 and 6 and for sustaining the remission in a dose repeated every 8 weeks. Maintenance treatment is recommended every 8 weeks when response to induction therapy is observed.(57) Available evidence does not justify further infliximab therapy in patients who have failed to respond to induction therapy. Patients who have attenuated response may be given higher dose infusions up to 10 mg/kg at 8-week intervals, or 5 mg/kg at shortened intervals as frequently as every 4 weeks (56).

The ACT-1 (Active Ulcerative Colitis Trial) study was a randomized placebo-controlled trial that showed the efficacy of infliximab to induce response and remission among outpatients with UC (56). Significantly greater numbers of patients receiving infliximab than placebo achieved clinical response or remission. Among those treated with infliximab 5 mg/kg, 69% achieved clinical response and 39% achieved clinical remission by week 8. Of those receiving 10 mg/kg, 62% achieved clinical response at week 8 and 32% achieved clinical remission at week 8. In contrast, only 37% and 15% of patients randomized to placebo achieved a response or remission during the same period. Clinical responses and remissions were generally maintained through week 30 and, in the ACT-1 study, through 54 weeks. Of patients who received infliximab 5 mg/kg, 52% maintained response and 34% maintained remission at week 30, rates were significantly higher than those among placebo-treated patients (58). Infliximab treatment also correlated with significant differences in the proportion of patients who experienced mucosal healing, defined as an endoscopic sub score of 0 or 1, at weeks 8, 30, and 54.

The ACT-2 study, which was of identical design but also included out patients refractory to aminosalicylate therapy and continued for only 30 weeks, showed similar results. Infliximab (5 mg/kg) treatment resulted in 47% response, 26% remission, and 46% mucosal healing at week 30 (56).

Infliximab can facilitate corticosteroid withdrawal in UC. In the ACT-1 trial, 24% of patients taking 5 mg/kg successfully discontinued corticosteroids at week 30, a rate more than twice that of those taking placebo (58). Similar results were seen in the ACT-2 study, where among those treated with infliximab 5 mg/kg, the corticosteroid discontinuation rate was 18%, compared with a rate of only 3% among those not receiving active drug (56).

In the retrospective study of Lees et al on 39 patients with acute severe UC, response (need to colectomy in 90 days follow up) was 66% (6). Su *et al.* in a retrospective review reported a 44% achieved remission in a median of 4 days and 22% had a partial response, from a total of 27 active UC patients who received infliximab. There were relapses and 95% of these relapses were successfully treated with repeated infusions. Steroid refractory patients were less likely to respond to infliximab therapy. They have reported a death attributable to the drug (59). In Gornet et al published a series of 30 patients, a 75% response rate (defined as a decrease of the clinical signs and no need for additional medical treatment or surgery) was found at the 7thday which lessened to 50% after a month. Long-term results were less favorable, with frequent relapses, and about one third of the patients required a colectomy (60). Chey *et al.* in a case series study on 16 refractory UC patients have shown 88% dramatic clinical, endoscopic, and histological responses after the first dose of infliximab. This study showed the steroid-sparing effect of the drug too (61,62). Kaser et al in their open label study on 6 severe steroid-refractory UC cases have shown 100% response to infliximab in short-term (7 days) (63). In another study which was done by Actis *et al.* on 8 steroid-refractory UC patients 50% response

rate is reported. They had used single initial dose of 5 mg/kg for body weight (64). Kohn et al in a series study on 13 severe refractory UC patients have reported 77% response after 2 days. Their prescription was single dose infusion of 5 mg/kg for body weight of infliximab (65). A randomized controlled trial that was done by Ochsenkuhn *et al.* on 13 acute moderate or severe UC patients showed good and similar results at weeks 3 and 13 in both infliximab and prednisolone groups (5/6 and 6/7 successful therapies in each group, respectively) (66).

Certolizumab (CDP-870)

Insufficient data currently support the use of certolizumab pegol, CDP-870, a humanized anti-TNF monoclonal antibody fragment (1), in the treatment of UC. Treatment with a subcutaneous injection of 400 mg at weeks 0, 2, and 4 is followed by maintenance therapy every 4 weeks. However there are not meta-analysis studies on UC patients (56).

Adalimumab

Its use for IBD is undergoing evaluation in clinical trials (1). Adalimumab is a fully human immunoglobulin G1 and a recombinant human monoclonal antibody obtained by expression in Chinese hamster ovary cells (54). The drug is administered in induction therapy in a dose of 80 mg by subcutaneous injection and then 40 mg in week 2. If a quick response to treatment is required, higher doses could be administered, i.e. 160 mg a week (a dose could be administered as 4 injections during 24 hr or 2 injections daily during 2 subsequent days), and then 80 mg in week 2. In order to sustain the remission, 40 mg is administered every second week. Clinical trials showed that in patients who did not respond to treatment within 4 weeks, continuation of maintenance treatment up to week 12 inclusive may be beneficial. In patients who do not respond to treatment within that time, continuation of such treatment should be reconsidered (54).

Until recently, only small open-label trials and case reports had suggested that adalimumab could also be effective for inducing clinical response and/or remission (56).

Natalizumab

Recently, natalizumab, a humanized IgG4 monoclonal antibody that antagonizes integrin heterodimers containing α 4-integrin, has been evaluated in one open study, in 10 patients with active ulcerative colitis (1). It is well tolerated, but is associated with an increased risk for infections, acute hypersensitivity reactions, and hepatotoxicity. The primary concern regarding natalizumab therapy has been the reactivation of latent human JC polyomavirus that can lead to a fatal central nervous system infection and progressive multifocal leukoencephalopathy. Therefore, natalizumab use has been restricted to monotherapy, nevertheless, natalizumab remains a viable option for patients who have lost a mechanistic response to anti-TNF-a agents (55).

Visilizumab

Visilizumab, a humanized anti-CD3 monoclonal antibody that binds the Cd3*e* chain of the T-cell receptor expressed on activated T cells, has been recently evaluated in a phase I study in 26 patients with severe steroid-resistant UC. Patients received two IV infusions of either 10 or 15 mg/kg of the studied drug on two consecutive days. 20 patients the trial reported mild-to moderate cytokine-release symptoms occurring in 60% of patients and included nausea, chills and arthralgia. Symptoms were transient, dose-related, occurred predominantly after the first infusion and resolved within 2 hr post-infusion (1).

Golimumab (CNTO 148)

It is a human monoclonal anti‑TNF‑α antibody. Golimumab was found well tolerated and effective in patients who sub-optimaly responded to methotrexate monotherap. Centocor phase III clinical trials using golimumab every 4 weeks in subcutaneous doses of 50 mg, 100 mg and 200 mg in patients with moderate and severe exacerbation of UC are currently underway (54).

Other biologics

Currently, insufficient data exist to recommend the following agents for clinical use in IBD: monoclonal antibodies to interleukin-12 (ABT-874, CNTO 1275), monoclonal antibodies to interferon gamma (fontolizumab), monoclonal antibodies to interleukin-6 receptors (tocilizumab), monoclonal antibodies to 4 7 integrins (MLN-02), antibodies to interleukin-2 receptor (basiliximab, daclizumab), antisense molecules for intercellular adhesion molecule 1 (alicaforsen), CTLA-4Ig, a fully human recombinant fusion protein categorized as a co-stimulatory or second-signal blocker of T-cell activation (abatacept), granulocyte-macrophage colony-stimulating factor (sargramostim) and growth factors (54-67).

Contraindications and risk-benefit assessment

All anti-TNF therapies share similar adverse effects, including increased risk of infections from intracellular

pathogens, most notably, TB, opportunistic infectionsbacterial and fungal infections (*aspergillosis, histoplasmosis, cryptococcosis, candidosis, listeriosis, pneumocystosis*) (54), autoimmunity, infusion reactions, and other rare, potential side effects such as neurologic disorders, congestive heart failure, and cancer (56).

Most experts agree that biologic therapies offer such important clinical benefits to patients with severe IBD, that their widespread use is definitely warranted. The risk–benefit assessment was recently addressed in a model looking specifically at lymphoma formation and mortality. The authors concluded that the benefits of infliximab outweigh the risks in properly selected patients. It is clear that certain measures need to be taken into account when biologics are started. Toxicity can be significantly reduced by routine tuberculosis screening, by avoiding anti-TNF agents in patients with heart failure and chronic infections, by careful timing of combination therapy with immunosuppressives and later switching back to single-agent therapy, by exploring neurological symptoms whenever they develop and by timely discontinuation of treatment and so on. A firm recommendation is that doctors need to see and examine their patients (including regular blood checks) every 8–12 weeks (3).

Efficacy of biologic therapies at inducing remission in active UC

The systematic review identified three RCTs(58, 68) involving 771 patients that compared biological therapy with placebo in moderately active UC and infliximab was more effective than placebo and 59 % of patients achieved remission with active treatment. There were two RCTs(35, 69) evaluating 56 patients that compared biological therapy with placebo in severely active UC. Infliximab was used in both trials and follow-up was done for 3 months. There was a trend for infliximab to be superior to placebo, but this was not statistically significant (P=0.08) (13). Review of similarly designed clinical trials, however, indicates that natalizumab has similar maintenance benefits to anti-TNFs (56). There were no trials performed to examine the efficacy of bio therapies at preventing relapse in quiescent UC. Data available were not sufficient to make a recommendation for biological therapy as maintenance therapy for UC and more studies are required (13).

Indications and goals of biologic therapy in UC

The present treatment goals include rapid induction of clinical remission, steroid-free maintenance of clinical remission, mucosal healing in luminal disease, avoidance of hospitalizations and surgeries, and improvement of quality of life in UC patients. The ultimate goal of therapy will be the ability to prevent long-term complications of progressive disease such as neoplasia, extra intestinal symptoms, or the need for surgery (55).

Continuing vs. stopping biologic therapy

Patients with UC refractory to conventional therapy which has responded to infliximab should best be considered for continuing therapy, since scheduled re-treatment is effective for maintaining response and reducing the risk of colectomy. In a recent adalimumab (ADA) study on moderate-severe UC patients, clinical remission at week 8 was attained in 18.5% of patients following induction with 160 mg ADA at week 0, 80 mg ADA at week 2, and 40 mg every other week thereafter (P=0.031) vs. 10% following induction with ADA 80 mg/40 mg and 9 % with placebo (not significant (NS)) Long-term results of this trial are awaited (70).

In patients with UC who have responded to a year of anti-TNF therapy, the benefits of continuing therapy should be weighed against the risks of discontinuation. As a rule, most patients who start biological therapy should continue treatment for the foreseeable future. Local policy, patient preference, or reimbursement may dictate stopping. Unfortunately, there are still insufficient data to make recommendations on when to stop anti-TNF therapy. Preliminary evidence suggests that for patients in clinical remission for >1 year, with a normal CRP and mucosal healing, an appreciable proportion will remain in remission during the year after stopping treatment. Randomized controlled data are required to confirm these observations. Potential consequences of discontinuation (relapse, lower response to re-induction, and risk of infusion reactions) should be discussed with individual patients (70).

Biologics and new goals of therapy

Currently, data do not exist to administer biologics as first-line therapy in UC. The numbers and roles of biologics in IBD are likely to continue expanding. Emerging data suggest that biologics may have the potential to prevent complications and limit disease progression. If such benefits are proven, biologics may be used in the future to modulate subclinical inflammation and to prevent the development of clinical disease. Ongoing research may identify roles for biologic therapies in a broad range of clinical scenarios.

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