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Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Ulcerative Colitis

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Abstract

Ulcerative colitis is a chronic inflammatory condition of the colon marked by rectal bleeding and diarrhea. In addition to its negative effects on quality of life, ulcerative colitis also increases the risk of colorectal cancer. Over a 30-year period, the cumulative risk of colorectal cancer is 18% in patients with ulcerative colitis, compared with less than 5% in the general population. The goal of therapy in patients with ulcerative colitis is to induce and maintain remission, and ultimately, to attain colonic mucosal healing in order to decrease the risk of future complications. 5-aminosalicylic acid (5-ASA) remains standard therapy for patients with mild-to-moderate ulcerative colitis and is often effective. Data on the efficacy of the thiopurine analogs azathioprine (AZA)/6-mercaptopurine (6-MP) for inducing or maintaining remission have been less consistent, although some studies have shown that AZA can maintain remission in patients who have previously responded to AZA. Corticosteroids can induce remission in patients with ulcerative colitis, but they do not maintain remission and their long-term use is prohibited by adverse effects of prolonged exposure. Currently, the only biologic agent approved for use in patients with ulcerative colitis is infliximab, a chimeric monoclonal antibody targeted against the inflammatory cytokine tumor necrosis factor-alpha (TNFα). Infliximab has demonstrated efficacy in the induction and maintenance of clinical response, remission, and mucosal healing in patients with ulcerative colitis not responding to conventional therapy. Recent and ongoing studies are investigating how to best use infliximab in patients with ulcerative colitis, and continue to evaluate its long-term efficacy and safety. Other studies are currently underway to examine the efficacy of additional biologic options for these patients.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with moderate-to-severe ulcerative colitis.

Statement of Need/Program Overview: The place of biologic therapies in the overall therapeutic armamentarium for ulcerative colitis must be understood, in terms of sustaining treatment benefit and minimizing risk associated with combination therapies that include steroids or immunomodulators. Recent evidence regarding the use of biologic monotherapies versus combinations and top-down versus step-up strategies should be further explored and incorporated into current treatment paradigms. Until these issues have been definitively addressed, physicians need to have up-to-date information on the nuances of current controversies in order to make well-considered recommendations for ongoing treatment.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the natural course of moderate-to-severe ulcerative colitis.
2. Cite current data on the use and limitations of 5-ASA agents and steroids in treating these patients.
3. Review the curative use of surgery including potential complications and its effects on patient QOL.
4. Describe the role of biologic therapy in these patients and its potential effect on disease course and surgical outcomes.

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Selecting Ulcerative Colitis Patients as Candidates for Biologic Therapy

Stephen B. Hanauer, MD

The proper selection of therapy is essential for maximizing efficacy and optimizing outcomes in the management of ulcerative colitis. Clinicians must evaluate patients carefully and consider all of the options when deciding whether biologic therapy is appropriate for individual patients. Factors to be considered include the patient's disease characteristics, treatment history, and treatment safety issues.

Defining Disease Severity in Ulcerative Colitis

Infliximab currently is the only biologic therapy with FDA approval for the treatment of ulcerative colitis and is indicated for patients with moderate-to-severe disease,[1] who are failing conventional therapies. Thus, a primary consideration in when to begin biologic treatment is whether the patient has moderate-to-severe disease. Clinicians must therefore have practical definitions for disease severity that can be applied in the clinical setting.

For patients with ulcerative colitis, disease severity can be defined based on the severity of symptoms themselves or on the persistence of symptoms refractory to active therapy.[2] With regard to symptom severity, moderate-to-severe disease is defined as having 6 or more bowel movements per day associated with rectal urgency, abdominal cramping, or nocturnal bowel movements with or without extraintestinal manifestations of colitis that interrupt the patient's day and interfere with usual life activities. This definition is rather broad, in order to account for the differences in symptoms among individual patients.

The second definition of moderate-to-severe disease relates to treatment history. The ongoing presence of symptoms despite optimal therapy with conventional agents, including 5-ASAs or a short course of corticosteroids, or dose-optimized therapy with an immunosuppressive, is indicative of refractory, and therefore moderately active, disease.[3]

Finally, the outcomes after induction and maintenance therapies should both be considered. Some patients are considered to have moderate-to-severe disease because they initially present with moderate-to-severe symptoms and fail to improve with conventional therapy. Other patients initially respond to conventional agents but fail maintenance therapy. Clinical assessments of patients with ulcerative colitis should also include an evaluation of the extent of disease (proctitis, left-sided colitis, or pancolitis), as this will help define the proper conventional therapeutic options.[2] Finally, mimics of active colitis such as concomitant *C. difficile* infection, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), or irritable bowel symptoms in the absence of active mucosal inflammation need to be ruled out.

Defining Treatment Failure in Patients with Ulcerative Colitis

The initial treatment approach for patients with mild-to-moderate symptoms of ulcerative colitis is a 5-ASA administered at 2–3 g daily, which is effective in the majority of patients.[2] Higher doses (up to 4.8 g daily) may be necessary in patients with more refractory disease, including those failing an initial course of 6–8 weeks of an oral 5-ASA, and those who have previously required rectal therapy or steroid therapy.[4]

The duration of therapy with higher-dose 5-ASA depends on the severity of the patient's symptoms. Generally, if a patient with mild symptoms of ulcerative colitis is not responding to a 5-ASA, I would increase the dose during that initial 6–8-week period. If this patient still does not respond, I would consider them a candidate for steroid therapy or a biologic, based on the failure of first-line therapies. However, the more severe the symptoms, the less time available for low-level therapies to take effect. For a patient with moderate symptoms of ulcerative colitis, I would not wait 6 weeks for a response and would instead step up therapy to steroids or a biologic sooner.[5,6]

For patients with distal ulcerative colitis—either ulcerative proctitis or left-sided colitis—topical treatment with 5-ASA suppositories or enemas is often the most effective therapy, regardless of whether patients are taking an oral 5-ASA or have required corticosteroids.

Patients can be considered failing to respond to 5-ASAs if they have extensive disease and do not respond to up to 4.8 g orally with or without rectal therapy, or if they have left-sided or distal ulcerative colitis and do not respond to

either oral mesalamine up to 4.8 g orally, with the addition of topical therapy with suppositories for patients with proctitis or enemas for patients with left-sided colitis. Patients who fail to attain disease remission with 5-ASAs or who fail maintenance therapy with the described regimens are considered 5-ASA failures.

The success of corticosteroid therapy during induction therapy should also be considered. Patients with moderate to severe symptoms who fail to respond to a 4-week course of oral corticosteroids up to 40–60 mg daily are considered to be failing induction therapy with corticosteroids.[7] A second definition of steroid failure would be the inability to taper off of steroids despite optimal dosing of 5-ASA and the addition of an immunomodulatory agent such as azathioprine or 6-MP.

Thiopurine treatment must also be optimized before conventional treatments are considered to have failed. Patients can be considered to have failed a thiopurine treatment if they do not attain responses after 3 months of azathioprine 2.5 mg/kg or 6-MP 1.5 mg/kg.[8,9] An inability to taper off steroids within 3-6 months of thiopurine initiation would also be considered a treatment failure.

A second method of optimizing a thiopurine relies on metabolite monitoring. Patients are considered thiopurine failures if they cannot withdraw from corticosteroids despite a white blood cell count of 3.5–5 or if they do not attain responses despite having thioguanine levels in the therapeutic range of 230–400 units/mL.[10] Patients are also considered to have failed thiopurine therapy if they develop unacceptable toxicities, including intolerance or allergic adverse events such as pancreatitis, nausea, vomiting, or fever. Finally, for any therapy, clinicians should ensure that patients have been adherent to their treatment regimen before considering the treatment a failure.

Patients meeting any of these criteria for treatment failure, who are unable to taper off steroids, are considered to have moderate-to-severe disease and are candidates for biologic therapy. In some cases, biologic therapy may be indicated before corticosteroids have been initiated. For example, some patients may not be suitable for corticosteroid therapy due to contraindications including osteoporosis, diabetes, uncontrolled high blood pressure, or because of anticipated side effects.[11]

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Optimizing Outcomes for Moderate-to-Severe Ulcerative Colitis Patients

Remo Panaccione, MD

Surgical Outcomes

The surgical treatment of ulcerative colitis has evolved considerably over the last 25 years, and the introduction of proctocolectomy with ileal pouch-anal anastomosis (IPAA) has been one of the biggest advances in the treatment of ulcerative colitis. For patients with moderate-to-severe disease, surgery can be associated with quality-of-life improvements.[1] However, there are limitations associated with the procedure, which should be considered before choosing this strategy.

Short-Term Complications of Surgery

Short-term complications associated with surgery include small bowel obstruction and leaks around the anastomotic site as well as fluid/electrolyte issues, which develop in 20–30% of patients. The risk of surgical complications can vary based on the experience level of the institution where the procedure is performed, with postsurgical mortality rates 62% lower at high-volume versus low-volume centers.[2] Thus, patients and physicians choosing surgery should ensure that the procedure is performed at a high-volume center.

Long-Term Complications of Surgery

Surgery is associated with significant functional outcomes that clinicians should discuss with their patients. A recent meta-analysis showed that surgery can reduce a woman's fecundity by anywhere from 26% to 51%.[3] Patients may require interventions, including in vitro fertilization, in order to become pregnant. Women of childbearing potential must understand this risk.

Another potential risk is pouchitis, which develops in about half of patients (more frequently in patients with primary sclerosing cholangitis [PSC]).[4] Pouchitis requires ongoing medical therapy with intermittent antibiotics, with 5–10% of patients requiring chronic antibiotic therapy. Stool seepage or leakage is another possible functional outcome, with 10–15% of patients experiencing symptoms during the day and 15–20% having symptoms at night. Even if the pouch is functioning well, patients can have 6–8 bowel movements per day. Clearly, surgery is not a curative treatment for ulcerative colitis and can have a significant impact on quality of life.

Role of Newer Therapies in Avoiding Surgery

The use of biologic therapy in ulcerative colitis can reduce the long-term need for surgery and, in turn, potentially improve quality of life. In the ACT 1 and ACT 2 trials, infliximab treatment of an outpatient population with moderate-to-severe disease decreased surgery rates. Thus, it is important for clinicians to identify patients who are candidates for biologic therapy and initiate treatment in a timely fashion, to avoid having to consider surgery as a competing strategy.

Minimizing Risk of Colorectal Cancer

The chronic inflammation of ulcerative colitis is associated with the development of dysplasia and colorectal cancer (CRC).[5] In patients with ulcerative colitis, factors that affect the degree of inflammation include the duration and extent of disease, comorbidity with PSC, and family history of CRC. A growing number of studies show that the presence of mucosal lesions, ongoing mucosal damage, and histological inflammation increase the risk over time of developing dysplasia and CRC.[6] However, effective treatment of ulcerative colitis has been shown to reduce inflammation. In the ACT 1 and 2 studies, infliximab therapy in patients with moderate to severe ulcerative colitis was associated with a significant improvement in mucosal healing at Weeks 8 and 30 and at Week 54 (in ACT 1).[7] An open-label series also showed histological improvement with infliximab.[8] Thus, our treatment strategy in patients with ulcerative colitis should focus not only on symptom management but also on the end-organ, to try to achieve mucosal healing and possibly histologic healing in these patients.

There is a potential concern that in patients with IBD, treatments that reduce the need for surgery, and thus keep the colon intact for a longer period of time, could have the unintentional consequence of increasing the risk of developing dysplasia and CRC. However, if we do our best to

control inflammation and mucosal damage, we may offset that risk.

Chemopreventive Strategies

Several strategies have been evaluated for preventing the development of dysplasia and CRC. Although data are conflicting regarding the use of 5-ASAs for chemoprevention, there is overall support for the use of moderate doses for chemoprevention.[9] Because of the large therapeutic window for 5-ASAs, even a patient receiving maintenance therapy with a biologic or immunosuppressant may gain additional chemopreventive effects with a 5-ASA.

Folic acid supplementation has also demonstrated a nonsignificant but numerical chemopreventive effect in patients with ulcerative colitis.[10] Moreover, in patients with PSC, data from the Mayo Clinic suggesting that ursodeoxycholic acid may prevent the development of dysplasia due to its ability to bind bile acids.[11]

Adherence is an important issue for patients undergoing maintenance treatment for ulcerative colitis. To try to motivate patients to take their 5-ASAs, I first ensure that the regimen is simple to take. As chemoprevention regimens do not require full doses of 5-ASAs, once-daily dosing with 2-3 pills per day is usually feasible with some preparations. Moreover, because 5-ASAs have a large therapeutic window, I always assure patients that the safety profile of these agents has been well established over the last half century, and taking them is most likely in their best interest.

Assessing the Risks and Benefits of Biologic Therapy for Ulcerative Colitis

After determining that a patient may be a candidate for biologic therapy, clinicians must discuss with patients the risks and benefits of the treatment and of the disease itself. Both undertreatment and overtreatment carry significant risks to patients with ulcerative colitis. For patients with a chronic, progressive, disabling disease course, failure to treat with the most aggressive therapies available may result in an unnecessarily negative clinical outcome.

The decision to use steroids in patients with ulcerative colitis should be weighed carefully, as steroid therapy has been shown to increase the chance of eventual surgical treatment. Population-based data from the Mayo Clinic suggest that about 40% of patients with ulcerative colitis who start prednisone will go to surgery within the first year, with many undergoing surgery within the first 3 months.[12] Steroid use should therefore be a tipping point after which clinicians should start thinking about alternative therapeutic strategies.

In discussing whether to initiate biologic therapy, clinicians should review with patients the risks associated with this type of treatment, including general infections, opportunistic infections, lymphoma, and solid organ malignancies. Anti-TNF therapy is associated with an increased risk of minor infections, including infections in the upper respiratory tract and urinary tract, which are generally manageable and do not lead to significant morbidity or mortality.[13] More serious infections have also been reported, including fungal dermatitis, reactivation of tuberculosis, pneumonia, and opportunistic infections, although the absolute risk of such events is extremely low, at approximately 1–2 per 10,000–15,000 patients treated.[14]

Immunosuppressive treatment is associated with a slightly increased risk of developing lymphoma, from a background risk of 1–2 per 10,000 individuals in the general population to 3–4 per 10,000 in patients receiving azathioprine and 4–6 per 10,000 in patients with Crohn's disease receiving anti-TNF therapy.[11] However, these absolute risks are small and should be viewed in the context of other risks in daily life. For example, the risk of developing a serious infection or lymphoma does not begin to approach the risk of dying in a motor vehicle accident, which is reportedly about 1 in 80 over a lifetime.

In deciding to initiate biologic therapy, clinicians and patients should consider not only the natural history of the disease but also the competing treatment, which in the case of disease refractory to standard therapy means doing nothing and allowing active disease to persist, which will certainly affect the patient's morbidity and quality of life. According to recent data from administrative databases, the mortality risk increases by 4-fold in patients with more than 2 comorbidities and in those over 60 years of age.

Patient Education and Pretreatment Screening

Clinicians should discuss up-front with patients the association between ulcerative colitis and the risk of developing dysplasia and CRC. It can be challenging, especially at diagnosis, to tell a patient that they have a chronic disease that may lead to the development of pre-cancerous dysplasia or cancer in a small percentage of patients. However, this important information should be discussed and provided for patients in writing, for several reasons: first, to ensure that the patient and family are aware of the risk; and second, because many patients who achieve remission and are receiving lower levels of therapy do not return to their gastroenterologist for regular visits. If patients understand the risks associated with this chronic disease, which are in some ways independent of disease activity, they may be more likely to return for the proper initial screening and surveillance biopsies.

Before initiating biologic therapy in patients with ulcerative colitis, clinicians can take steps to optimize the risk/benefit ratio of therapy. The medical history is an obvious first step. If patients have a history of infection, includ-

ing sinusitis, or mucocutaneous candidiasis, strategies can be taken to minimize the infection risk when starting a biologic. Patients should also be evaluated for history of heart failure or heart disease because of reports of an increased risk of heart failure in association with biologics. Biologic therapy is also contraindicated in patients with a history of optic neuritis or other demyelinating disease.

Because of the association between biologic treatment and tuberculosis (TB) reactivation, all patients should receive a PPD test or QuantiFERON® test. However, the sensitivity of the PPD test can vary if patients are on steroids or immunosuppressants. Therefore, patients should also undergo chest radiography if they are in a high-endemic area or have a relative exposed to TB. Patients previously exposed to TB who have not been treated should start treatment. For patients with active TB, the anti-TB treatment can be initiated along with infliximab.

Reactivation of hepatitis B virus has also been reported with biologic therapy, and has on rare occasions led to fulminant hepatic failure. Patients should therefore also undergo hepatitis B testing before starting therapy.

Immunizations should also be reviewed in patients with ulcerative colitis. Because live attenuated vaccines should not be used in patients receiving biologics, all vaccinations should be brought up to date before biologics are needed. Clinicians should inquire about any intended travel to areas in which a live vaccine would be needed, such as Africa or South America. The annual influenza vaccine should also be administered before starting therapy.

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Applying Clinical Trial Data to Biologic Treatment of Ulcerative Colitis

Gary R. Lichtenstein, MD

Two large, randomized, controlled trials have evaluated infliximab in patients with ulcerative colitis. The double-blind, placebo-controlled ACT 1 and 2 trials each compared the efficacy and safety of infliximab 5 mg/kg and 10 mg/kg infusions versus placebo for induction and maintenance therapy in 364 adults with moderate-to-severe active ulcerative colitis refractory to standard therapy.[1] Intravenous infliximab or placebo was administered at Weeks 0, 2, and 6 and then every 8 weeks through week 46 (ACT 1) or Week 22 (ACT 2).

In ACT 1, Week 8 clinical response rates with 5 mg/kg infliximab, 10 mg/kg, and placebo were 69%, 61%, and 37%, respectively ($P<.001$ for both comparisons vs placebo). Week 8 response rates were similar in ACT 2 (64%, 69%, and 29%, respectively [$P<.001$ for both comparisons vs placebo]). Patients receiving infliximab were also significantly more likely than those receiving placebo to attain clinical remission and mucosal healing (Figure 1) by Week 8.

With regard to toxicity, ACT 1 and ACT 2 revealed no new safety findings beyond those previously reported in patients with Crohn's disease. Adverse events included worsening of disease (generally due to inadequate efficacy in that population), abdominal pain, nausea, upper respiratory infection such as sinusitis, pain, rashes, headache, fever, anemia and fatigue. There was also evidence of infectious complications. Although these adverse events are important to consider, discontinuation rates were not affected by them and were similar among infliximab 5 mg/kg, 10 mg/kg, and placebo arms (8.3%, 9%, and 9%, respectively).

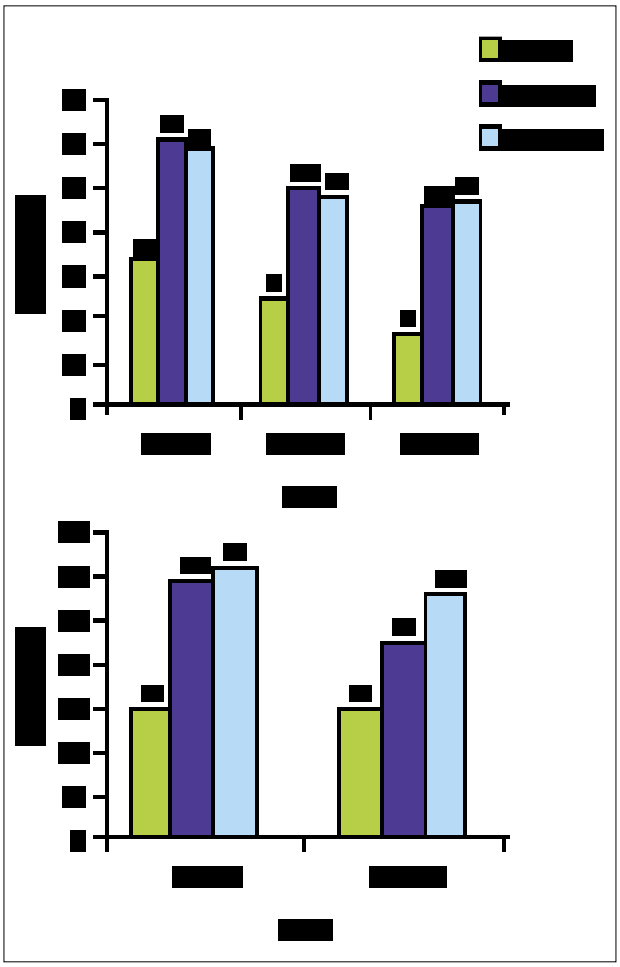


Figure 1. Mucosal healing rates for the ACT 1 and ACT 2 trials of infliximab for the induction and maintenance of ulcerative colitis remission.

* $P<.001$ vs placebo.
† $P=.009$ vs placebo.

Data from Rutgeerts et al.[1]

Clinical Implications of ACT 1 and ACT 2

In general, when evaluating data on the use of biologics for the treatment of ulcerative colitis, clinicians should keep in mind that clinical trial data do not necessarily correspond to the treatment of patients in the office. The first difference is the use of inclusion and exclusion criteria in clinical trials. These requirements should be carefully evaluated to determine whether an individual patient in the office has the same disease background as the patients in a clinical trial. For example, some trials might exclude patients with proctitis whereas others may only evaluate patients taking concurrent immunomodulators. Clinicians must also evaluate to what degree the clinical trial data can be generalized to specific populations. Trials may exclude patients over the age of 65 or pediatric patients.

With those caveats in mind, ACT 1 and ACT 2 clearly showed that in patients with moderate to severely active ulcerative colitis, infliximab is superior to placebo in terms of clinical responses at Weeks 8, 30, and 54, remission rates, and mucosal healing. These findings are significant, given that many patients had not attained responses with the other currently available medications (mesalamine, corticosteroids and immunomodulators). Between 50% and 60% of patients in ACT 1 and ACT 2 were receiving concomitant corticosteroids and 40–50% were receiving azathioprine or 6-MP. However, some patients are unable to be treated with infliximab due to adverse effects, lack of response, or prior loss of response. Thus, there is still a need for future development of other compounds to help treat this patient population. An ongoing study is evaluating the efficacy and safety of the anti-TNF agent adalimumab in patients with ulcerative colitis.

Applying Crohn's Disease Data to Ulcerative Colitis

Crohn's disease and ulcerative colitis are two different entities, and biological differences between the two may affect the treatment strategies. One difference is in the natural history of the two diseases. Over time, Crohn's disease can progress to transmural complications, strictures, and fistulae, requiring surgical treatment, whereas ulcerative colitis is not associated with this same progression. This makes Crohn's disease somewhat similar to rheumatoid arthritis, for which conventional treatments can lead to the development of structural damage to the joints. For patients with RA, early and aggressive treatment may prevent that structural damage. A similar approach of early aggressive therapy may prevent this progression in Crohn's disease. This concept would not apply in ulcerative colitis.

However, whether early aggressive intervention would prevent later complications of ulcerative colitis, such as neoplasia, is unknown. In Crohn's disease, evidence suggests that steroids help some patients heal the mucosa but in others might worsen the mucosal inflammation. In ulcerative colitis, the role of biologics versus corticosteroids requires examination of the same issue, which has not yet been addressed.

Because of these differences, data from clinical trials in Crohn's disease cannot be directly applied to patients with ulcerative colitis. However, biologic agents have been more widely studied in patients with Crohn's disease, and these clinical trials do provide valuable information that can be helpful in guiding the treatment of patients with ulcerative colitis.

TREAT Registry

The ongoing, prospective TREAT registry is evaluating the long-term safety of therapies in 6,290 patients receiving infliximab or other treatments for Crohn's disease, mostly in community-based practices.[2] Patients are not assigned a particular treatment protocol but rather are treated as is standard by the reporting physician. Patients receiving conventional therapies can rollover to infliximab or other biologics as needed. The TREAT registry has revealed that corticosteroid use is associated with a 2-fold increase in the risk of serious infections (OR, 2.21; 95% CI, 1.46–3.34; $P<.001$) and mortality (OR, 2.10; 95% CI, 1.15–3.83; $P=.016$). Compared with other therapies, neither infliximab nor immunomodulators were associated with an increased risk of infections. The registry also showed a higher rate of serious infections in patients taking narcotics (OR, 2.38; 95% CI, 1.56–3.63; $P<.001$). Perhaps the use of narcotics is itself a marker of more severe disease or disease activity. However, the nature of this effect cannot be discerned from the available data.

Overall, these findings confirm other data suggesting that corticosteroids are often the driver for severe infectious complications. Therefore, although this study should certainly be reproduced in patients with ulcerative colitis, we have no reason to believe that corticosteroids would pose less of a risk in patients with ulcerative colitis treated similarly to those with Crohn's disease.

SONIC Trial

Another important recent study of biologics in Crohn's disease is the phase IIIB SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's) trial, which randomized 508 patients to azathioprine 2.5 mg/kg, infliximab 5 mg/kg, or azathioprine plus infliximab.[3] At 30 weeks, the combination was most effective, followed by infliximab alone, followed by azathioprine alone. These data conflict with the recent shift away from continued immune modulator therapy in patients receiving infliximab after having been treated with azathioprine or 6-MP. However, patients in the SONIC trial had not previously received immune modulators. Perhaps combination treatment with infliximab plus azathioprine or 6-MP provides a synergistic or additive benefit if patients are treated early in the course of disease. Regardless, these data show that infliximab monotherapy is an effective early treatment option.

With regard to safety, the SONIC trial showed similar adverse event rates with dual therapy vs infliximab or azathioprine alone. Although we await 1-year follow up data, the findings thus far suggest that in patients with Crohn's disease, we should initiate infliximab earlier in the disease course, holding azathioprine for those patients considered to have failed infliximab. Alternatively, we could begin earlier with infliximab and azathioprine combination therapy.

The applicability of these findings to ulcerative colitis is unclear, given that ulcerative colitis and Crohn's disease

are two different entities. We do recognize that 6-MP/azathioprine have not demonstrated a clear efficacy benefit in clinical trials for ulcerative colitis. A recent meta-analysis found minimal benefit from azathioprine/6-MP in these patients. However, these agents have been used in clinical practice for many years, and some patients do benefit from them. The relative efficacy of immunosuppressive therapy versus biologic therapy in ulcerative colitis has yet to be formally determined.

COMMIT Trial

The phase III COMMIT (Combination of Maintenance Methotrexate-Infliximab Trial) is also providing important data on the role of biologic therapy in Crohn's disease.[4] In this double-blind, placebo-controlled study, Feagan and colleagues randomized 126 patients with active Crohn's disease requiring steroid therapy to infliximab plus methotrexate or infliximab plus placebo. The primary endpoint, failure to enter a steroid-free remission—defined as a Crohn's disease Activity Index < 150 at Week 14—or failure to maintain remission through week 50 was 30.6% in the methotrexate group and 29/8% in the placebo group. The proportion of patients attaining remission and tapering off steroids was similar between the two arms, suggesting that in patients who require prednisone, there is not a clear need for combination therapy with methotrexate.

Methotrexate may have advantages other than its potential efficacy, allowing for decreased immunogenicity to biologic cotherapy. Further, its oral application has been embraced by rheumatologists for long-term therapy. To date, methotrexate has not been adequately evaluated in patients with ulcerative colitis. A double-blind, randomized, multicenter Israeli study failed to find a benefit of oral methotrexate 12.5 mg/week versus placebo for inducing or maintaining remission in patients with chronic steroid-dependent ulcerative colitis.[5] A future study with the Crohn's & Colitis Foundation will evaluating the efficacy of subcutaneous methotrexate 25 mg/week. This trial should inform us as to the efficacy of methotrexate in patients with ulcerative colitis.

References

1. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462-2476.
2. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol.* 2006;4:621-630.
3. Sandborn W, Rutgeerts P, Reinisch W, et al. SONIC: a randomized, double-blind, controlled trial comparing infliximab and infliximab plus azathioprine to azathioprinein patients with Crohn's disease naive to immunomodulators and biologic therapy. *Am J Gastroenterol*. 2008;103 (suppl 1):S436.
4. Feagan BG, McDonald JWD, Panaccione R, et al. A randomized trial of methotrexate (MTX) in combination with infliximab (IFX) for the treatment of Crohn's disease (CD). Late breaking abstract presented at Digestive Disease Week. May 18–23, 2008. San Diego, Ca.
5. Oren R, Arber N, Odes S, Moshkowitz M, et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology*. 1996;110:1416-1421.

Slide Library

IPAA Technical Issues

Most cases are completed in two stages
- Acute:
  1. Subtotal colectomy and ileostomy;
  2. Proctectomy / IPAA
- Subacute:
  1. Restorative proctocolectomy / IPAA/ loop ileostomy;
  2. Closure ileostomy

Three stages are reserved for technical problems; (tension on the pouch, anastomotic problems) and high risk patients
1. Subtotal colectomy and ileostomy;
2. Proctectomy/IPAA and loop ileostomy
3. Closure ileostomy

IPAA Technical Issues

Pouch shape (J vs S vs W vs H)
- does not equate with function[1]
- J pouch is technically easiest and most common

Preservation of the anal transition zone
- Mucosectomy (remove last 2–3 cm of mucosa)
  - Preferred for dysplasia or rectal cancer
- Double staple technique
  - Improvement in seepage and incontinence[2]
  - Higher mean resting sphincter pressure[3]
  - Improved sensation[3]

[1]Beck DE. *Semin Colon Rectal Surg.* 1996;17:108.
[2]Tjandra W. *Am J Surg.* 1991;161:90.
[3]Miller R. *Dis Colon Rectum.* 1990;33:414.

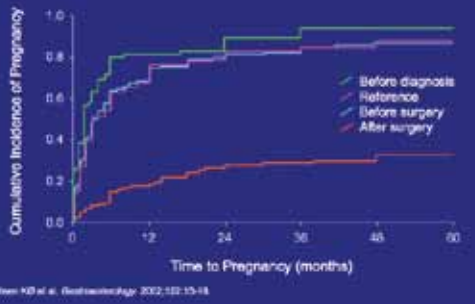
Fertility

- With both UC and CD, the risk of infertility prior to surgery appears to be similar to the general population
  - Infertility in NE Scotland population based study
    - 15% UC (n=138) vs. 14% general population
    - 14% CD (n=177) vs., 14% general population
      - Surgical therapy: 20% Medical therapy: 8%
- Olsen: 290 women with UC with IPAA
  - After diagnosis of UC: FR = 1.01
  - After surgery IPAA: FR* = 0 .20

Olsen KB et al. *Gastroenterology.* 2002;122:15-19.
Hultcrantz. *Int J Gynaecol Obstet.* 1997;58:229-237.

IPAA

- Cumulative Incidence of Pregnancy Within 5 Years



Olsen KB et al. *Gastroenterology.* 2002;122:15-19.

Ulcerative Colitis Ileoanal Pouch Complications

Acute:	
Pelvic abscess	5%
Anastomotic leak	2–10%
Vaginal fistula	5%
Anal stricture	5%
Small bowel obstruction	15–44% (20%)
– 5–21% need surgery	
Chronic:	
Pouchitis	40% lifetime
– 10-15% intractable	
Sexual dysfunction	4–7%
– Impotence 2% (Viagra), retrograde ejaculation 2%	
– Dyspareunia 7%	
Complete failure	10%
– (functional, Crohn's, pouchitis, pelvic sepsis)	

Pouchitis

- Acute and chronic inflammation of the ileal reservoir (incidence 7–59%)
- PDAI - clinical, endoscopic and microscopic criteria
- Highest risk initial 6 months
- Cumulative risk*
  - 1 yr 20%
  - 5 yr 32%
  - 10 yr 40%
- < 10% have chronic pouchitis only 1–3% require pouch removal
- Risk factors PSC (79% @ 10 yr), extraintestinal manifestations
- Smoking protective

Lapidus et al. *Dis Col Rectum.* 2002;45:1288.*
Penna et al. *Gut.* 1996;38:234-239.
Lohmuller et al. *Ann Surg.* 1990;211:622.

Pouchitis

- Etiology (theories)
  - Stasis and proliferation of bacteria "colonization of the pouch"
  - Deficiency of nutrients (SCFA);
    - butyrate and glutamine ineffective
  - Mucosal ischemia oxygen free radicals
    - Allopurinol ineffective
  - Pathogenic strains including *C. perfringens* and hemolytic *E coli*.
    - Antibiotics against anaerobes and aerobes

Complications After IPAA—Meta-Analysis of 43 Studies

Pooled incidences of pouch-related complications in 43 studies analyzed

Complication	Pooled %	95% CI %
Pouch failure	6.8	5.4–8.4
Pouch failure, follow-up >5 yr	8.5	5.4–13.2
Pelvic sepsis	9.5	8.2–10.9
Fistula	5.5	4.3–7.0
Stricture	9.2	6.8–12.4
Other	3.4	2.4–4.8
Sexual dysfunction	3.6	2.7–4.7
Pouchitis	18.8	15.7–22.4

Hueting WE et al. *Dig Surg* 2005;22:69-79.

Functional Outcome After IPAA—Meta-Analysis of 43 Studies

Pooled incidences of functional results after IPAA in 43 studies analyzed

Fecal incontinence	Pooled %	95% CI %
Incontinence day mild	17	12.8–22.2
Incontinence day severe	3.7	2.8–4.8
Incontinence night mild	13.1	9.5–17.9
Incontinence night severe	4.5	3.0–6.7
Urgency	7.3	4.5–11.6
Frequency		
Frequency day	5.2	4.0–6.7
Frequency night	1.0	0.6–1.6
Frequency 24 h	5.2	4.4–6.1

Hueting WE, et al. *Dig Surg* 2005;22:69-79.

Opportunistic Infections and Anti-TNF Therapies

Ex: from Risk Factors for Opportunistic Infections in IBD A Case-Control Study of 100 Patients (1998–2003)

	Odds Ratio (95% CI)	*P* Value
Any medication (5-ASA, AZA/6MP, steroids, MTX, Infliximab)	3.50 (1.98–6.08)	<.0001
5-ASA	0.98 (0.61–1.56)	.94
Corticosteroids	3.35 (1.82–6.16)	<.0001
AZA/6MP	3.07 (1.72–5.48)	.0001
MTX	4.00 (0.36–4.11)	.26
Infliximab	4.43 (1.15–17.09)	.03
One medication	2.65 (1.45–4.82)	.0014
Two medications	9.66 (3.31–28.19)	<.0001

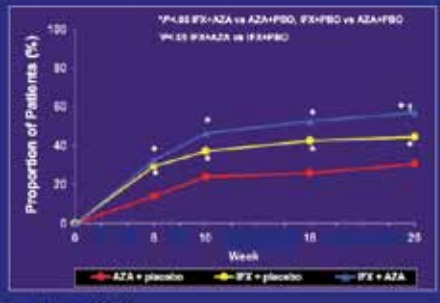
Tarunar Gastroenterol. 2005.

Recent Anti-TNF Biologic Trials

Step-up/Top-down (Steroid-naïve)	Steroids ⇨ Steroids ⇨ IS	Infliximab + IS
COMMIT (Steroid-induced, IS naïve)	Infliximab	Infliximab + MTX
SONIC (Steroid-refractory, IS naïve)	Infliximab	Infliximab + AZA
		AZA

SONIC

Corticosteroid-Free Clinical Remission of Crohn's Disease Through Week 26



Sandborn, WJ et al. ACG 2008.

For a free electronic download of these slides, please direct your browser to the following web address:
http://www.clinicaladvances.com/index.php/our_publications/gastro_hep-issue/gh_may_2009/

Notes

Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Ulcerative Colitis

CME Post-Test: *Circle the correct answer for each question below.*

1. Ulcerative colitis patients with extensive therapy should be considered 5-ASA failures if they do not respond to which of the following regimens?

   a. 2.4 g oral 5-ASA daily
   b. 2.4 g oral 5-ASA plus rectal therapy
   c. 4.8 g oral 5-ASA with or without rectal therapy
   d. None of the above

2. Approximately what proportion of patients who start corticosteroid therapy will require surgery for their ulcerative colitis within the first year?

   a. 10%
   b. 25%
   c. 40%
   d. 67%

3. Infliximab therapy is contraindicated in patients with which of the following conditions?

   a. History of optic neuritis
   b. Active tuberculosis
   c. Hypertension
   d. All of the above

4. What is the relative risk of lymphoma in patients receiving anti-TNF therapy?

   a. 1–2 per 10,000 individuals
   b. 4–6 per 10,000 individuals
   c. 20 per 10,000 individuals
   d. 50 per 10,000 individuals

5. Which of the following patients are considered to have failed a 5-ASA?

   a. Those with extensive disease not responding to 2 g 5-ASA by 8 weeks
   b. Those not responding to 40-60 mg oral corticosteroids by 2 weeks
   c. Those not responding to azathioprine 2.5 mg/kg by 2 months
   d. Those with distal ulcerative colitis not responding to topical mesalamine

6. TRUE or FALSE: Patients are considered to have failed corticosteroid therapy if they cannot taper off steroids despite receiving an optimal dose of 5-ASA plus azathioprine.

   a. True
   b. False

7. Which of the following statements is TRUE regarding the ACT 1 and ACT 2 trials?

   a. These trials evaluated infliximab in patients with previously untreated ulcerative colitis.
   b. Discontinuation rates were significantly higher with infliximab versus placebo.
   c. ACT 1 and ACT 2 revealed new adverse events associated with infliximab that were not seen in patients with Crohn's disease.
   d. More than half of patients in ACT 1 and ACT 2 were receiving concomitant corticosteroids.

8. In ACT 1 and ACT 2, mucosal healing was evident by what time point in infliximab-treated patients?

   a. Week 8
   b. Week 24
   c. Week 30
   d. Week 54

9. In the TREAT registry, which of the following therapies was associated with a significantly increased risk of serious infections compared other therapies?

   a. Infliximab
   b. Corticosteroids
   c. Azathioprine
   d. 6-MP

10. TRUE or FALSE: in the COMMIT trial of patients with active Crohn's disease requiring steroids, infliximab plus methotrexate was more effective than infliximab alone.

    a. True
    b. False

Evaluation Form: Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Ulcerative Colitis

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the natural course of moderate-to-severe ulcerative colitis.	1	2	3	4	5
2. Cite current data on the use and limitations of 5-ASA agents and steroids in treating these patients.	1	2	3	4	5
3. Review the curative use of surgery including potential complications and its effects on patient QOL.	1	2	3	4	5
4. Describe the role of biologic therapy in these patients and its potential effect on disease course and surgical outcomes.	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

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