GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

January 2010 www.clinicaladvances.com Volume 6, Issue 1, Supplement 2

Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting

A Review of Selected Presentations from the 74th Annual American College of Gastroenterology Annual Scientific Meeting
October 23–28, 2009
San Diego, Calif.

With commentary by:
David G. Binion, MD
Co-Director, Inflammatory Bowel Disease Center
Division of Gastroenterology, Hepatology, and Nutrition
University of Pittsburgh

A CME Activity
Approved for
1.0 *AMA PRA*
Category 1 Credit(s)™

Release date: January 2010
Expiration date: January 31, 2011
Estimated time to complete activity: 1.0 hours

PIM Postgraduate Institute for Medicine

Supported through an educational grant from Abbott Laboratories.

Sponsored by Postgraduate Institute for Medicine.

Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with Crohn's disease.

Statement of Need/Program Overview: The abstract review monograph *Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting* will present the most current data updates emerging within this therapeutic area. The development and use of targeted biologic agents has demonstrated efficacy in inducing and maintaining remission in many patients with Crohn's disease. There is a clear educational need that exists in the gastroenterology community for an updated understanding of the appropriate use of biologic therapies, including the optimal timing of their use.

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

1. Review the current role of biologic therapies in the treatment of moderate-to-severe Crohn's disease.
2. Outline emerging data on the use of biologics as they relate to use in clinical practice.
3. Describe new strategies to maximize biologic efficacy and durability of response.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*.

Credit Designation: Postgraduate Institute for Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure of Conflicts of Interest:
Postgraduate Institute for Medicine (PIM) assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by PIM for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. PIM is committed to providing its learners with high-quality CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest.

The faculty reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

David G. Binion, MD: Dr. Binion discloses the following. Consulting fees: Abbott Laboratories, UCB, Inc.

The planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

The following PIM planners and managers, Jan Hixon, RN, BSN, MA, Trace Hutchison, PharmD, Julia Kirkwood, RN, BSN, Samantha Mattiucci, PharmD and Jan Schultz, RN, MSN, CCMEP hereby state that they or their spouse/life partner do not have any financial relationships or relationships to products or devices with any commercial interest related to the content of this activity of any amount during the past 12 months.

Method of Participation: There are no fees for participating and receiving CME credit for this activity. During the period January 2010 through January 31, 2011, participants must 1) read the learning objectives and faculty disclosures; 2) study the educational activity; 3) complete the post-test by recording the best answer to each question in the answer key on the evaluation form; 4) complete the evaluation form; and 5) mail or fax the evaluation form with answer key to Postgraduate Institute for Medicine.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed post-test with a score of 70% or better. Your statement of credit will be mailed to you within three weeks.

If you wish to receive acknowledgment for completing 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. You may also complete the post-test online at www.cmeuniversity.com. Click on "Find Post-tests by Course" on the navigation menu, and search by project ID 6460. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Media: Monograph

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Postgraduate Institute for Medicine (PIM), *Gastroenterology & Hepatology,* and Abbott Laboratories do not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of PIM, Gastro-Hep Communications, and Abbott Laboratories. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

Table of Contents

Included in EMBASE

Disclaimer
Funding for this abstract summary report has been provided through an educational grant from Abbott Laboratories. Support of this monograph does not imply the supporter's agreement with the views expressed herein. Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Gastro-Hep Communications, Inc., the supporters, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

Introduction

The Evolving Picture of IBD

The past ten years have witnessed tremendous advances in our understanding of inflammatory bowel disease (IBD) etiopathogenesis and our ability to treat patients suffering from its two major forms, Crohn's disease (CD) and ulcerative colitis (UC). In prior decades, IBD patients endured a lack of effective treatment options, and patients with moderate-to-severe CD and UC were often relegated to prolonged systemic corticosteroid therapy and surgery as their only options. From the late 1990s onward, there has been a significant change in IBD therapy, specifically the widespread adoption of maintenance immunomodulators and the advent of biologic agents. Although highly effective, these new therapeutic approaches have been accompanied by important questions regarding medication safety, specifically in the setting of long-term maintenance treatment. Additional questions have emerged about how to best use these agents, along with a pressing need to define optimal treatment algorithms for specific IBD subgroups (ie, patients with pan-enteric inflammation, patients requiring hospitalization, patients with rapid recurrence of disease following resection/re-anastomosis). Understanding the natural history of these at-risk IBD patient subgroups, particularly early identification of patients with the potential for severe disease and its associated complications, will ultimately determine an optimal clinical approach that incorporates appropriate risk-benefit assessment for disease modifying therapy.

Hallmark Features of IBD Activity and Strategies to Monitor Inflammatory Disease Activity

Both CD and UC are chronic inflammatory conditions characterized by progressive damage to the gastrointestinal tract, which will manifest with diarrhea, abdominal pain, and bleeding per rectum. Although most commonly affecting the lower gastrointestinal tract (ie, the ileum and colon), CD chronic inflammation can affect more proximal regions of the digestive tract, as well as causing extraintestinal manifestations including skin lesions (erythema nodosum, pyoderma gangrenosum) and peripheral and central arthritis. Other IBD extraintestinal manifestations, again common to both CD and UC, may include fatigue, anemia and hypercoagulability. Unlike UC, in which the intestinal inflammation is usually continuous and superficial beginning at the anal verge and extending proximally, CD inflammation is patchy, widespread throughout the GI tract, and can affect all layers of the intestinal lining. At present, there is no single perfect clinical assay, disease activity score, or laboratory parameter that reliably and accurately assesses and quantifies inflammatory activity in all patients with IBD. In CD, clinical trials have relied on the Crohn's Disease Activity Index (CDAI) to quantify the degree of disease activity, but this clinical scoring instrument has received increasing criticism. The CDAI requires a 7-day diary, which makes it essentially impossible for routine use in clinical management of CD patients. It has also been criticized for its heavy reliance on subjective findings (self-reported general well being and abdominal pain) and the composite score is heavily weighted towards diarrheal symptoms. In addition, the CDAI lacks any objective measure of inflammation, with no serum markers of inflammation and no incorporation of endoscopic data. Although often presenting with more mild-to-moderate symptoms based on the CDAI scale, the clinical course of CD may worsen as disease-related complications emerge over time, specifically strictures and fistulas in the gastrointestinal tract. Thus, the CDAI may give a measure of disease activity at a point in time but may not provide prognostic information regarding the potential for disease severity, or the burden of inflammatory damage that a patient may face over the course of their lifetime.

The practical need for a disease activity score that provides better overall guidance for treatment stems from new data, which have demonstrated that treatment early in the disease course, prior to the passage of multiple years of cumulative damage, may provide the best approach for patients. These data suggest that medical treatment options are less efficacious in longstanding disease, which is characterized by the accumulation of intestinal scarring and permanent remodeling of the gastrointestinal tract. CD will typically demonstrate a relapsing-remitting clinical course and the historical rate of symptomatic relapse has been estimated to be as high as 20% of patients experiencing relapse every year.[1]

The Burden of CD: Direct and Indirect Costs and Impaired Quality of Life

CD exerts a significant burden on healthcare expenditures in the United States. Recent estimates place the prevalence of CD at 174–201 cases per 100,000 persons in the United States.[2,3] Since 1991, the prevalence of CD has increased by approximately 31%.[2] Research has demonstrated a bimodal distribution of age at diagnosis, with a large peak in incidence between the ages of 20 and 30, and a second, smaller peak that typically occurs between the ages of 60 and 70.[4] As the US population grows older, new, unanswered questions regarding the effects of aging on CD as well as the natural history of IBD in the geriatric population remain to be answered.

At a patient level, CD exerts a significant burden not only on an individual's health, but also on their ability to function in the workplace as well as their quality of life (QoL). During periods of active disease, IBD patients experience increased morbidity and decreased QoL. Studies over the past decade have confirmed that diminished QoL in IBD correlates directly with increased disease severity, and there is new interest in the routine use of QoL instruments not only in trials but also in the clinic to monitor patient status over time. In a study by Canavan and colleagues, researchers found that, among a group of 394 CD patients in the United Kingdom, QoL was equally poor among newly-diagnosed patients and those with established disease. As a component of assessing patient perspectives on CD, areas of the patients' concern were queried. The self-reported areas of greatest concern included: 1) the possible need for surgery; 2) the uncertain nature of CD symptom onset; and 3) the lack of energy (fatigue) that is a common symptom of the disease.[5] Other recent studies have reintroduced the interplay between chronic inflammatory disease and psychologic status of patients and have found a strong correlation between CD and depression.[6]

Research over the past decade has also demonstrated the evolving nature of CD over time, which is characterized by tissue remodeling in areas of chronic inflammation. Damage associated with chronic inflammation will often lead to the formation of scarring and strictures and then fistulas, which may represent the body's attempt to bypass areas of stenosis. The majority of CD patients demonstrate these features of tissue remodeling over time, with the most severely ill patients rapidly progressing to these complications both after diagnosis and following surgical resection and re-anastomosis, typically performed to address these complications. Natural history studies confirming this hypothesis have demonstrated that strictures/fistulas, found in less than 10% of patients at diagnosis, will evolve over time. At twenty years post-diagnosis of CD, the rates of inflammatory, stricturing, and penetrating disease are 12%, 18%, and 70%, respectively.[7] In addition, the probability of needing surgical resection of the colon at 15 years after CD diagnosis is approximately 70%.[8] However, the majority of surgical intervention in CD is not curative, as approximately half of patients requiring an initial resection will need a second resection by 15 years following diagnosis. This clinically significant recurrence of CD post-operatively also implies that many patients will require ongoing medical therapy to manage their disease in the post-operative time period. An additional important complication of chronic inflammation over time is the emergence of dysplasia and adenocarcinoma in areas of the GI tract exposed to prolonged chronic inflammatory damage. A recent study from Sweden has demonstrated that the risks of cancer are higher for patients with CD: 7.1% of a group of 378 Crohn's colitis patients developed colorectal cancer between 1996 and 2006, compared with a 0.29% rate in the general population of Stockholm County during the same time period.[9]

There are important indirect costs associated with CD, beyond the direct medical expenditures mentioned previously. In economic terms, CD exacts a substantial toll: the disease has direct and indirect annual costs estimated at $826 million in the United States.[10] In addition to the costs of medical and surgical therapy, the costs of missed work are high, because CD often strikes people during their most productive work years. One analysis estimated that the proportion of patients with CD who are capable of full-time work is only 75%, compared with 90% among those who suffer from ulcerative colitis.[11]

Advances in Defining the Etiopathogenesis of CD

The exact etiology of CD remains incompletely understood, although genetic predisposition may play an important role in the development of the disease. Five to 20% of CD cases correlate with a positive family history,[12] and in the United States, the disease appears to be most prevalent among people with a European American ancestry.[13] Environmental triggers such as smoking or diet may also be implicated in the etiology of CD. Ongoing research is examining the potential contributors to the pathogenesis of inflammation in CD, including variations in the gut epithelium, dysregulation of the mucosal immune system, and the presence of certain gut microflora.

Traditional Therapies for Crohn's Disease

Traditionally, corticosteroids have been the mainstay inductive treatment for moderate-to-severe CD. The

American College of Gastroenterology (ACG) Practice Guidelines for the Management of Crohn's Disease in Adults[14] note that the usual treatment for moderate-to-severe CD is prednisone at doses of 40–60 mg daily until the resolution of symptoms, which generally takes 7–28 days to achieve. In a population-based study of corticosteroid therapy, Faubion and colleagues reported that 58% of patients achieved remission with corticosteroids, but only 32% were able to remain in remission at 1 year without the use of additional steroids. Furthermore, 28% of patients developed corticosteroid dependence over the course of the year.[15] The risks of long-term use of corticosteroids are numerous, but prominent among these are bone damage (ie, demineralization, avascular necrosis) and increased susceptibility to infection. It is also important to note that systemic corticosteroids have never demonstrated longterm maintenance benefit in CD.

The immunomodulators 6-mercaptopurine (6MP) and azathioprine are often used for maintaining remission in moderate-to-severe CD. Although effective, they have a slow onset of action and a high risk of side effects and adverse events. Among the most concerning long-term side effects, is a low, but increased risk of lymphoma.

Biologic Therapies for Crohn's Disease

One of the breakthrough observations over the past two decades was the identification of the critical role of tumor necrosis factor alpha (TNFα) in the pathogenesis of chronic gut inflammation in CD. TNF is a cytokine produced by macrophages and lymphocytes and is felt to play an essential role in the amplification and perpetuation of inflammatory responses in the gut. When activated in CD, TNF triggers a cascade of other proinflammatory cytokines within the immune system. New understanding of the importance of this mechanism in CD pathogenesis, combined with the limited efficacy and poor safety/tolerability profiles of previously available drugs, provided the impetus for the development of biologic agents targeting cytokines in the treatment of CD. The first biologic agent approved for CD was infliximab, a humanized chimeric monoclonal antibody that binds to TNFα and causes apoptosis of macrophages and activated T lymphocytes. The 2009 ACG guidelines state that infliximab is effective in patients who are refractory to other treatment options.[14] Infliximab is administered via intravenous infusion.

Recently, several other biologic agents have been developed and approved for the treatment of CD. Adalimumab is another anti-TNF monoclonal antibody that demonstrated efficacy in two pivotal CD trials: CLASSIC I[16] and GAIN.[17] The ACG guidelines state that adalimumab is effective in patients who are naïve to biologic therapy, as well as in those who have lost response to previous treatment with infliximab.[14] Certolizumab pegol, a pegylated Fab antibody fragment, is also directed against TNFα, and has been shown to be efficacious in the PRECiSE 1 and PRECiSE 2 trials.[18,19] Unlike infliximab, both adalimumab and certolizumab pegol are both administered as subcutaneous injections.

Natalizumab is a humanized monoclonal antibody that targets the cellular adhesion molecule α4-integrin, expressed on leukocytes, which normally home to the mucosal immune compartment and are known to play a critical role in CD pathogenesis. The ENCORE trial showed that natalizumab is effective in patients with moderate-to-severe CD who are refractory to TNF inhibitors and other CD therapies.[20] However, natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML) caused by the reactivation of the latent human JC polyoma virus. Other adverse events associated with this agent are infusion reactions and increased risk of other infections. This adverse reaction profile has resulted in FDA approval with additional stipulations, specifically the requirement that the drug be used in CD patients only after a prior trial of anti-TNF therapy, as well as mandating its long-term use as monotherapy with no concomitant immunosuppressive agents, in the hope of preventing PML.

Improved understanding of how biologic agents can help patients with CD has resulted in increased utilization, but concerns regarding the safety profile of these agents remain, especially in the setting of long-term maintenance therapy.[21] An additional area of uncertainty and concern surrounds the use of biologic agents during pregnancy. To date, the anti-TNF class of drugs has demonstrated a favorable safety profile, resulting in an FDA class B designation during pregnancy. Natalizumab is classified as a class C agent during pregnancy, because of the possible adverse fetal effects seen in animal studies. Registries are currently in place to monitor the safety of biologic agents when used during pregnancy.[22]

Recent Advances in CD Biologic Treatment: the 2009 ACG Meeting

In October 2009, the American College of Gastroenterology held its 74th Annual Scientific Meeting in San Diego, California. Researchers provided new information regarding CD treatment, specifically data on the use of biologics in the treatment of CD, including data on efficacy, long-term remission rates, QoL improvements, optimization of dosing schedules, and the long-term safety profile of these agents. Highlights of these clinical abstracts are provided below.

References

1. Munkholm P, Langholz E, Davidsen M, et al. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol*. 1995;30: 699-706.
2. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis*. 2007;13:254-261.
3. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol*. 2007;5:1424-1429.
4. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. *Aliment Pharmacol Ther*. 2002;16:51-60.
5. Canavan C, Abrams KR, Hawthorne B, et al. Long-term prognosis in Crohn's disease: factors that affect quality of life. *Aliment Pharmacol Ther*. 2006;23: 377-385.
6. Fuller-Thomson E, Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflamm Bowel Dis*. 2006;12:697-707.
7. Cosnes J, Cattan S, Blain A. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis*. 2002;8:244-250.
8. Munkholm P, Langholz E, Davidsen M, et al. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology*. 1993;105:1716-1723.
9. Rubio CA, Kapraali M, Befrits R. Further studies on the frequency of colorectal cancer in Crohn's colitis: an 11-year survey in the Northwest Stockholm County. *Anticancer Res*. 2009;29:4291-4295.
10. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology*. 2002;122:1500-1511.
11. Ward FM, Bodger K, Daly MJ, et al. Clinical economics review: medical management of inflammatory bowel disease. *Aliment Pharmacol Ther*. 1999;13:15-25.
12. Binder V. Genetic epidemiology in inflammatory bowel disease. *Dig Dis Sci*. 1998;16:351-355.
13. Cho JH. The genetics and immunopathogeneisis of inflammatory bowel disease. *Nat Rev Immunol*. 2008;8:458-466.
14. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009;104:465-483.
15. Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*. 2001;121:255-260.
16. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006;130:323-333.
17. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007:146:829-838.
18. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med*. 2007;357:228-238.
19. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's Disease. *N Engl J Med*. 2007;357:239-250.
20. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE trial. *Gastroenterology*. 2007;132:1672-1683.
21. Caviglia R, Boskoski I, Cicala M. Long-term treatment with infliximab in inflammatory bowel disease: safety and tolerability issues. *Expert Opin Drug Saf*. 2008;7:617-632.
22. Roux CH, Brocq O, Breuil V, et al. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. *Rheumatology (Oxford)*. 2007;46:695-698.

Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting

1213 Long-term Remission with Certolizumab Pegol in Crohn's Disease over 3.5 Years: Results from the PRECiSE 3 Study

G Lichtenstein, O Thomsen, S Schreiber, I Lawrance, S Hanauer, R Bloomfield, W Sandborn

In the PRECiSE 1 Study, certolizumab pegol (CZP) was associated with a modest improvement in response rates compared with placebo in patients with moderate-to-severe CD.[1] In PRECiSE 2, investigators found that patients who had responded to 6-week induction doses of CZP were more likely to maintain remission at 26 weeks than those who were switched to placebo.[2] In the present study, Lichtenstein and colleagues assessed the long-term efficacy of CZP by providing an additional 3 years of therapy in PRECiSE 3.[3]

All patients who completed PRECiSE 2 were eligible to enter PRECiSE 3 and receive up to 154 weeks of additional CZP treatment. As in PRECiSE 2, the dose of CZP was 400 mg delivered subcutaneously every 4 weeks. Disease activity was measured by the Harvey-Bradshaw Index, where remission is defined as a score of 4 or lower. The maintenance of remission was analyzed in patients who were in remission at week 26 of the PRECiSE 2 trial.

In total, 141 patients who received CZP in PRECiSE 2 entered PRECiSE 3. Of these, 75% were in remission at the start of PRECiSE 3. The remission rates for the overall study population were 56% at 1.5 years, 38% at 2.5 years, and 31% at 3.5 years. For those patients who were in remission at the start of the study, 61%, 41%, and 36% continued to be in remission at 1, 2, and 3 years of treatment, respectively. The investigators concluded that CZP demonstrated long-term remission rates over 3.5 years, without the need for dose escalation. The drug was well tolerated, with no new safety concerns emerging over the study period.

1214 Regain of Response and Remission by Dose Adjustment in Patients with Crohn's Disease who Responded to Certolizumab Pegol: Results from the WELCOME Study

W Sandborn, G D'Haens, S Vermeire, J Colombel, R Fedorak, M Spehlmann, D Wolf, K Mitchev, C Jamoul, M Abreu, P Rutgeerts

The WELCOME study prospectively evaluated CZP in moderate to severe CD patients who had previously responded but had subsequently lost response to infliximab, or who had initially responded but developed hypersensitivity. In this analysis, Sandborn and colleagues reported on the efficacy of CZP for regaining response in patients who initially responded to therapy but who then relapsed.[4] The WELCOME trial was a 26-week Phase IIIb study of 539 patients that consisted of a 6-week open-label induction with 400 mg of CZP at weeks 0, 2, and 4, followed by a double-blind randomized maintenance phase. Patients who achieved a clinical response at week 6 were randomized to receive the same dose every 2 or 4 weeks through week 24. Patients who relapsed after randomization were allowed to receive open-label CZP every 2 weeks through week 24. Clinical response was defined as a decrease of 100 or more points in the Crohn's Disease Activity Index (CDAI) from baseline, and remission was defined as a CDAI score of 150 points or lower.

At week 6, 62% of the patients who had received CZP induction had responded. Of these, 161 were randomized to receive CZP every 2 weeks, and 168 were randomized to receive it every 4 weeks. At week 26, response rates were 36.6% for the group who received CZP every two weeks, and 39.9% for those on the 4-week schedule. Remission rates were 30.4% and 29.2% for the 2-week and 4-week schedules, respectively. Overall, no significant differences were observed between the two dosing regimens.

Table 1. Response, Remission, and Regained Response After Open-Label Switch in the WELCOME Study

No. visits post-switch	Response, % (n) (N=125)	Remission, % (n) (N=125)	Regained response, n (N=93)
1	49 (61)	28 (35)	37
2	47 (59)	27 (34)	10
3	42 (53)	26 (32)	6
Cumulative rate through week 26	n/a	n/a	66

During the course of the study, 125 of the 329 randomized patients switched to open-label 2-week dosing regimens. After the switch, response and remission occurred in almost one half (42%) and over one quarter (26%) of the patients, respectively, within 3 visits (Table 1). At the time of switch to open-label therapy, 93 patients were not in response (including 53 from the 4-week regimen group and 40 from the 2-week regimen group). Of these 93 patients, 71% regained response with 2-week dosing. For 80% of responsive patients, the response occurred within the 3-dose re-induction period. No new safety concerns emerged during this study.

The investigators concluded that, among patients who responded to induction therapy with CZP, 4-week dosing is as effective as 2-week dosing for the maintenance of response and remission through week 26. In addition, for those patients who achieve a response with CZP but then relapse during the maintenance phase, re-induction on a 2-week schedule is an effective management strategy.

1232 Long-Term Follow-up of Patients Enrolled in the Randomized Controlled Trial of Infliximab for Prevention of Postoperative Crohn's Disease (CD)

M Regueiro, K Kip, W Schraut, L Baidoo, S El-Hachem, J Harrison, M Pesci, A Watson, D Binion

In a previous trial that included 24 patients,[5] Regueiro and colleagues found that infliximab was more effective than placebo in preventing the recurrence of Crohn's disease at 1 year after intestinal resective surgery. In that trial, 9.1% of patients receiving infliximab had endoscopic recurrence, which was significantly lower than in the placebo group (84.6%, P=.0006). The investigators also found significantly lower rates for histologic recurrence (27.3% for infliximab vs 84.6% for placebo, P=.01) and a nonsignificant increase in the rate of clinical remission (80.0% for infliximab vs 53.8% for placebo, P=.38)[6] In this follow-up study, the investigators provide data on remission and recurrence rates for up to 4 years for the patients in the original post-operative trial.[6]

In the original one-year trial, 11 patients received infliximab and 13 received placebo. At the end of the study period, all patients had a colonoscopy and were offered open-label infliximab. All patients in the long-term trial had at least one colonoscopy at years 2 and/or 3.

At the time of the analysis of follow-up data, 2, 3, and 4 year testing had been performed on 16, 6, and 2 patients, respectively. At the end of the initial one-year trial, 7 of the original placebo patients opted for

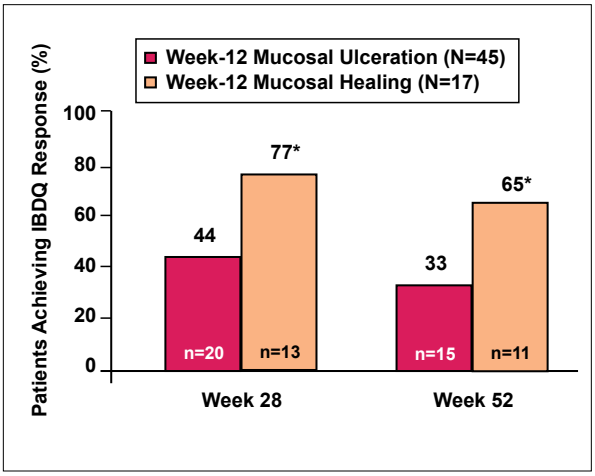

Figure 1. Patients with IBDQ response (≥16-point improvement from baseline) in the EXTEND trial of adalimumab. At week 28 and week 52, the percentages of patients achieving IBDQ responses were significantly greater for those who had mucoal healing at week 12, compared to those who had not.

*P=.05.

Reproduced from Rutgeerts et al.[8]

infliximab therapy, with 5 (71%) in remission at the 2-year follow-up visit. In contrast, 3 infliximab patients stopped therapy after the initial one-year period, and all had CD recurrence at year 2. When the investigators pooled the information from 48 post-surgical endoscopies, they found a strong gradient relationship between the use of infliximab or other anti-TNF therapies and the presence of endoscopic remission.

The researchers concluded that patients who are treated with infliximab after surgery maintain remission with ongoing therapy but relapse when therapy is stopped. In addition, patients who do not receive any anti-TNF therapy can be effectively treated with infliximab if they experience endoscopic recurrence one year after resective surgery.

1237 Quality-of-life Improvements in Adalimumab-treated Patients with Mucosal Healing: Results from the EXTEND Trial

P Rutgeerts, K Geboes, A Camez, N Chen, J Chao, P Mulani

The EXTEND trial was an open-label study of adalimumab that found induction plus maintenance therapy to be better than induction therapy alone in maintaining remission in patients with moderate to severe ileocolonic CD. After 52 weeks, 24% of adalimumab patients had maintained mucosal healing, compared with none of the placebo patients.[7]

In the current analysis, Rutgeerts and colleagues assessed the association between the mucosal healing found in the EXTEND trial and subsequent improvement in quality of life (QoL).[8] All patients received open-label adalimumab at induction doses of 160 mg at week 0 and 80 mg at week 2. At week 4, patients were randomized to receive maintenance therapy of adalimumab at doses of 40 mg every other week or placebo through week 52. Beginning in week 8 of the study, patients with flares or nonresponse were eligible to receive open-label adalimumab at a dose of 40 mg every other week, or every week if flares or nonresponse continued. Patients underwent colonoscopy at baseline, week 12 (or at the time of switch in the case of flares/nonresponse), and week 52. The researchers analyzed the relationship between mucosal healing at week 12 and improvement of at least 16 points on the Inflammatory Bowel Disease Questionnaire at weeks 28 and 52.

Of the 64 patients who were randomized to receive adalimumab, 62 had mucosal ulceration at baseline and were included in the analysis. The researchers found that the 17 patients who had achieved mucosal healing at week 12 were significantly more likely to gain improvement in QoL at weeks 28 and 52 compared with patients who continued to have ulceration at week 12 (Figure 1). Rutgeerts and associates conclude that mucosal healing in patients with moderate to severe ileocolonic CD is associated with subsequent improvements in QoL.

1244 Adalimumab-treated Patients with Moderate to Severe Crohn's Disease Experienced Reductions in Extraintestinal Manifestations: Data from CHARM

D Schwartz, R Lofberg, P Pollack, N Chen, P Mulani, J Chao

Recent reports place the prevalence of extraintestinal manifestations (EIMs) of CD at 19–46%.[9,10] These manifestations can include primary sclerosing cholangitis, deep vein thrombosis, arthritis, and skin rashes.

The CHARM trial was a 56-week, double-blind Phase III trial that evaluated the efficacy and safety of adalimumab and found the drug to be more effective than placebo in maintaining CD remission through 56 weeks, whether provided weekly or every other week.[11] Subsequent analyses of the CHARM trial focused on optimizing adalimumab dosing strategies[12] and on quantifying the

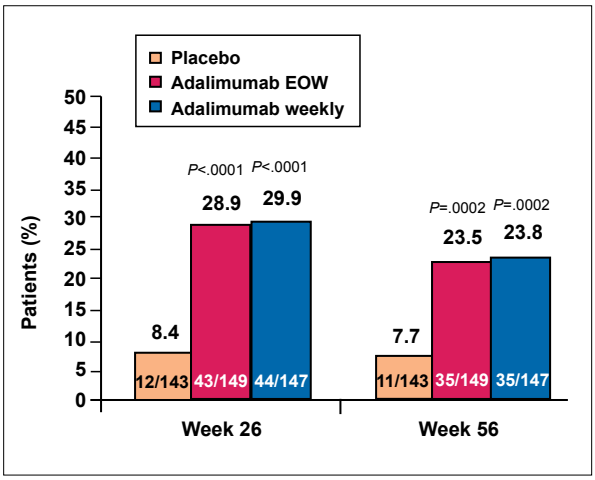

Figure 2. Complete absence of any extraintestinal Crohn's disease manifestation (EIM), by randomized group (NRI analysis), in the CHARM trial. At weeks 26 and 56, the percent of patients experiencing resolution of EIM was significantly greater for adalimumab-treated than placebo patients.

Reproduced from Schwartz et al.[14]

improvements to QoL afforded by adalimumab therapy.[13] In the current analysis, Schwartz and colleagues assessed the effect of adalimumab on reducing the incidence of EIMs in the CHARM trial population.[14]

In the CHARM study, all patients received open-label adalimumab induction therapy of 80 mg at week 0 and 40 mg at week 2. At 4 weeks, patients were randomized to receive 40 mg adalimumab every week, 40 mg every other week, or placebo. Starting at week 12, nonresponders or patients who experienced UC flares could receive open-label adalimumab at doses of 40 mg every other week (or every week if flares or nonresponse continued). The presence of extraintestinal manifestations was compared at baseline, week 26, and week 56 between treatment groups (Figure 2). The manifestations included in the analysis were related to Question 4 of the Crohn's Disease Activity Index, evaluating the presence of manifestations including arthritis/arthralgia, iritis/uveitis, and erythema nodosum/pyroderma gangrenosum/aphthous stomatitis. Of the 778 patients randomized in CHARM, 420 (54.0%) had arthritis/arthralgia at baseline and were included in the analysis. The investigators found that, of the patients who had arthritis/arthralgia at baseline, resolution occurred in a significantly greater percentage of patients who received adalimumab compared with placebo. The absence of this manifestation was evident at week 26 and continued through the end of the study. Thirty-eight patients (4.9%) had other EIMs, including erythema nodosum, pyoderma gangrenosum, or aphthous stomatitis at baseline. Because of the small sample sizes for these manifestations, they were excluded from the analysis. Schwartz and associates concluded that adalimumab was effective in reducing arthritis/arthralgia in patients with moderately or severely active CD.

1252 Infliximab for Crohn's Disease: The First 262 Patients, Ten Years Later

J Seminerio, E Loftus, W Harmsen, P Thapa, A Zinsmeister, W Sandborn

Seminerio and colleagues provided long-term data on the safety profile and usage patterns of infliximab in patients with Crohn's disease.[15] The researchers analyzed data from 1998–2001 on 262 patients who received at least one infusion of infliximab. They reviewed the medical records of these patients to determine the occurrence of adverse events and the length of treatment with infliximab.

There were 194 patients who received induction and 68 who received maintenance therapy during their initial infliximab courses. Of the patients who started on induction therapy, 22 received maintenance treatment during subsequent visits. For 70 patients, there was more than one time period during which infliximab was administered, and a total of 90 patients received maintenance therapy. Over the past 10 years, 55 out of the 90 patients required dose escalation and/or a shortened dosing interval. The median follow-up after the first infusion was 7.2 years (with a range of 0.01–10.7 years).

The investigators found that the cumulative probability of any bacterial complication at 30 days, one year, 5 years, and 10 years was 1%, 7%, 34%, and 39%, respectively. The cumulative probability of fungal infection at 30 days, 5 years, and 10 years was 0.5%, 9%, and 9%, respectively. There were 12 documented cases of cancer and dysplasia, with a cumulative probability of malignancy at 30 days, 1 year, 5 years and 10 years of 1%, 3%, 7%, and 14%, respectively. The cumulative probability of any viral infection at 30 days, 1 year, 5 years and 10 years was 1%, 3%, 7% and 10%, respectively. Other adverse events included delayed hypersensitivity reactions in 30 patients, infusion reactions in 30 patients, and lupus reactions in 7 patients.

Of the 68 patients who received maintenance therapy during the initial course of treatment with infliximab, the cumulative probability of discontinuation was 60.3% at 5 years and 91.2% at 10 years. The cumulative probability of death was 8% at 5 years and 15% at 10 years.

The researchers determined that the persistency rate among patients treated with infliximab maintenance therapy was 40% at 5 years and 9% at 10 years. They

concluded that the long-term safety of infliximab proved to be consistent with current knowledge, with observed adverse events including infections, infusion and autoimmune reactions, and malignancy.

1259 Natalizumab Use in Patients with Crohn's Disease and Relapsing Multiple Sclerosis: Updated Utilization and Safety Results from the TOUCH Prescribing Program, the Pregnancy Registry, and the INFORM and TYGRIS Studies

A Pepio, L Taylor, M Kooijmans, C Bozic, G Quinn

Natalizumab is a humanized monoclonal antibody that reduces inflammation by targeting the cellular adhesion molecule □4-integrin. In two randomized trials, natalizumab demonstrated efficacy in treating relapsing multiple sclerosis (MS).[16] A systematic review of 4 randomized controlled trials in CD found that natalizumab is effective for the induction of response and remission in some patients with moderate to severely active CD.[17] The drug was approved, initially for MS treatment, in 2004. However, safety concerns over the incidence of progressive multifocal leukoencephalopathy (PML) caused it to be withdrawn from the market in 2005. It was reintroduced 16 months later, with risk management programs put in place to monitor adverse events.[18,19]

The TYSABRI Outreach: Unified Commitment to Health (TOUCH) program is a mandatory prescribing program for all patients, physicians, and infusion centers in the United States, designed to ensure appropriate and informed use of natalizumab. The purpose of the program is to monitor patients for signs and symptoms of PML and to assess the incidence of opportunistic infections.

Investigating Natalizumab through Further Observational Research and Monitoring (INFORM) is a voluntary US study that collects information on efficacy, QoL outcomes, and serious adverse events in CD patients. The study collects information on efficacy based on the Harvey Bradshaw Index (HBI). TYGRIS is a voluntary global study evaluating the long-term safety of natalizumab in MS patients. A separate pregnancy registry collects data on pregnancy outcomes in natalizumab patients. In countries that do not participate in these programs, post-marketing surveillance data are also collected.

In this presentation, Pepio and colleagues provided updates on natalizumab utilization and safety data from surveillance programs in CD and MS patients.[20] As of the end of March 2009, approximately 52,000 patients had been exposed to natalizumab in the post-marketing setting, approximately 99% of whom were MS patients. As of the time of this analysis, there were 10 confirmed cases of PML, one of which was fatal. All cases of PML occurred in the MS population.

INFORM enrolled 25 patients with an average HBI of 6.4 at baseline. For the 10 patients with an HBI assessment after 6 months of therapy, the average score was 5.6, representing a mean decrease of 1.5 in these patients. The overall incidence of serious adverse events was 4%. There were 132 women enrolled in the pregnancy registry (104 prospective and 28 retrospective) and 262 prospectively reported pregnancy cases. The investigators conclude that cumulative data from all available registries for both indications suggest that the safety profile of natalizumab is consistent with that observed in clinical trials.

1276 Adalimumab Improves Work Productivity and Reduces Indirect Costs with Patients with Moderate to Severe Crohn's Disease: A Meta-analysis

D Binion, E Louis, A Yu, A Bensimon, E Wu, J Chao, P Mulani

Earlier studies have suggested that only 75% of CD patients are capable of full-time work, and that the total direct and indirect cost of inflammatory bowel disease in the United States is approximately $2 billion per year.[21] Binion and associates performed a meta-analysis to assess the effect of adalimumab treatment on work productivity in patients with moderate to severe CD.[22] They also estimated the one-year indirect cost savings of the drug from the employer's perspective. The researchers pooled data from all clinical trials of adalimumab for moderate to severe CD in which work productivity outcomes were evaluated. Outcomes from the Work Productivity and Activity Impairment Questionnaire (WPAI) were extracted for each cohort. The mean WPAI improvements reported for the visit closest to week 26 were used to approximate midyear outcomes, and the researchers applied random-effects meta-analyses to estimate a one-year estimate of accumulated productivity benefits. Pooled estimates of accumulated improvements in absenteeism and time-weighted productivity index (TWPI) were multiplied by the 2007 US national average annual salary ($42,504) to estimate the per-patient one-year indirect cost savings associated with adalimumab treatment.

The investigators identified four trials—ACCESS, CARE, CHOICE, and EXTEND, with a total of 1,202 employed adalimumab-treated patients enrolled at baseline. Each study followed patients for at least 20 weeks. Overall, pooled estimates of the improvements in WPAI scores were -9% (95% confidence interval [CI]: -11%,

-7%) in absenteeism, -23% (95% CI: -30%, -17%) in presenteeism (lost productivity due to employees working while ill), and -26% (95% CI: -34%, -19%) in TWPI. Pooled TWPI improvements translated into an estimated per-patient indirect cost savings of US $11,168 (95% CI: $7,972, $14, 363) owing to reductions in CD-related work loss and productivity impairment. Pooled results for absenteeism alone indicated an expected cost savings of $3,876 (95% CI: $2,971, $4780) per year through reduced work loss.

Binion and colleagues concluded that adalimumab-treated patients with moderate-to-severe CD experienced clinically significant improvements in work productivity. The researchers noted that for employers, such improvements can translate into substantial indirect cost savings.

References

1. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab Pegol for the Treatment of Crohn's Disease. *N Engl J Med*. 2007;357:228-238.
2. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's Disease. *N Engl J Med*. 2007;357:239-250.
3. Lichtenstein G, Thomsen O, Schreiber S, et al. Long-term remission with certolizumab pegol in Crohn's Disease over 3.5 years: results from the PRECiSE 3 study. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1213.
4. Sandborn W, D'Haens G, Vermeire S, et al. Regain of response and remission by dose adjustment in patients with Crohn's Disease who responded to certolizumab pegol: results from the WELCOME study. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1214.
5. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. *Gastroenterology*. 2009;136:441-450.
6. Regueiro M, Kip K, Schraut W, et al. Long-term follow-up of patients enrolled in the randomized controlled trial (RCT) of infliximab (INF) for prevention of postoperative Crohn's disease. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1232.
7. Rutgeerts P et al. Adalimumab induces and maintains mucosal healing in patients with moderate to severe ileocolonic Crohn's disease: first results of the EXTEND trial. Presentation at the 2009 Digestive Disease Week: Abstract 751e.
8. Rutgeerts P, Geboes K, Camez A, et al. Quality-of-life improvements in adalimumab-treated patients with mucosal healing: results from the EXTEND trial. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1237.
9. Bruining DH, Siddiki HA, Fletcher JG, et al. Prevalence of penetrating disease and extraintestinal manifestations of Crohn's disease detected with CT enterography. *Inflamm Bowel Dis*. 2008;14:1701-1706.
10. Williams H, Walker D, Orchard TR. Extraintestinal manifestations of inflammatory bowel disease. *Curr Gastroenterol Rep*. 2008;10:597-605.
11. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132:52-65.
12. Colombel JF, Sandborn WJ, Rutgeerts P. Comparison of two adalimumab treatment schedule strategies for moderate-to-severe Crohn's disease: results from the CHARM trial. *Am J Gastroenterol.* 2009;104:1170-1179.
13. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology*. 2008;135:1493-1499.
14. Schwartz D, Lofberg R, Pollack P, et al. Adalimumab-treated patients with moderate to severe Crohn's disease experienced reductions in extraintestinal manifestations: data from CHARM. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1244.
15. Seminerio J, Loftus E, Harmsen W, et al. Infliximab for Crohn's disease: the first 262 patients, ten years later. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1252.
16. Johnson KP. Natalizumab (Tysabri) treatment for relapsing multiple sclerosis. *Neurologist.* 2007;13:182-187.
17. MacDonald JK, McDonald JW. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007;24:CD006097.
18. Iaffaldano P, D'Onghia M, Trojano M. Safety profile of Tysabri: international risk management plan. *Neurol Sci.* 2009;30 Suppl 2:S159-162.
19. Huggett B. How Tysabri survived. *Nat Biotechnol.* 2009;27:986.
20. Pepio A, Taylor L, Kooijmans M, et al. Natalizumab use in patients with Crohn's disease and relapsing multiple sclerosis: updated utilization and safety results from the TOUCH Prescribing Program, the Pregnancy Registry, and the INFORM and TYGRIS studies. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28:Abstract 1259.
21. Ward FM, Bodger K, Daly MJ et al. Clinical economics review: medical management of inflammatory bowel disease. *Aliment Pharmacol Ther.* 1999;13:15-25.
22. Binion D, Louis E, Yu A, et al. Adalimumab improves work productivity and reduces indirect costs with patients with moderate to severe Crohn's disease: a meta-analysis. Presentation at the 74th American College of Gastroenterology Annual Scientific Meeting, San Diego, California 2009;October 23-28: Abstract 1276.

Commentary

David G. Binion, MD

Co-Director, Inflammatory Bowel Disease Center
Division of Gastroenterology, Hepatology, and Nutrition
University of Pittsburgh

The PRECiSE 3 study, reported by Lichtenstein and colleagues, demonstrated important new data regarding the long-term efficacy of biologic therapy in a cohort of CD patients enrolled in a CZP extension program. The initial maintenance efficacy of CZP was demonstrated based on 26 week data and this new study confirmed that CZP will continue to benefit patients over an extended, multiyear time period.

However, along with confirming long-term efficacy, a second issue regarding the durability of CZP treatment becomes apparent. As time progressed, there was a gradual attrition of patients who were previously doing well on CZP, but fell out of remission. By the end of the 3-year study period, only one third of patients remained in remission. Understanding how long biologic therapy will remain efficacious in CD patients is an important consideration when maintenance treatment regimens are being devised. Data from extended, multi-year biologic maintenance protocols will provide a critical piece of information in this regard.

The need for dose escalation (shortened treatment intervals and/or increased drug dose) has been commonly encountered in biologic management of CD. Dose escalation recommendations are readily available for patients treated with infliximab and adalimumab. A unique aspect of CZP therapy for CD has been the lack of dose escalation information for patients who lose response to treatment over time. The WELCOME study provides dose escalation information for CZP-treated patients. In this study, Sandborn and colleagues demonstrated that CD patients who have relapsed in the setting of effective CZP maintenance treatment can regain response/remission with a dose intensification regimen involving a repeat induction regimen. Initial CZP responders who were recaptured with repeat induction also appeared to benefit from receiving single subcutaneous injections on an every-2-week basis, as opposed to receiving two injections once a month. This analysis of the WELCOME trial clearly demonstrates a role for intensified CZP dosing in patients whose CD is breaking through stable maintenance, after an initial response to drug. This study also highlights that higher dosages/more frequent administration of CZP initially did not demonstrate significant benefit at the start of therapy, but did improve outcomes in patients who had been on drug over an extended time. This growing experience with alternative dosing regimens for subcutaneous anti-TNF agents for CD suggests that flexibility in CZP dosing will be an important component to optimize clinical results in patients receiving long-term therapy.

Regueiro and colleagues demonstrated markedly improved efficacy of infliximab when used in the postoperative period to maintain remission, which was defined using a novel endoscopic primary endpoint (assessing the neo-terminal ileal anastomotic mucosa one year after re-anastomosis). This novel use of biologic therapy demonstrated extremely high rates of endoscopic remission, seen in more than 90% of patients, which was markedly higher than endoscopic remission rates seen in the patients randomized to receive placebo infusions added on to standard agents. This rate of endoscopic remission in the post-operative biologic treated patients (>90%), was also markedly higher than rates demonstrated in the pivotal trials assessing medically induced remission, where patients with longstanding disease would typically demonstrate endoscopic remission rates of less than 40%. The present study provides additional long-term follow-up data in a subgroup of the original patients who were followed for up to 4 years post-surgery. This work suggests that postoperative biologic prophylaxis is durable and endoscopic remission predicts durable clinical remission with biologic therapy in CD patients following terminal ileal resection and re-anastomosis. The use of postoperative biologic therapy may represent a unique strategy to optimize treatment efficacy for the sickest cohort of CD patients, who would ultimately require biologic therapy at a later time point following surgery regardless, but with potentially diminished effectiveness. Tissue remodeling, which accompanies chronic inflammation in CD, appears to diminish treatment efficacy, providing rationale for the early use of biologic therapy, before damage diminishes the potential for medical benefit. The challenge for the use of post-operative biologic therapy is to determine who will best benefit from this approach (ie, the subset of CD patients with the most aggressive disease).

This study also suggests a series of novel therapeutic approaches for CD management—specifically removal of damaged intestine followed by institution of maximum therapy prior to the recurrence of inflammation, which may yield the highest rates of remission ever seen in the treatment of adult CD. This study has also confirms that endoscopic lesions appear earliest, prior to CRP elevation and symptoms, which will emerge last in the natural

history of post-operative disease recurrence. Finally, this study further highlights the need for better, more accurate and objective clinical assays/tests/tools for monitoring disease recurrence and activity.

The practice of targeting mucosal healing as the optimal therapeutic endpoint in the clinical care of CD patients is gaining momentum. However, mucosal healing has not been uniformly embraced nor has it been validated as the best treatment goal in CD management. Measuring quality of life with clinical instruments that reflect disease status has emerged as a very relevant and effective strategy to assess disease in lieu of a perfect clinical marker or serum assay to guide therapy. In addition, one of the major concerns of patients suffering from chronic illness is the desire to feel well, which is accurately reflected in quality-of-life scores. The EXTEND study by Rutgeerts and colleagues assessed endoscopic response to adalimumab in a cohort of CD patients who were receiving open-label therapy and correlated these findings with prospectively assessed quality of life. When patients demonstrated optimal endoscopic response to treatment with complete mucosal healing, this corresponded to the most improvement in quality of life scores, further substantiating the rationale for this therapeutic target. Thus analysis of the adalimumab-treated clinical trial population further supports the rationale and benefit of mucosal healing for improving how CD patients will feel, as reflected by optimal quality of life, over multiple years of treatment.

Extra-intestinal manifestations (EIM) are an important manifestation of IBD, and EIM will sometimes constitute the primary clinical issue before bowel-related symptoms in patients with both CD and UC. Schwartz and colleagues evaluated patients from an adalimumab maintenance (CHARM trial) population for the activity of arthritis/arthralgia, one of the most common EIM seen in active IBD. Patients who responded to adalimumab demonstrated a significant and sustained improvement in this EIM over both 6- and 12-month time periods. This work confirms the profound benefit of anti-TNF biologic therapy in the management of EIM in CD patients.

As biologic therapy has become a commonly used strategy in the treatment of moderate-to-severe CD patients, new questions regarding the durability of therapy have emerged. Seminerio and colleagues reviewed the Mayo Clinic's long-term experience with infliximab therapy in a large cohort of 262 CD patients. In this group, the loss/discontinuation of infliximab treatment emerged over time in almost all patients who were followed for a 10-year period. Among the long-term infliximab-treated patients, 40% were still receiving drug at 5 years and only 9% continued to receive infliximab 10 years after initiation. The overall safety profile demonstrated that infections were the most commonly encountered complications, emerging in over one third of patients over the decade-long time period of usage.

These important data highlights a previously underappreciated facet of biologic therapy in CD, the attrition of biologic agents over time. These data also emphasize a new clinical research priority of how to maximize the durability of biologic treatment over time.

Concerns regarding the use of natalizumab associated with the emergence of a serious brain infection, PML, has significantly limited the use of this compound in CD management, but has not had as profound a deterring effect on treatment of patients with MS. The study by Pepio and colleagues provides a comprehensive safety review of a large group of natalizumab-treated MS and CD patients. Over 52,000 patients were enrolled in this safety registry and available for analysis, almost all of whom had MS. Out of this natalizumab-treated cohort, there were a total of 10 PML cases detected, one of which was fatal. None of the patients receiving routine natalizumab therapy who developed PML were receiving treatment for CD. However, the total number of CD patients enrolled in the registry was extremely low (<1% of total). CD patients enrolled in the safety registry (n=25) demonstrated clear benefit from natalizumab treatment. A natalizumab pregnancy registry followed a total of 132 patients. No new safety signals were identified, providing additional reassurance regarding the use natalizumab in the setting of pregnancy.

Active CD will often lead to disability and impact the ability of a person to function in the workplace. Because CD typically presents in young adults, who are at a peak time of work participation, this may represent one of the most important sequelae of active disease. Understanding how medical treatment may improve not only patients' health, but also their ability to work, is an important economic factor that must be considered when analyzing the cost-benefit ratio to society. Our study reviewed a pooled dataset that included a large number of CD patients who were enrolled in clinical trials, to determine the effect of adalimumab on work capacity. Essentially all measures of work status improved in these moderate-to-severe CD patients treated with biologic therapy. These data suggest that at a societal level, the cost of biologic therapy may be offset by significant improvements in the ability of CD patients to maintain work productivity.

Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting

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

1. Since 1991, the incidence of Crohn's disease has increased by ___%.

   a. 31
   b. 15
   c. 42
   d. 26

2. Which trial studied the use of natalizumab in patients with moderate to severe Crohn's disease?

   a. CLASSIC I
   b. ENCORE
   c. GAIN
   d. WELCOME

3. True or False? In PRECISE 3, most patients required escalating doses of certolizumab pegol to maintain remission rates over a period of 3.5 years.

   a. True
   b. False

4. At week 26 of the WELCOME study presented by Sandborn and colleagues, response rates were 36.6% for the group who received certolizumab pegol every two weeks, and ____ for those on the 4-week schedule.

   a. 20.3%
   b. 39.9%
   c. 31.6%
   d. 42.5%

5. True or false? In a study of infliximab for post-operative CD, Regueiro and colleagues found a strong gradient relationship between the use of infliximab or other anti-TNF therapies and the presence of endoscopic remission.

   a. True
   b. False

6. Which biologic agent was examined in the EXTEND trial by Rutgeerts and colleagues?

   a. Adalimumab
   b. Infliximab
   c. Certolizumab pegol
   d. Natalizumab

7. Of the 778 patients enrolled in CHARM, what percentage had arthritis/arthralgia at baseline?

   a. 26%
   b. 35%
   c. 54%
   d. 48%

8. In the 10-year follow-up data on infliximab provided by Seminerio and colleagues, the cumulative probability of any bacterial complication at 10 years was:

   a. 17%
   b. 29%
   c. 45%
   d. 39%

9. True or false? All 10 cases of progressive multifocal leukoencephalopathy reported in post-marketing registry data for 52,000 patients exposed to natalizumab occurred in the multiple sclerosis population.

   a. True
   b. False

10. In Safdi's trial of patients who had failed mesalamine therapy, what percentage achieved remission after 8 weeks of balsalazide therapy?

    a. 47%
    b. 31%
    c. 56%
    d. 35%

Evaluation Form Biologic Therapies for Crohn's Disease: Update from the 2009 ACG Meeting

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. 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 rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating this activity, I am now better able to:

1. Review the current role of biologic therapies in the treatment of moderate-to-severe Crohn's disease.	1 2 3 4 5
2. Outline emerging data on the use of biologics as they relate to use in clinical practice.	1 2 3 4 5
3. Describe new strategies to maximize biologic efficacy and durability of response.	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

_____

What barriers do you see to making a change in your practice? _____

_____

Which of the following best describes the impact of this activity on your performance?
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

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

_____

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

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, Zip _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

For Physicians Only: I certify my actual time spent to complete this educational activity to be: _____
❒ I participated in the entire activity and claim 1.0 credits.
❒ I participated in only part of the activity and claim _____ credits.

Project ID: 6460