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Faculty

William J. Sandborn, MD
Mayo Clinic College of Medicine
Rochester, MN

Maria T. Abreu, MD
University of Miami
School of Medicine
Miami, FL

David W. Brandes, MS, MD
Northridge Neurological Center
Northridge, CA

Remo Panaccione, MD
University of Calgary
Calgary, Alberta, Canada

Updates from the Front Lines of Crohn's Disease: Achieving a Balance Between Safety and Efficacy

A Report of a Symposium Presented During
Digestive Disease Week
May 20, 2008
San Diego, California

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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 Crohn's disease.

Statement of Need/Program Overview: The dysregulated inflammatory response associated with Crohn's disease leads to an imbalance between proinflammatory and anti-inflammatory mediators, tissue damage, and clinical symptoms, including bleeding, diarrhea, abdominal pain, and weight loss. Many newer treatments for Crohn's disease aim to dampen the inflammatory response by skewing the cytokine balance and altering leukocyte functions. Although they share the same target, subtle differences exist among the tumor necrosis factor (TNF) antagonists, including the pharmacokinetic and pharmacodynamic properties of each antibody. The efficacy of each antibody may vary, depending on the affinity and avidity of the antibody to TNF. By specifically targeting the adhesion proteins $\alpha 4\beta 1$-integrin and $\alpha 4\beta 7$-integrin, the humanized monoclonal antibody natalizumab blocks the migration of leukocytes to the sites of inflammation. In prescribing these therapies, clinicians should also be aware of the minor and major adverse events that have been associated with them. Biologic therapies have been associated with events ranging from infusion-site reaction to rare cases of serious infection, lymphoma, and progressive multifocal leukoencephalopathy. However, concerns with patient safety must be balanced against patient preferences for effective therapy, particularly in chronic illnesses, such as Crohn's disease, which can profoundly effect overall quality of life.

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

1. Describe the current treatment algorithm guidelines in the management of patients with Crohn's disease.
2. Review the benefit-risk profiles of new treatment options for Crohn's disease.
3. Identify the potential for neurologic and demyelinating disorders that may be associated with use of biologics in Crohn's disease.
4. Explain how to integrate new therapies into treatment strategies to improve outcomes.

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Updates from the Front Lines of Crohn's Disease: Achieving a Balance Between Safety and Efficacy

A Report of a Symposium Presented During
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Defining Failure and Success in the Treatment of Crohn's Disease

Maria Abreu, MD, of the University of Miami, opened the program, discussing different definitions for evaluating the activity of biologic agents in Crohn's disease (CD). Dr. Abreu then addressed how these definitions affect the interpretation of clinical study results.

Failure and Success—Response Versus Remission

Dr. Abreu noted that before attempting to compare the efficacy of biologics, it is important to discuss the definitions of response and remission in different clinical trials. The key trials that have examined the induction efficacy of biologic agents in CD have all used slightly different primary endpoints. For example, one of the initial studies evaluating infliximab for CD treatment defined response as a decrease in the CD activity index (CDAI) of 70 points or more at week 4, following a single infusion.[1] The CLASSIC-I study, which examined treatment with adalimumab, defined response as a drop in CDAI of 70 points or more at week 4, after patients had received injections at weeks 0 and 2.[2] The PRECISE 1 study noted response to certolizumab pegol as a decrease in the CDAI of 100 points or more at week 6 and also at weeks 6 and 26.[3] Conversely, in the ENACT-1 study, response to natalizumab was recorded as a decrease in the CDAI of 70 points or more after 10 weeks of therapy, while the ENCORE trial defined natalizumab response as the same decrease in CDAI, but maintained from week 8 to week 12.[4,5] Despite the discrepancies in how response was measured in each of these trials, each showed a significant increase in the proportion of patients achieving a response compared with placebo. For this reason, these agents have all been approved for the treatment of CD.

Because many CD trials have defined clinical response as a decrease in the CDAI of 70 points or more, it is important to assess what that translates to in terms of clinical symptoms. The CDAI is comprised of several clinical and laboratory variables, all of which are multiplied by distinct weighting factors. Because of this, small changes can have a significant impact on the CDAI score. Hypothetically, a patient may change their CDAI score by experiencing a decrease in the number of loose stools from 10 to 5 per day. Although this sole reduction in loose stools would account for a 70-point-or-greater decrease in CDAI, the other symptoms the patient is experiencing, some of which may be quite serious, may not be alleviated. Therefore, even though this hypothetical case would qualify as a response in several clinical trials, it is important to note that the patient's symptoms and disease activity are not eliminated. Because assessment of response may not truly represent an overall improvement in the patient's disease activity and well-being, remission is a more rigorous measurement of an agent's activity in CD.

Failure and Success—Short-Versus Long-term Efficacy

CD is a chronic disease. The efficacy of biologic agents as long-term treatments is therefore an important endpoint. To evaluate this endpoint, several studies have monitored remission rates after 1 year of maintenance therapy.

In the ACCENT I trial, 28% of patients were in remission at 1-year follow-up. This was significantly superior to the 14% rate in the placebo group (P=.007).[6] The percentage of patients who achieved early remission and sustained it through every time point in the study was also greater than that achieved among patients in the placebo arm (25% vs 11%, respectively).[7] Similarly, in the CHARM trial, adalimumab maintenance therapy produced significantly superior 1-year remission rates compared to placebo, although the proportion was slightly higher in the group receiving a weekly dosage compared to every other week (41% and 36%, respectively, both

compared to placebo 12%; $P \leq .008$).[8] The ENACT-2 study showed that natalizumab produced significantly higher remission rates after 60 weeks of maintenance therapy compared with placebo (55% vs 22%; $P \leq .003$).[4] If one considers the patients that maintained remission continuously over 60 weeks, the number of patients in remission is still much higher than that in the placebo group. Although this rate was reduced for the subset of patients sustaining remission at every assessment over the 60-week trial, it was still significantly superior to placebo (39% vs 15%, respectively; $P \leq .003$).

Loss of Response to Anti-TNF Therapies

Many patients experience a secondary loss of response to anti-TNF agents, evidenced by the need for dose escalation. This may be due to several factors, including immunogenicity against the antibody, the development of improved clearance of the biologic, or an alteration in the immunological mechanism causing the inflammation. Further analysis of the ACCENT I trial showed that 30% of patients receiving 5 mg/kg infliximab and 26% receiving 10 mg/kg infliximab required dose escalation either up to 10 mg/kg or 15 mg/kg, respectively.[9] This intervention is often used in the clinical setting for patients not responding to the recommended dosage of 5 mg/kg and it has been shown that response can be recaptured in 84.2% of these patients. Similarly, 46% of patients receiving open-label maintenance adalimumab required dose escalation from every other week to weekly administration.[10]

For patients who have lost response to one anti-tumor necrosis factor (TNF) agent, response may still be achieved with alternate anti-TNF agents. Because infliximab was the first anti-TNF agent approved for CD, patients who have lost response to this agent are now under evaluation for their ability to respond to other anti-TNF agents. The GAIN trial has assessed the activity of adalimumab in patients who have either experienced a previous loss of response to infliximab or are unable to tolerate infliximab.[11] In this study, patients were randomly assigned to receive either placebo or adalimumab at weeks 0 and 2. Significantly more patients in the adalimumab group achieved a remission at week 4 compared to placebo (21% vs 7%, respectively; $P < .001$). Similarly, more patients also achieved a response, measured by a 70-point decrease in CDAI (52% vs 34%, respectively; $P = .001$). However, although each of these rates of response and remission were superior to placebo, it should be understood that they are lower than those observed in infliximab-naïve patients. When the GAIN trial was compared to the CLASSIC study, which tested similar adalimumab regimens in an infliximab-naïve population, there was a 15% difference in the proportion of patients achieving remission (21% vs 36%, respectively).[2] The CHARM trial also showed that infliximab-naïve patients maintained superior rates of remission to week 56 of adalimumab therapy, compared with those patients who had previously failed or were unable to receive infliximab. This was true both for doses given every other week (42% vs 31%, respectively) and weekly (48% vs 34%, respectively). This trend is not specific for adalimumab, as data from the PRECISE II trial of certolizumab pegol revealed. When patients were stratified according to previous infliximab exposure, more infliximab-naïve patients maintained a response from week 6 to week 26, compared to those who had previously received infliximab (69% vs 44%, respectively), although the response rates in both groups were significantly superior to placebo.[12]

Roughly one third of patients do not respond to an anti-TNF agent, which is defined as a primary lack of response. This has been attributed to several factors, including the different mechanisms of inflammation that do not involve or depend on TNF and patients with no inflammation present. One study has associated high levels of systemic inflammation, measured by elevated C-reactive protein (CRP) levels, with a better response to anti-TNF agents, and therefore patients with normal levels may have a reduced response.[13] Other factors, including a positive perinuclear antineutrophil cytoplasmic antibody, have been associated with reduced response, whereas polymorphism in the immunoglobulin G Fc receptor IIIa gene is associated with increased response to infliximab, although this has not yet been validated.[14-16] Smoking is highly contraindicated for patients receiving anti-TNF therapy, as the response rate in these patients is similar to placebo.[17]

Whether patients with a primary lack of response would benefit from subsequent anti-TNF therapy has not been tested, although clues may be garnered from the original infliximab study. In this trial, patients were originally blindly randomized to receive either infliximab or placebo.[1] After an evaluation at week 4, nonresponders were allowed to receive open-label infliximab. Of these patients who had initially received placebo, 58% and 48% went on to experience a response or remission to open-label infliximab, respectively. However, a smaller number of patients who had originally received infliximab went on to achieve a response or remission during the open-label portion of the trial (34% and 17%, respectively). Although the total number of the patients in the open-label portion of this study was small, the results indicate that some patients simply will not respond to anti-TNF therapy. Therefore, these patients may respond to other biologic agents not directed against the TNF-based mechanism of inflammation.

Natalizumab is a humanized monoclonal antibody directed against the α4-integrins, which are cell sur-

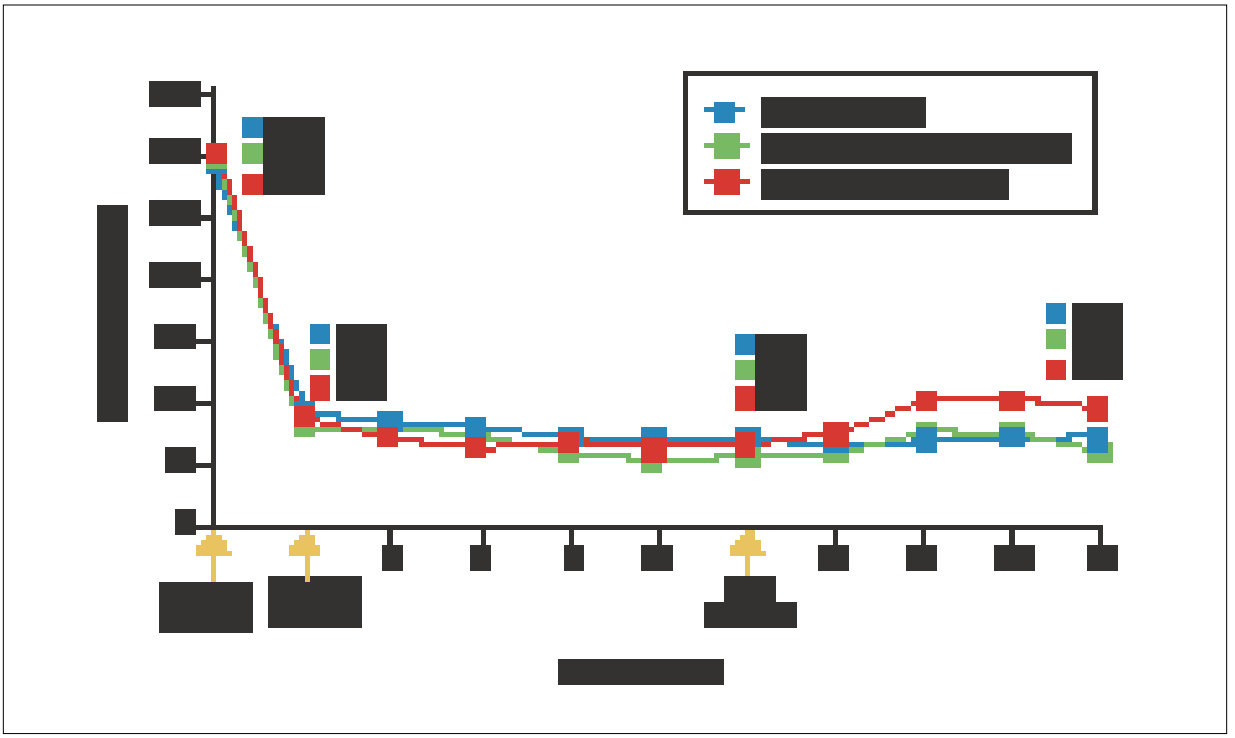

Figure 1. Long-term efficacy of natalizumab: mean Crohn's Disease Activity Index (CDAI) Score over 24 months of continuous treatment.

OLE=open-label extension; TNF=tumor necrosis factor.

Adapted from Panaccione R, et al.[21]

face molecules expressed on the surface of leukocytes. α4-integrins, in association with either the β1- or β7-integrins, are required for adhesion to and migration of leukocytes across the epithelium. This occurs through interaction of the α4/β1- and α4/β7-integrin heterodimers with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and vascular cell adhesion molecule-1 (VCAM-1) ligands on the surface of endothelial cells.[18,19] Natalizumab was designed to block the α4-integrin, thereby inhibiting leukocyte migration into the intestinal epithelium.

Importantly, this unique mechanism of action may allow patients who do not respond to anti-TNF therapy to benefit from natalizumab. Indeed, data from the ENACT-2 trial showed similar rates of 1-year remission in patients with or without prior anti-TNF exposure.[20] Additionally, when patient response to natalizumab was monitored over the long term, through the ENACT-1 and -2 trials, followed by the open-label extension trial, there was virtually no difference in patients who had previously been exposed to an anti-TNF agent, those who had failed a previous anti-TNF, and the overall treatment population (Figure 1).[21]

Patient Considerations of Risk/Benefit

Although technical definitions of efficacy to biologic agents are important for clinical decisions, an important point to consider is what the patient considers an appropriate benefit-risk ratio. In one survey of CD patients, patients were presented with different scenarios of events that could occur after receiving a particular therapy.[22] These scenarios included the possibility of developing progressive multifocal leukoencephalopathy (PML), tuberculosis (TB), or lymphoma. Patients were then offered the possibility that their disease symptoms could improve within defined limits, but they would run the risk of developing each of these toxicities. Overall, patients were willing to accept a far greater risk of toxicity than the risk actually associated with these biologic agents. This was especially true for patients with severe disease who were offered the potential to reduce severity to either mild symptoms or complete remission.

Long-term Outcomes

In addition to achieving remission, the ability of these agents to prevent or reduce hospitalization and surgery is also an important factor when considering therapy. Data

from ACCENT I show that patients receiving a scheduled regimen of infliximab had significantly fewer hospitalizations and required significantly fewer surgical resections.[9] Similarly, adalimumab therapy produced a dramatic reduction in the number of hospitalizations required compared to placebo over a 12-month period (8.0% vs 15.7%, respectively).[23] Hospitalizations were also reduced with natalizumab therapy in a pooled analysis of the ENACT-1 and ENCORE trials, particularly in patients that failed anti-TNF therapy.[24]

The Role of Biologics in Corticosteroid Sparing

Remo Panaccione, MD, of the University of Calgary, spoke about the use of corticosteroids in the treatment of CD. By first reviewing the original studies that showed the efficacy of corticosteroids in inducing disease remission, Dr. Panaccione illustrated the benefit these drugs have in disease control. He then discussed the drawbacks of corticosteroid therapy for CD, including the serious toxicities associated with treatment. This was followed by a discussion summarizing the role of other agents, particularly biologic therapies, as corticosteroid-sparing treatments.

Corticosteroids in CD

The routine clinical use of corticosteroids in CD is based on the success of three historical and pivotal trials. In the NCCDS study, prednisone (0.25–0.75 mg/kg/day) administered over 17 weeks resulted in a 61% remission rate, compared to only 40% in patients receiving placebo.[25] Higher doses of prednisone (60 mg/day) were subsequently tested in the ECCDS trial, which showed an 83% remission rate in the prednisone arm, compared with 38% in the placebo arm, after 18 weeks.[26] Finally, the GETAID study tested prednisolone (1 mg/kg/day) administered over at least 3 but not more than 7 weeks.[27] A remarkably high rate of remission, 92%, was noted by 7 weeks of therapy. However, no benefit for maintenance of remission was noted for corticosteroids compared to placebo in either the NCCDS study (25% vs 24%, respectively) or the ECCDS trial (23% vs 30%, respectively).[25,26]

In an important population-based study of prednisone treatment for CD, Munkholm and colleagues created a model to predict CD patient response to corticosteroid therapy (Figure 2).[28] In this study of 109 patients, 20% were found to have no initial response to prednisone treatment after 1 month, 32% experienced an improvement in CD symptoms, and the remaining 48% achieved clinical remission. However, when responding patients were followed over the course of 1 year, a large proportion experienced a disease relapse after discontinuation of corticosteroids (43% and 46% of those originally experiencing either disease improvement or remission, respectively). This led Munkholm to predict that in a given CD patient population, although 44% have a prolonged response to corticosteroid treatment, 56% of patients develop an undesirable outcome, with 20% exhibiting initial corticosteroid-refractory disease and 36% developing corticosteroid-dependent disease.

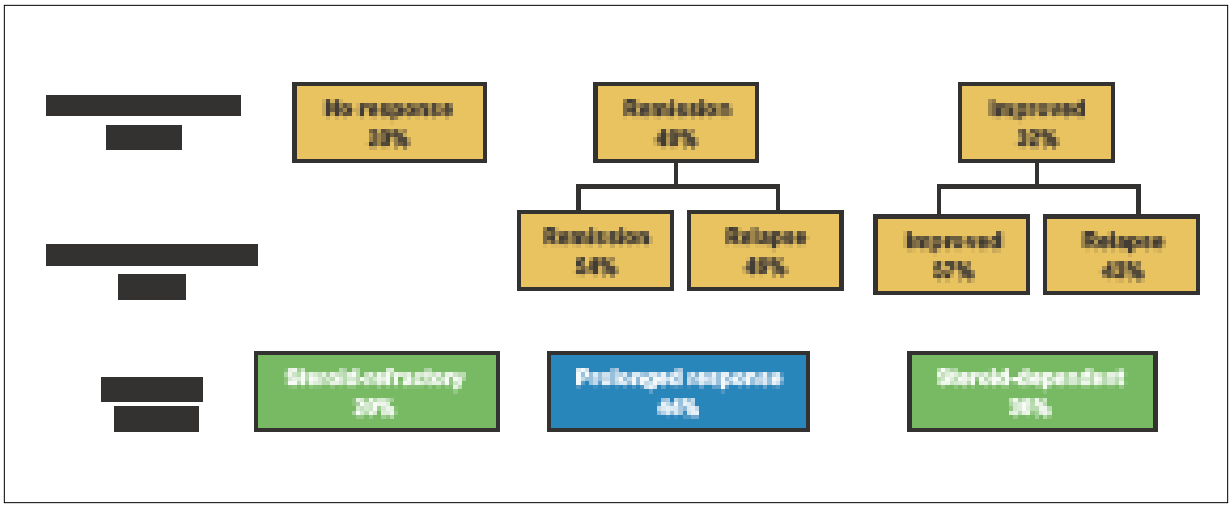

Figure 2. Why the present paradigm must change: natural history of corticosteroid therapy.

Adapted from Munkholm P, et al.[28]

Because this study was performed in a European cohort, a similar study was performed in the United States to account for population differences.[29] The results of the US study were strikingly similar, showing that 1 year after the initiation of prednisone, 32% of CD patients experienced a prolonged response but 28% developed corticosteroid-dependent CD. Additionally, this study further showed that 38% of patients actually required a surgical resection because of increased disease activity following prednisone withdrawal.

One explanation for the lack of long-term efficacy in so many patients may be revealed by a careful analysis of the GETAID trial.[27] Although a very high (92%) rate of remission was documented in CD patients following prednisolone therapy, only 29% of these individuals actually exhibited mucosal remission upon endoscopy. In fact, 9% actually displayed worsening of the intestinal mucosa. Together, this endoscopic analysis reveals that although corticosteroids offer a great deal of benefit in alleviating the symptoms of CD, they are unable to truly improve the mucosal damage resulting from CD inflammation. For this reason, responses and remissions induced by corticosteroids are unlikely to have long-reaching effects.

Additionally, significant toxicities have long been attributed to long-term corticosteroid use. Over the decades in which corticosteroids have been used for the treatment of CD, numerous toxicities have been described. These include metabolic, musculoskeletal, gastrointestinal, cutaneous, ocular, and neuropsychiatric toxicities, as well as growth inhibition in pediatric patients. The TREAT registry, which at last report contained 6,290 CD patients, is an ongoing study allowing for long-term follow-up of patients receiving both biologic and nonbiologic treatments for CD.[30] One of the most worrisome realizations from initial analyses of the TREAT registry is that prednisone use is associated with a far greater risk of both serious infection (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.46–3.34; $P<.001$) and mortality (OR, 2.10, 95% CI, 1.15–3.83; $P=.016$) than both infliximab and immunosuppressants. Similarly, the recently reported results of the ENCORE registry, a postmarketing safety surveillance registry from Europe, also showed that prednisone use carries a serious safety concern.[31] In this registry, prednisone was found to be independently associated with the development of serious infection ($P=.009$).

Biologic Strategies to Eliminate Corticosteroids for CD

Both infliximab and adalimumab have shown promising ability to induce and maintain corticosteroid-free remission in CD patients. In the ACCENT I trial, 2 doses of infliximab (5 mg/kg and 10 mg/kg) administered over 54 weeks both resulted in modest rates of corticosteroid-free remission (24% and 32%, respectively).[6] Comparatively, adalimumab (40 mg) produced similar corticosteroid-free remission rates in the 56-week CHARM study, when administered either every week (23%) or every other week (29%).[8] The recently reported results of an open-label extension of CHARM further showed that 25% of patients who had entered the CHARM study on corticosteroid therapy were in corticosteroid-free remission after 24 months of adalimumab therapy.[32]

Although these results are promising, the goal remains to improve long-term remission rates beyond 25%. One possible strategy to attain this goal is to utilize biologic agents earlier in the course of CD. This was recently tested in a study comparing the standard step-up versus the more aggressive top-down strategy.[33] In this study, 133 CD patients were randomized to receive either conventional treatment consisting of corticosteroids followed by sequential immunosuppressants and infliximab as needed or the top-down regimen, in which patients skipped the corticosteroids and received infliximab in combination with azathioprine. After 1 year, the rate of corticosteroid-free remission induced by the top-down approach was nearly twice that seen with infliximab alone in the ACCENT I study (62% vs 24%, respectively). Importantly, this 62% remission rate was significantly higher than that observed in patients receiving step-up therapy (42%; $P=.028$). However, at 2 years, there was no difference between patients receiving either step-up or top-down therapy (50% vs 57%, respectively; $P=.431$).

Natalizumab has also gained attention for its ability to induce and maintain corticosteroid-free remission in CD patients. In fact, data from the ENACT-2 study have revealed that the majority of patients categorized as responding to natalizumab also achieved disease remission.[34] Further, the ENACT trials have shown that natalizumab can effectively lead to long-term corticosteroid elimination. At 15 months, the proportion of patients successfully eliminating corticosteroid therapy was statistically superior in the natalizumab arm compared to placebo (49% vs 20%, respectively; $P<.001$). This resulted in significantly superior rates of corticosteroid-free remission in patients receiving natalizumab after 15 months compared to placebo (42% vs 15%, respectively; $P<.001$).[4]

Data from an open-label extension study of natalizumab have also provided encouraging evidence of the ability of natalizumab to maintain long-term (greater than 2 years) disease remission.[35] For patients who were in remission after 12 months of continued natalizumab therapy in the ENACT-2 study, 86% of patients continued to maintain disease remission for an additional 12 months in the open-label ENABLE study. Those patients with previous exposure to an anti-TNF biologic agent, 91%

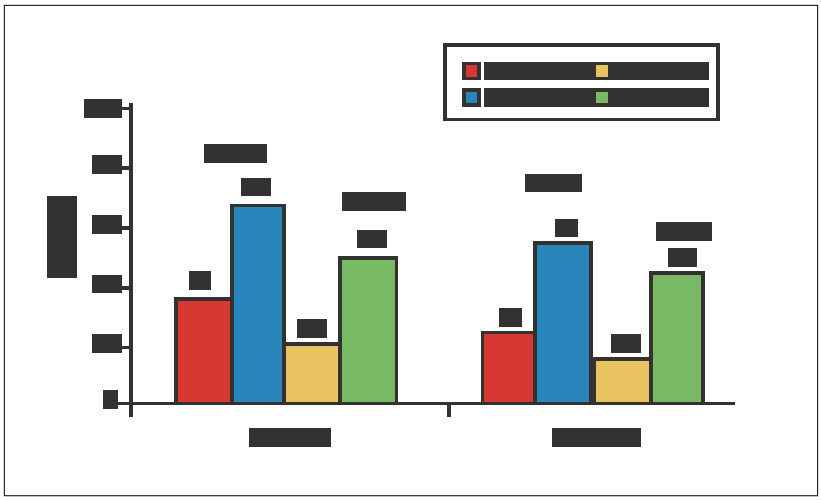

Figure 3. Corticosteroid sparing with and without concomitant immunosuppressants: data from ENACT-2.

Adapted from Panaccione, et al.[36]

maintained disease remission with extended natalizumab therapy. Importantly, 82% of patients who had previously failed an anti-TNF agent were able to maintain CD remission on extended natalizumab therapy. Similar proportions of patients also experienced corticosteroid-free remission, the gold standard for determining the success of CD therapy.[21]

Another important point from the ENACT-2 trial was that the concomitant use of immunosuppressant therapy had no statistical effect on the ability of natalizumab to allow successful corticosteroid elimination for CD therapy. After 12 months of treatment, the difference in patients receiving immunomodulators with either placebo or natalizumab (P=.011) was similar to the difference in patients receiving either placebo or natalizumab with no concomitant immunomodulators (P=.011; Figure 3).[36] The ENCORE induction study and ENACT-2 maintenance trial both also showed similar rates of response and remission, respectively, for patients receiving natalizumab either with or without concomitant immunomodulators and corticosteroids.[20]

Neurologic Concerns in the Biologic Treatment of CD

In his discussion, David Brandes, MS, MD, of the Northridge Neurological Center, summarized the current understanding of the relationship between CD and neurologic abnormalities. As a neurologist, he first discussed evidence of a possible link between inflammatory bowel disease (IBD) and multiple sclerosis (MS). This was followed by a review of the neurologic toxicities associated with agents used in the treatment of CD.

Association Between IBD and MS

Although a link between MS and IBD has long been suggested, the lack of large-scale population-based studies has not allowed a definitive association to be made. The concept that diseases such as MS and IBD stem from a general susceptibility for autoimmunity disorders has received increasing attention with the publication of several studies addressing the clustering of autoimmune diseases within families.[37,38] In one study, US families with at least 2 members with clinically diagnosed MS were analyzed for patterns of coexisting autoimmune diseases.[39] The dataset included 210 MS patients from 176 index cases and 1,317 first-degree relatives (comprised of 656 siblings, 309 children, and 352 parents). In the overall distribution of coexisting autoimmune disorders among MS patients, IBD was found to be among the most prevalent, with 3% of MS patients reporting coexisting IBD disease. In this analysis, both ulcerative colitis (UC) and CD were considered. When the family members of these index cases were then analyzed, a similar pattern of coexisting autoimmune disorders was apparent. Among the first-degree relatives of the 176 MS index cases, the overall prevalence of IBD was again found to be 2%.

Another study explored the link between MS and IBD from the opposite direction. This report assessed the relative risk of developing other chronic inflammatory diseases in patients with IBD.[40] Using a database from the University of Manitoba in Canada, patients diagnosed with IBD were cross-referenced for coexisting diagnoses of chronic inflammatory diseases. Of the 8,072 IBD cases identified over a 10-year period, 3,879 were UC and 4,193 were CD. Only UC patients, and not those with CD, exhibited an increased risk for developing MS (prevalence

ratio [PR], 1.90; 95% CI, 1.19–3.03). Interestingly, this increased risk for UC patients was confined to males, despite the higher prevalence of MS in the female population.[41] Conversely, a link between CD and MS was found in a retrospective cross-sectional analysis from the United Kingdom's General Practice Research Database.[42] Here, CD patients were shown to have a 54% increased risk of developing demyelinating disorders, including MS (OR, 1.54; 95% CI, 1.03–2.32). However, as with the Manitoba study, the risk in UC patients was higher, up to 75% (OR, 1.75; 95% CI, 1.28–2.39). In addition to these two studies, other recent reports have also detailed increased risks for developing MS among patients with IBD.[43-45]

Together, both the familial and patient studies discussed here lend further evidence to a putative relationship between IBD and MS and suggest that these diseases share common etiologic factors. Although the link appears stronger between MS and UC, the relationship between these autoimmune diseases is not fully understood, and it is clear that future studies in both UC and CD patients are needed to more fully examine these associations. However, the possible relationship between IBD and MS is of particular concern in light of the fact that several therapies used to treat CD show an increased potential for the development of neurologic toxicities.

Neurologic Toxicities of CD Therapies

Metronidazole is an oral synthetic agent with both antiprotozoal and antibacterial properties, commonly used in treating CD. However, long-term use of metronidazole may result in neurologic toxicities, especially peripheral neuropathy.[46] Case-based reports have shown that these symptoms are most often reported in patients who receive high doses of metronidazole (15–20 mg/kg/day), particularly after a cumulative dose of more than 30 g.[47-49] Although the neurologic symptoms that result from metronidazole administration are generally reversible upon discontinuation of the drug, symptoms in some patients may persist for up to 2 years.[50]

Neurologic toxicities have also become an apparent adverse effect of the biologic therapies used to treat CD. Several reports have been made of patients receiving anti-TNF therapy who either experienced a new onset of MS or a flare of existing MS.[51-54] Other neurologic events have also been reported after administration of anti-TNF agents, including various demyelinating disorders, optic neuritis, seizure, and systemic vasculitis that manifested within the central nervous system (CNS).[54,55] Because TNF is thought to be part of the triggering mechanism for the onset of MS, the induction of MS symptoms by anti-TNF agents is especially confusing, and several clinical trials testing anti-TNF agents for treatment of MS have failed.[56-58] Although no specific monitoring of neurologic toxicities is prescribed for CD patients receiving anti-TNF therapy, cautious use is advised in patients with either preexisting or recent onset of demyelinating or seizure disorders.[59]

Unlike the anti-TNF agents, natalizumab has come under intense scrutiny for its potential to promote the rare and often fatal infection, PML. Originally approved for the treatment of MS, it was voluntarily withdrawn from the market in February 2005 after 3 confirmed cases of PML were reported in clinical trials. Of these cases, 2 occurred in patients receiving treatment for MS, while 1 occurred in a CD patient.[60-62] These patients all received combination therapy with immune-affecting drugs (interferon or azathioprine). After these cases were discovered, an extensive review of all patients who had received natalizumab was performed. In a total of 3,116 patients (with a mean of 17.9 monthly natalizumab doses) who underwent evaluation for PML, no further cases were detected.[63] Therefore, this finding equated to an estimated risk of approximately 1 in 1,000 (95% CI, 0.2–2.8 in 1,000) for the development of PML. This risk was considered to be extremely low, causing the US Food and Drug Administration to recommend that the drug be returned to the market.[64] Natalizumab was re-introduced for MS as monotherapy and subsequently approved for the treatment of CD in patients wtih evidence of inflammation who have not responded to conventional therapies and anti-TNF agents.

PML is a serious and often fatal condition caused by infection with the JC polyomavirus.[65] Although infection by the JC virus can be a common event, especially during childhood, the infection generally remains latent and therefore asymptomatic. However, reactivation of the virus in immunosuppressed individuals can result in PML. Two clinical presentations have been described to identify the onset of PML.[66] Patients may experience subacute progression of focal neurologic deficits, leading to visual, motor, or sensory losses. PML may also present as cognitive impairments or behavioral alterations.

The sobering nature of a PML diagnosis is a reflection of the lack of effective treatments for the condition.[65] No antivirals are known to be effective as treatment, and only investigational drugs are currently available as treatment for PML. At a recent meeting of the American Academy of Neurology, two abstracts established plasma exchange as the best potential therapy currently available in the event of natalizumab-induced PML. The PLEX study was an open-label single-arm exploratory trial designed to test if natalizumab was effectively removed after plasma exchange. In an analysis of 12 patients, plasma exchange was found to accelerate the decline of natalizumab plasma concentration.[67] A substudy analysis of these patients further showed that

removal of natalizumab from the circulation removed natalizumab from the leukocyte surface and facilitated the penetration of leukocytes into the CNS, where they could potentially more effectively fight off a JC viral infection.[68] From these studies, it is now apparent that in the event of natalizumab-induced PML, the best immediate response is to subject the patient to 5 plasma exchanges, spaced out every other day.

Monitoring the Risk of Natalizumab-associated PML

Currently, natalizumab is only available in the United States through the TYSABRI Outreach: Unified Commitment to Health (TOUCH) prescribing program. This restricted distribution program was designed both to ensure that natalizumab was appropriately administered and to closely monitor patients for the onset of any symptoms suggestive of PML.[64] Under the TOUCH program, only enrolled prescribers and patients may prescribe and receive natalizumab, and only registered pharmacies and infusion centers may dispense and administer the agent. All parties involved receive extensive education regarding the proper use and possible adverse effects of natalizumab.[69] Although monitoring for PML symptoms is especially emphasized, all adverse events are reported through this program, allowing a complete overall safety profile of natalizumab to be developed.

With the approval of natalizumab for CD, the TOUCH program was slightly modified for CD patients. Because natalizumab is indicated for reducing the inflammatory activity of CD, patient response can be determined relatively quickly, unlike in the MS setting. For CD patients, natalizumab is discontinued if no response is observed within 12 weeks of treatment initiation. Additionally, although the concomitant use of immunosuppressants such as azathioprine and methotrexate is not permitted, CD patients are allowed to continue concomitant corticosteroid therapy for up to 6 months after natalizumab is initiated.

To augment the TOUCH program, several other monitoring databases have been established to follow patients receiving natalizumab. The TYGRIS program, with an expected enrollment of approximately 5,000 MS patients, is currently evaluating the long-term safety of natalizumab therapy in a clinical practice setting.[70] A similar program, INFORM, plans to enroll approximately 2,000 CD patients. STRATA is a study designed to follow patients who discontinued natalizumab, after it was removed from the market, and have since re-initiated therapy. Preliminary data from the STRATA study show that infusion reactions with re-initiated natalizumab are much more likely to occur in patients receiving only 1–2 initial doses compared with those receiving more than 5 initial infusions.[71]

Overall, over 36,000 patients have received natalizumab. Each of these patients has undergone careful monitoring and no further cases of PML have been documented. However, it is important to note that the initial 3 cases did not arise until after 2–3 years of therapy, and because most patients have not yet received long-term natalizumab therapy, continued follow-up is warranted.

Treatment Algorithms: Decision-Making That Achieves an Appropriate Balance

William Sandborn, MD, of the Mayo Clinic in Rochester, Minn., concluded the symposium with a discussion of how recent advances in the treatment of CD can best be incorporated into clinical practice. Dr. Sandborn first addressed the current step-up treatment modality used for CD.

Management of Mild-to-Moderate CD

According to the American College of Gastroenterology (ACG), mild-to-moderate CD refers to ambulatory patients who can tolerate an oral diet without exhibiting signs of dehydration, abdominal tenderness, a painful mass or obstruction, a greater than 10% weight loss, or symptoms of toxicity, including high fever, rigors, or prostration.[72] In the 2001 ACG guidelines, frontline therapy for mild-to-moderate CD is limited to oral aminosalicylates such as mesalamine (5-aminosalicylate) and sulfasalazine, metronidazole for patients not responsive to sulfasalazine, the antibiotic ciprofloxacin, and the controlled ileal-release formulation of budesonide, a corticosteroid with fewer associated adverse events. However, many patients continue to experience symptoms associated with the progression of CD while on these therapies. Because of this, future ACG guidelines are expected to highlight the general lack of evidence for the efficacy of oral aminosalicylates and antibiotics in mild-to-moderate disease. Instead, budesonide will be highlighted as effective treatment options for patients with CD limited to the terminal ileal and proximal colon.

More recent guidelines published by the American Gastroenterological Association (AGA) in 2006 specifically address the use of corticosteroids in both induction and maintenance therapy for mild-to-moderate CD.[73] The AGA also recommends controlled ileal-release budesonide for CD with ileal and proximal colonic involvement, based on evidence showing that budesonide is more active than mesalamine and nearly as effective as conventional corticosteroids with fewer associated adverse effects.[74] Although budesonide is active as induction therapy, studies that have evaluated budesonide as maintenance therapy show it is effective for only

short-term maintenance (approximately 3 months) and fails to produce a long-term response over extended (1-year) administration.[74]

Recently, an evidence-based treatment algorithm was developed specifically for induction therapy in patients with mild-to-moderate CD, dependent on the degree of colonic involvement.[75] The evidence for the treatment of CD involving the ileum or the proximal colon is fairly strong, warranting budesonide therapy (9 mg/day) for 8–16 weeks. For patients with CD of the left colon, the algorithm suggests sulfasalazine (3–6 g/day) over a course of 16 weeks. In both cases, prednisone (40–60 mg/day) is recommended for patients who fail or are unable to tolerate these recommended treatments. However, the continued maintenance therapy for mild-to-moderate CD is less clear, consisting of relatively few options.[75] One option is to continue maintenance therapy with budesonide (6 mg/day) after budesonide induction, although this is currently limited to a recommended 3 months of therapy.[74] A second option is to transition the patient immediately to immunosuppressants. However, although this has been shown to be efficacious for maintaining corticosteroid-induced remissions, there is currently no evidence showing it is capable of maintaining sulfasalazine-induced remissions. Finally, some physicians may opt to discontinue therapy altogether during the maintenance phase, which is associated with a 75% risk of relapse over the course of 1 year.[75] As of yet, the optimal maintenance therapy for mild-to-moderate CD has not been identified, and therefore most patients will eventually progress to more severe disease requiring more effective therapies.

Management of Moderate-to-Severe CD

According to the ACG, patients with moderate-to-severe CD have either failed to respond to previous corticosteroid therapy or exhibit more prominent disease symptoms, including high fevers, significant weight loss, abdominal pain, significant anemia, or intermittent nausea and vomiting without associated obstructions.[72] Using the 2001 ACG guidelines, induction therapy of moderate-to-severe CD begins with corticosteroids, either prednisone or budesonide, generally continued over 7–28 days or until symptom resolution or weight gain. For maintenance therapy of moderate-to-severe CD, the ACG guidelines recommend against the long-term use of corticosteroids and instead suggest immunosuppressant agents. Although the guidelines recommend mesalamine or azathioprine as maintenance therapy following ileocolonic resection, more recent evidence suggests that these are not very effective in the postoperative setting.[76]

Similarly, the more recent guidelines published by the AGA in 2006 also recommend corticosteroid use as induction therapy for all forms of moderate-to-severe CD, except in the case of perianal fistulas.[73] In the setting of active corticosteroid-dependent CD, azathioprine and 6-MP are recommended. These immunosuppressants are also suggested for patients with a high risk of postoperative recurrence or who have existing perianal and enteric fistulas. Alternatively, methotrexate is recommended for parenteral induction of remission. Conventional corticosteroids are not recommended for long-term maintenance therapy of moderate-to-severe CD, and budesonide is only recommended for maintenance therapy up to approximately 3 months. Instead, the immunosuppressants azathioprine, 6-MP, and methotrexate are all indicated for use as maintenance therapy following corticosteroid-induced remission.

Recently, an important summary of the AGA Consensus Development Panel on the use of biologic therapy was published, which compared all four biologic agents currently available for CD: infliximab, adalimumab, certolizumab pegol, and natalizumab.[77] All four agents are indicated for both induction and maintenance of response and remission in CD, although natalizumab has the additional caveat of being used only in patients with evidence of active inflammation. However, among the four, there are no data for the use of certolizumab pegol in corticosteroid-sparing disease. No studies have tested certolizumab pegol or natalizumab in fistulizing disease, and therefore only infliximab and adalimumab have been demonstrated effective in this setting, with adalimumab being reserved for treatment of only perianal fistulas. Currently, only infliximab is recommended for use in hospitalized patients with severe disease. Infliximab is also suggested for alleviation of extraintestinal CD manifestations. Adalimumab, certolizumab pegol, and natalizumab all carry indications for use in patients with either a loss of response or intolerance to infliximab. This same report also summarized the current consensus on the recommended doses of each of these biologic agents, both as induction and maintenance therapy.[77]

The AGA Consensus Development Panel also described several factors which should be considered as contraindications for the use of biologic agents in CD.[77] These include a known severe hypersensitivity to these agents, an active infection or a latent TB infection, pre-existing demyelinating disorders, congestive heart failure, or a current or recent malignancy. In addition to these contraindications, natalizumab also carries a recommendation against use in patients with previous PML disorders. The panel recommended against continued biologic therapy in the event of either a lack of response or a short response duration with induction therapy.

Table 1. American Gastroenterological Association Consensus Development Panel on Use of Biologics: Dosing

Infliximab	Induction	• 5 mg/kg intravenous at wk 0, 2, and 6 (benefit of 6-wk infusion not established) • Primary nonresponse can be determined after 2 doses – Benefit from third infusion has not been shown – Patients not responding to the initial 2 doses should be discontinued
	Maintenance	• Every 8 wk beginning at wk 14 in responding patients • Attenuated response – Higher doses ≤10 mg/kg at 8-wk intervals – 5 mg/kg at shortened intervals as frequently as every 4 wk
Adalimumab	Induction	• 160 mg subcutaneous (SC) on day 1 of wk 0, followed by 80 mg SC on day 1 of wk 2 – 80 mg followed by 40 mg may also be effective – Subsequent response in 4-wk nonresponders has not been established
	Maintenance	• 40 mg SC every other wk in responding patients • Suboptimal response – Increase frequency of dosing to 40 mg SC weekly or 80 mg every other week • Episodic dosing not evaluated; may increase immunogenicity
Certolizumab pegol	Induction	• 400 mg SC at wk 0, 2, and 4 – No evidence of benefit for additional treatment in wk 6 nonresponders
	Maintenance	• 400 mg SC every 4 wk in responding patients – Anticipate similar recommendations to other anti-TNFs regarding higher dose/reduced-interval treatment
Natalizumab	Induction	• 300 mg intravenously given at wks 0, 4, and 8
	Maintenance	• 300 mg intravenously given every 4 wks

Adapted from Clark M, et al.[77]

Future Treatment Algorithms for CD

Although the current step-up CD therapeutic strategy is the most frequently used, an alternative treatment plan has gained increasing attention. The top-down strategy begins induction treatment with biologic therapy, which can be followed by maintenance therapy with the biologic agent plus immunosuppressants. In response to disease progression, the patient undergoes re-treatment with the biologic agents, and subsequently corticosteroids.

Two trials have tested the need for concomitant immunosuppressants with infliximab during maintenance therapy. The IMID trial was designed to evaluate the efficacy of infliximab as single-agent maintenance therapy.[78] This study included patients experiencing more than 6 months of remission while receiving a maintenance regimen of infliximab combined with azathioprine. Patients were randomized to either continued maintenance therapy with this combination, or discontinued azathioprine, receiving only infliximab monotherapy. Over a 2-year follow-up, no significant differences in either clinical or endoscopic outcomes were noted between the two groups. The COMMIT trial showed similar results in a population with corticosteroid-refractory disease who were naïve to both biologic agents and immunosuppressants.[79] In this study, patients were randomized to receive either single-agent infliximab or infliximab combined with methotrexate. After a 1-year follow-up, no differences in the rate of corticosteroid-free remissions were noted between the treatment groups. Given the increased risk of infection and lymphoma associated with the combination of immunosuppressants and biologic agents, the results of both the IMID and COMMIT trials suggest that infliximab monotherapy should be considered as maintenance therapy, and immunosuppressants should be avoided in this situation.

In conclusion, biologic agents have added an important option in the treatment strategy for CD. Although most current recommendations suggest a step-up approach to therapy, emerging data suggest a top-down approach may be a more effective alternative. In the future, many treatment algorithms will seek to improve the overall risk-benefit profile of therapy, including the reduction of immunosuppressant agents.

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Updates from the Front Lines of Crohn's Disease: Achieving a Balance Between Safety and Efficacy

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

1. The GAIN trial showed that _____ of patients with previous exposure to infliximab achieved disease remission at week 4 following _____ therapy.

   a. 7%; adalimumab
   b. 21%; adalimumab
   c. 52%; adalimumab
   d. 21%; infliximab

2. The unique mechanism of action of _____, which is a humanized monoclonal antibody directed against the α4-integrin, may benefit patients who do not respond to anti-TNF agents.

   a. adalimumab
   b. infliximab
   c. natalizumab
   d. certolizumab pegol

3. The GETAID trial provided evidence for why corticosteroids do not induce a long-term benefit in CD, when it was shown that only _____ of patients exhibited mucosal remission after prednisone therapy.

   a. 9%
   b. 29%
   c. 38%
   d. 92%

4. In the TREAT registry, corticosteroid use has been associated with an increased risk of mortality, with an OR of _____.

   a. 2.10
   b. 2.21
   c. 2.45
   d. 3.10

5. The ENACT trials have shown that after 15 months, natalizumab produces a significantly superior rate of steroid-free remission, _____, compared with placebo.

   a. 15%
   b. 36%
   c. 42%
   d. 49%

6. A study from the United Kingdom's General Practice Research Database shows CD patients have a _____ increased risk for developing demyelinating disorders.

   a. 27%
   b. 49%
   c. 54%
   d. 75%

7. The risk associated with the use of natalizumab, PML, is carefully monitored through the _____ program.

   a. PLEX
   b. ACCENT
   c. TYSABRI
   d. TOUCH

8. According to the ACG guidelines, frontline therapy for mild-to-moderate CD consists of _____, in addition to metronidazole, ciprofloxacin, and budesonide.

   a. oral aminosalicylates
   b. azathioprine
   c. infliximab
   d. natalizumab

9. Using the step-up approach for treating moderate-to-severe CD, patients begin induction therapy with _____.

   a. immunosuppressants
   b. oral aminosalicylates
   c. corticosteroids
   d. either b or c

10. True or false? According to results from the IMID and COMMIT trials, single-agent infliximab can be considered as maintenance therapy for moderate-to-severe CD instead of in combination with immunosuppressants.

    a. True
    b. False

Evaluation Form: Updates from the Front Lines of Crohn's Disease: Achieving a Balance Between Safety and Efficacy

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 current treatment algorithm guidelines in the management of patients with Crohn's disease.	1 2 3 4 5
2. Review the benefit-risk profiles of new treatment options for Crohn's disease.	1 2 3 4 5
3. Identify the potential for neurologic and demyelinating disorders that may be associated with use of biologics in Crohn's disease.	1 2 3 4 5
4. Explain how to integrate new therapies into treatment strategies to improve 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

Name _____ Degree _____

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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 1.25 credits.

☐ I participated in only part of the activity and claim _____ credits.

Project ID: 5450ES34