

Clinical Roundtable Monograph

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Clinical Trials in Biologic Therapy for Crohn's Disease: Comparing Designs and Data

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Abstract: Crohn's disease is a chronic inflammatory bowel disease with no known cure, estimated to occur in more than 500,000 Americans. Induction and long-term maintenance of remission are the major goals of Crohn's disease therapy. Over the past several decades, standard therapy for Crohn's disease patients has included immunomodulatory drugs such as azathioprine and 6-mercaptopurine, anti-inflammatory drugs such as 5-aminosalicylate, steroids, and antibiotics. Unfortunately, many patients become refractory to therapy over time or dependent on therapies such as corticosteroids, which are not feasible for long-term use. Over the past decade, several biologic agents have emerged with potential to induce response of active disease and maintain remission in Crohn's disease patients. Most of these agents, including infliximab, adalimumab, and certolizumab pegol, target the pro-inflammatory cytokine tumor necrosis factor. Several pivotal clinical trials have been conducted to investigate the safety and efficacy potential of these agents. Infliximab was evaluated in the key ACCENT I and II studies, while certolizumab pegol has been studied in the PRECiSE 1-4 trials. Adalimumab has been extensively studied in CLASSIC I and II, as well as the GAIN and CHARM trials. Several thousands of CD patients treated with infliximab have also been followed through the TREAT registry, in order to determine long-term effects of the therapy. Although each of these trials have provided considerable data regarding individual agents, these agents have not been directly evaluated in a head-to-head comparison. Varying clinical designs and endpoints make comparison of data across clinical trials a complex task. This monograph will focus on methods and criteria to consider when judging similarities and differences among these biologic agents.

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: As research and approval of biologic therapies for Crohn's disease continues to develop, physicians need to understand the differences among the various therapeutic options in order to make informed treatment decisions for both short- and long-term care. The molecular differences of the various agents comprise only one component of this understanding. Clinical trials of these agents have varied significantly in terms of the patient populations recruited, definitions of response and remission utilized, and other clinical endpoints examined. A discussion among thought leaders, providing a nuanced understanding of different trial results, would be of value in comparing agents and tailoring therapy to individual patients. This discussion is best facilitated within the framework of a clinical roundtable monograph.

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

1. Summarize historic research of the biologic options for Crohn's disease.
2. Describe differences in trial design of different agents and how they may have effected outcomes.
3. Compare data from different trials while weighing the effect of trial designs on efficacy and safety outcomes.

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Examining Patient Populations Across Clinical Trials of Biologics

Edward V. Loftus, Jr., MD

Comparing Inclusion Criteria

The baseline characteristics and inclusion criteria of clinical trial populations are an important consideration when comparing outcomes.¹ Different trials have varying inclusion criteria, and therefore the baseline characteristics may differ across studies. These characteristics often influence the clinical response to biologic therapy, and therefore must be taken into account in order to fairly and accurately interpret differences in data. The inclusion criteria for a study population can be broad, increasing the ease with which patients can be recruited into the trial and allowing the results to be applied to the general population. However, broad inclusion criteria allow for the possibility that less responsive patients will be included, therefore risking a decrease in the overall response to the tested therapy. Narrow inclusion criteria produce a more homogeneous patient population that may prove to be more responsive to the test therapy, but may slow patient recruitment.²

Crohn's Disease Activity Index

The most widely used instrument to assess Crohn's disease (CD) severity in study participants is the Crohn's Disease Activity Index (CDAI), which is calculated by assessing eight distinct weighted clinical variables to compute a score that ranges from 0 to 600.³ These variables include the number of soft stools per day, the extent of abdominal pain, an assessment of general well-being, the number of existing complications (including fever, arthritis, and fistula among others), the need for antidiarrhetic medication, the presence of abdominal mass, the hematocrit level, and deviation of body weight. In general, patients with scores less than 150 are considered to be in disease remission, while scores greater than 450 are indicative of severely active disease. Nearly all of the randomized controlled trials which have assessed biologic therapy in CD describe an inclusion-criteria CDAI score between 220–450 points, denoting moderately active disease. Generally, the mean CDAI score within each trial is approximately 300 and is equally distributed across the treatment arms. In ACCENT I, the median CDAI was 297, while in PRECISE 1 and 2 the mean CDAI scores were 297–300 and 301–306, respectively.^{4–6} A major exception to this is the ACCENT II trial, which only focused on patients with fistulizing CD, in whom the CDAI score would not accurately reflect the degree of CD severity but

rather the extent of fistulizing disease.⁷ Despite its widespread acceptance, several criticisms of the CDAI have been raised, including the subjective nature and dependence on a patient's diary to calculate some of the variables.³ Other indexes to define CD severity exist, and other clinical assessments, including endoscopic or histologic disease activity, may also be used.^{8,9}

Duration of Disease

Another disease characteristic that can determine patient response to biologic therapy is the duration of CD. Several analyses of clinical trial results have found a correlation between a shorter time from diagnosis and better response to biologic therapy. For example, 26-week follow-up in the CHARM trial found that although patients with 5 years of disease or longer had superior remission rates over placebo (41% vs 14%, $P < .001$), this was still a smaller proportion than that in patients with diagnosed disease of 2 years or less (59%).¹⁰ Decreased response and remission rates in patients with longer durations of CD were also shown in a similar 26-week follow-up in the PRECISE 2 study.¹¹ Although remission rates remained superior in the treatment versus placebo groups, they fell from 68% in patients with a CD duration of less than 1 year to 44% in patients with a CD duration of greater than 5 years. Therefore, when comparing across clinical study results, the mean or median duration of disease of the enrolled patients should be considered to properly interpret any comparisons. The ACCENT I and II trials, which evaluated infliximab therapy in CD, comprised mainly patients with longer disease durations compared with other biologic therapy studies. This is not surprising when considering that infliximab was the first biologic therapy evaluated for CD patients at a time when many had exhausted all their other therapeutic options. In ACCENT I, the median duration of disease among all 573 tested patients was 7.9 years (range: 3.9–14.7 years).⁴ Interestingly, the mean disease duration was lower in patients who had responded to infliximab by week 2 compared with those who did not (7.5 years vs 9.3 years, respectively). The mean disease duration in the 282 patients randomly assigned to treatment arms in ACCENT II was even higher, 12.2±5.9 years.¹² Because the patients enrolled in ACCENT I and II had a relatively long duration of CD, their response to a biologic therapy such as infliximab could be predicted to be lower than expected. In contrast, the median disease duration in the PRECISE 1

and 2 trials were 5 years (range: <1–44 years) and 5–7 years (range: <1–43 years), respectively.^{5,6} The duration since CD diagnosis was not reported for either the CHARM or GAIN trials and thus cannot be taken into account when comparing efficacy results.

Surgical History and Fistulas

Various other complications and comorbidities may also impact response to a biologic therapy. If a patient had a previous surgical resection, there is evidence that they may not respond as well to treatment. Again, patients in the ACCENT I and II trials had a higher rate of previous surgical resection history (51% and 55–57%, respectively).^{4,7,12} Interestingly, when responders and nonresponders after 2 weeks of infliximab treatment were separately assessed in ACCENT I, a higher percentage of patients in the nonresponding group had a history of surgical resection versus those in the responding group (60% vs 44%, respectively). The rate of previous surgical resection history in PRECiSE 1 was 34–36%, and in PRECiSE 2 it was 30–35%.^{5,6} History of surgical resection was not noted for patients in either the CHARM or GAIN trials. Another baseline characteristic that varies among clinical trials is the presence of fistulas, a common complication of CD.¹³ Infliximab has been shown to be effective against fistulizing CD, and the ACCENT II study further showed that cumulative infliximab exposure did not lead to additional abscess development, as was previously speculated.^{12,14} The ACCENT II trial enrolled only patients with fistulizing CD, whereas 15.2% and 13–15% of patients in the CHARM and GAIN trials, respectively, had abdominal or perianal fistulas at baseline.^{4,15,16} A potentially important but still debated marker of response to biologic therapy is cigarette smoking.^{17,18} Although smoking is associated with CD activity, the relationship between smoking and the disease pathology is complex and not well understood.^{19,20} For the purposes of comparing across clinical trials of biologic agents for CD, the prevalence of smokers is generally similar (30–36%), with the exception of ACCENT II, which enrolled 38–45%.^{7,12}

Baseline C-Reactive Protein Levels

Several biomarkers have been investigated for their potential prognostic ability to determine response to biologic therapy.²¹ Chief among these is C-reactive protein (CRP), a pro-inflammatory cytokine-induced factor. A study in 104 CD patients found that elevated CRP level, defined as greater than 0.8 mg/dL, was significantly associated with moderate-to-severe clinical activity and endoscopically and histologically confirmed active disease (overall risk [OR]: 4.5, 95% confidence interval [CI]: 1.1–18.3).²³ Most clinical trials evaluating biologic therapies define elevated CRP levels as greater than 1 mg/dL, and it has been speculated that higher

CRP levels at baseline are predictive of a better response to biologic therapy. In PRECiSE 1, 43.8–47.0% of the enrolled patients had elevated CRP.⁶ Although an earlier study of certolizumab had suggested better efficacy among the subgroup of patients with elevated baseline CRP,²³ the two primary endpoints in PRECiSE 1 (response at week 6 and response at both weeks 6 and 26) were achieved in both the high-CRP subgroup and the overall population. The week 6 response rate to open-label induction therapy and the week 26 response rate among week 6 responders (primary endpoint) were similar in the high-CRP patients and the overall group.⁶ A similar percentage of patients with elevated CRP levels were enrolled in the GAIN (41–48%) and CHARM (47.7%) trials.^{15,16} Although the ACCENT I trial did not report the percentage of patients with elevated CRP levels, the median CRP concentration was 0.8 mg/dL.⁴

Biologic-naïve Patients or Previous Nonresponders/Lost Response

Multiple secondary clinical trial analyses have shown that previous biologic therapy exposure is a negative predictor of response to future biologic treatments. Therefore, the percentage of study participants who had previously received anti-tumor necrosis factor (TNF) biologic agents within each trial should be noted in order to fairly compare across clinical trials. The CLASSIC trial enrolled only anti-TNF agent-naïve patients, whereas the GAIN trial, by definition, enrolled only patients who either had previously lost a response to an anti-TNF agent or were intolerant of that agent.^{15,24} Although the GAIN study showed that adalimumab could indeed elicit a clinical remission more frequently than placebo in patients with prior infliximab exposure, comparing this rate of remission to that achieved in the CLASSIC trial of anti-TNFα naïve patients showed that prior exposure reduced response to the second agent (36% vs 21%). Because infliximab was the first anti-TNF biologic therapy tested in CD, the ACCENT I and II trials contained no patients with previous exposure to biologic therapy.^{4,12} A total of 26–30% of patients in PRECiSE 1 and 24% in PRECiSE 2 had previously received infliximab therapy.^{5,6} Data from the PRECiSE 2 trial revealed a reduced 6-week response rate in patients with prior infliximab therapy compared to infliximab-naïve patients (53.9% vs 68.4%, respectively).⁵ The CHARM trial enrolled an even higher number of patients previously exposed to an anti-TNF agent (49.6%).¹⁶

Use of Concomitant Medications

Most clinical trials testing the efficacy of biologic agents allow for the continued use of concomitant medication,

including steroids and immunomodulators. An assumption often made about concomitant medication use is that a higher prevalence is indicative of more severely ill patients. However, this has not been conclusively shown. Additionally, when comparing across clinical trials, what may be interpreted as minor differences in the usage of steroid therapy may be accounted for by associated changes in immunomodulator use. For example, the rate of concomitant steroid use was higher in the ACCENT I study compared with ACCENT II (51% vs 33.3%, respectively), and the rate of immunomodulator therapy in ACCENT I was 27–29%, compared with 19.0–29.6% in ACCENT II.^{4,12} On the other hand, the prevalence of concomitant steroids in the CHARM trial was slightly lower (44%) and the rate of concomitant immunomodulators was slightly higher (46.7%).¹⁶ In PRECISE 1 and 2, the rates of concomitant steroid use were 39–40% and 35–37%, respectively, whereas the rates of concomitant immunomodulators were 37–38% and 40–41%, respectively.^{5,6} The GAIN trial had the highest rates of concomitant immunomodulator therapy (46–51%), but similar rates of concomitant steroid treatment (35–44%).¹⁵

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Examining Efficacy Results Across Clinical Trials of Biologics

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When interpreting the results of clinical trials evaluating biologic agents in CD, an important point to differentiate is the type of study utilized. Acute induction trials are generally short, ranging from 4 to 12 weeks, and are designed to determine if there is a response or remission induced by the study treatment. The majority of acute trials are double-blind and randomized patients who are refractory to conventional therapy, and the baseline characteristics of these study populations

generally include longer disease durations and various prior therapy exposures. For example, a phase II study by Present and colleagues randomized CD patients with primarily perianal fistulas to receive 3 doses of either infliximab or placebo at weeks 0, 2, and 6.¹ The primary study endpoint was closure of 50% of fistulae and patients were monitored for up to 18 weeks of follow-up. Both reduction in fistula drainage and complete cessation of drainage of all fistulae were significantly attained by infliximab versus placebo.

Conversely, maintenance trials are typically comprised of one of two study designs. In one design, patients receive an open-label study agent as induction therapy and are assessed for response to treatment. Responding patients are then randomized to either placebo or continued study drug for longer-term maintenance therapy. Several clinical trials have been patterned after this design, including ACCENT I and II, CHARM, and PRECiSE 2. In the second design, the maintenance period is not enriched for open-label responders. Instead, response to therapy is first assessed after an initial induction phase, and then a second assessment is made after maintenance therapy in order to determine which patients maintained their initial response. Therefore, this type of trial has two primary endpoints—the first is response after initial induction therapy, and the second is response after both induction and maintenance therapy. An illustration of this type of study is the PRECiSE 1 trial, which randomly assigned patients to receive induction therapy with either placebo or certolizumab pegol at weeks 0, 2, and 4, and then continued therapy every 4 weeks.² Response was measured at both weeks 6 and 26, and patients with responses at both time points were considered overall responders. Another point when comparing between trials is that the response rates in acute, randomized induction trials are typically lower than those seen in the open-label induction portions of induction-maintenance trials.

Comparing Definitions of Response/Remission

In general, response is considered a reduction in the signs and symptoms of CD, assessed by the CDAI, whereas remission is defined according to the CDAI score (typically <150).³ Different levels of response are often noted, depending on the magnitude of reduction in the CDAI score. Reductions in CDAI score are categorized as either greater than 70 points or greater than 100 points, and more patients will fall into the first group compared with the second. This is comparable to clinical trials of rheumatoid arthritis patients receiving anti-TNF agents, which assess response to therapy using the American College of Rheumatology (ACR) criteria. Responding patients are subdivided into different categories, depending on the magnitude of the drop in ACR points (ACR 20, ACR 50, ACR 70). For fistulizing CD specifically, fistula drainage is a standard assessment of response to therapy. This is measured by comparing the percentage of fistulas in which drainage has stopped. Again, a larger proportion of patients will have a 50% reduction in fistula drainage.

Comparing Clinical Endpoints

In addition to rates of response and remission, several other secondary endpoints are often determined to fully assess the therapeutic agent. Endoscopic examinations may reveal evidence of mucosal healing, as shown in a substudy of the

ACCENT I trial.⁴ This analysis correlated sustained mucosal healing with an improvement in CD activity induced by infliximab. Most of the CD biologic therapy clinical trials also included quality-of-life measurements, usually measured by the Inflammatory Bowel Disease Questionnaire (IBDQ).⁵ Because the IBDQ was designed to correlate with the CDAI, it generally reflects similar trends in changes in the CDAI in response to treatment.^{6,7} Another substudy of the ACCENT I trial found a significant association between infliximab-induced remission, defined by the CDAI, and several economic and quality-of-life indicators. Compared with patients not in remission, those who achieved remission had reduced hospitalizations ($P<.01$), reduced surgeries ($P<.05$), and increased employment ($P<.05$).

Extension Study Patients: Who Gets Selected for Trials of Maintenance Therapy?

Several of the clinical trials investigating biologic agents in CD are designed to include long-term extension phases. For example, patients who completed PRECiSE 1 or 2 were allowed to enroll in PRECiSE 3, an open-label extended maintenance study.⁸ Patients who responded at Week 6 in PRECiSE 2 and were treated with certolizumab pegol continuously for 74 additional weeks (80 weeks total treatment) demonstrated clinical response and remission of 44.2% and 37.2% respectively at Week 80. Those patients who had initially responded to certolizumab pegol in PRECiSE 2, but lost that response during the randomized maintenance phase were able to continue in PRECiSE 4 where they received a re-induction regimen, followed by open-label maintenance with certolizumab pegol. In these patients, a single administration of certolizumab pegol restored a number of patients' previous response, which was durable during maintenance dosing. Interim data at Week 4 and 52 after re-induction demonstrated that 57.1% and 38.8% of patients were in clinical response.⁹

When comparing extension studies, the trial design is very important to consider in order to fairly evaluate treatment responses. Because open-label induction phases generally elicit higher response rates compared with randomized induction, these two designs may not be able to be directly compared. Additionally, the amount and dosage of the study drug needed in order to regain a response may also significantly differ between trials. For example, a patient may regain their response to therapy after a single dose of treatment followed by maintenance therapy, or after a higher-dose maintenance phase.

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Safety Data in Clinical Trials of Biologics

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In medicine, an adverse event or effect (AE) is described as a harmful or undesirable effect resulting from a medication or other specific interventional therapy. AEs can occur during all points of exposure to therapy or only at certain points, such as initiation, discontinuation, or dose alteration of an agent. A serious AE is one that results in death, a life-threatening condition with a risk of death, inpatient hospitalization, persistent or significant disability or incapacitation, or a congenital anomaly or birth defect. In CD patients, serious AEs can lead to complications that negatively affect patient prognosis. Even minor AEs brought about by medication often lead to patient noncompliance, which contributes to a poor prognosis or worsening of the condition.

It can be difficult to interpret which symptoms are attributable to an AE or simply a cause of the disease itself. Although a drug or intervention may directly cause an AE, it may not be solely responsible, as other co-occurring variables may contribute to the symptoms of an AE. Severely active CD is often treated with appropriately aggressive therapy, and therefore differentiation between treatment and disease-related AEs is particularly difficult. When determining the risk for a particular AE, incidence should be compared against the expected occurrence in the general population as well as the disease-specific expected occurrence.

Several sources contribute to the safety profiles of biologic agents for CD. Randomized controlled trials provide excellent information because confounding variables are often eliminated in the randomization process and there is generally precise reporting of AEs. However, these trials are usually statistically powered to determine efficacy, not safety, and therefore the study population may not be large enough to allow the reporting of very rare AE occurrences. For example, to detect an AE with 95% confidence that occurs at a frequency of 1%, 300 study patients are needed. This

number increases to 3,000 to detect an AE with a frequency of 0.1%. Also, these studies generally have a short follow-up time. Conversely, observational cohort studies may have larger patient populations and longer follow-up periods, but they may contain intrinsic bias or confounding variables, which contribute to AE symptoms. Case-controlled studies are also an effective source of safety data, but identifying proper control populations of a sufficient size is often a difficult task, and therefore estimates of absolute risk may not be determined. Case reports provide only weak evidence of causality.

Minor Adverse Events

Infusion or Injection-site Reactions and Immunogenicity

Infusion-related reactions are generally not severe. They can manifest as a variety of clinical symptoms, which may be described as occurring acutely (<24 hours after infusion) or delayed (>48 hours after infusion).¹ Possible symptoms of acute infusion reactions include shortness of breath, chest pain, palpitations, flushing, fever, and headache. Additionally, type I hypersensitivity reactions such as urticaria (hives) and acute hypertension may occur, indicative of an anaphylactic-type allergic reaction. In these instances especially, the inducing biologic agent should be immediately discontinued. Symptoms and signs that are attributable to delayed infusion reactions include arthralgia and myalgia, rash, and leukocytosis.

When considering the number of total infliximab infusions in all patients, the number of infliximab infusions inducing reactions was relatively low (4.0% of 36,485 total infliximab infusions vs 1.6% of 15,379 total placebo infusions).² Importantly, only 0.1% of the infliximab infusion reactions were considered serious. This low rate

of infliximab infusion-related reactions is maintained when comparing across clinical trials (ACCENT I: 4.5%, ACCENT II: 3.3%, ACT I: 2.0%, ACT II: 3.4%).² Interestingly, in PRECiSE 1, significantly more patients in the placebo group compared with the certolizumab pegol-receiving group experienced injection-related reactions (14% vs 3%, respectively, $P < .001$).³ These results were recapitulated in PRECiSE 2 (15% vs 3%, respectively).⁴

Another important point to consider when analyzing injection-related AEs is the specific symptoms reported. For example, in CLASSIC I, adalimumab-induced injection-related reactions were as high as 38% compared with 16% in the placebo group.⁵ When the different types of injection-site reactions were specifically compared, injection-site burning was the most prevalent (15% at the highest adalimumab dose vs 8% in placebo patients), whereas injection-site pain occurred at comparable frequency between treatment and placebo groups (8% in each group). Other minor injection-site reactions included erythema, bruising, and pruritus. Interestingly, when data from all of the adalimumab trials using dosages of 40 mg either weekly or every other week are pooled, injection-site reactions occur at 30% and 42%, respectively, compared to 21% in the placebo groups.⁶

Immunogenicity, or the development of antibodies directed against the biologic agent, can result in several clinical complications, including an attenuated response to treatment, acute and delayed infusion reactions, lower serum levels of the agent, and serum sickness-like reactions.⁷ Episodic administration of biologic agents can induce high rates of immunogenicity, although this rate is lowered during the maintenance phase of treatment. For example, in ACCENT I, 28% of patients developed anti-infliximab antibodies while on episodic treatment, compared with only 9% and 6% of patients in the low- and high-dose maintenance groups, respectively.⁸ Co-immunomodulator therapy also resulted in a lower instance of anti-infliximab antibody formation compared with not using concomitant immunomodulators (10% vs 18%, $P = .02$), although this difference was not significant.⁹ A significant difference was observed in another study evaluating infliximab immunogenicity, which showed that patients not taking immunomodulators were more likely to develop anti-infliximab antibodies compared with patients taking concomitant therapy (75% vs 43%, respectively, $P < .01$).¹⁰ Comparatively, 8% of patients receiving certolizumab pegol developed agent-specific antibodies in PRECiSE 1.³ Fewer patients receiving concomitant immunosuppressive therapy exhibited these antibodies compared with those not receiving concomitant therapy (4% vs 10%, respectively). Immunogenicity was noted in 8% of the patients who had received certolizumab pegol in the maintenance portion of PRECiSE 2.⁴ Of these, a minority (2%) occurred in patients receiving concomitant immunosuppressive therapy; the remaining occurrences were in patients not receiving such therapy. Finally, adalimumab therapy resulted

in immunogenicity in 3.7% and 2.8% of patients in either the CLASSIC I or CLASSIC II trial, respectively.^{5,11}

Autoimmunity

Lupus-like syndrome is characterized by inflammatory arthritis, rash, and a high level of autoimmune antibodies, including antinuclear and anti-double-stranded DNA.¹² Though rare, this syndrome is most associated with infliximab therapy. Recently, a large study of 5,706 patients with various inflammatory disorders treated with infliximab showed that this syndrome occurred in only 0.29% of patients.² The PRECiSE 1 and 2 trials assessed the development of these autoimmune antibodies in response to certolizumab pegol.^{3,4} In PRECiSE 1, 1.1% and 1.8% of the placebo and treatment groups, respectively, developed autoimmune antibodies. In PRECiSE 2, 8% of certolizumab-treated patients developed these antibodies, compared with 1% of placebo patients; however, new anti-double-stranded DNA antibodies developed in an equal percentage of patients in each group (1%). Because these symptoms generally resolve with discontinuation and short-term medical treatment, this syndrome is considered a minor AE.

Major Adverse Events and Mortality

Infections

Because of their associated complications, infections are often considered a major AE in the context of biologic therapy. An important study that assessed the safety profile of infliximab in 500 CD patients reported that 8.2% experienced an infectious event attributed to therapy.¹³ Of these 41 cases, 20 were described as serious, including 2 cases of fatal sepsis and 2 cases of fatal pneumonia. Pooled data from several clinical trials confirm that the number of infections occurring in placebo-treated groups is lower than in infliximab-treated groups (115.6 vs 132.3 per 100 patient-years, respectively).² The number of infections requiring treatment was similarly higher in the infliximab group as well (54.8 vs 61.2 per 100 patient-years, respectively). The TREAT registry, which has enrolled 6,290 CD patients, showed an unadjusted increased risk for infection associated with infliximab therapy.¹⁴ However, multivariate analysis determined that infliximab use did not independently predict serious infections, though prednisone use did (OR: 2.21, 95% CI: 1.46–3.34, $P < .001$). Interestingly, moderate-to-severe disease activity (OR: 2.11, 95% CI: 1.10–4.05, $P = .024$) and narcotic analgesic use (OR: 2.38, 95% CI: 1.56–3.63, $P < .001$) also independently predicted a higher risk of serious infection. Various infectious events can occur as a result of biologic agent therapy, including herpes, endocarditis, Epstein-Barr virus, cytomegalovirus, and sepsis. Tuberculosis is another important potential infection that has been reported with certolizumab pegol, adalimumab, and infliximab.¹⁵ Since the establishment of an association between the use of these

agents and tuberculosis, extensive clinician education to inform of the risk of infection has led to a decline in the rate of infliximab-induced tuberculosis infection. In order to continue to prevent tuberculosis emergence, patients should be screened for latent tuberculosis prior to receiving a biologic agent, although this will not completely prevent all tuberculosis infections.^{16,17}

Malignancies

Lymphomas and other malignancies are a major AE associated with the use of biologic therapy among rheumatoid arthritis patients. Using the National Databank for Rheumatic Diseases as an example, there were 105.9 cases of lymphoma per 100,000 person-years, resulting in an incidence ratio of 1.8 (95% CI: 1.5–2.2) when compared with the SEER database.¹⁸ Importantly, infliximab therapy did not increase the risk for lymphoma development, a result confirmed in an analysis of a similar Swedish registry.¹⁹ In CD, there is conflicting evidence of an increased association of lymphoma.²⁰ Data from several trials show a possibly increased risk of lymphoma due to CD alone, ranging from a 1.4- to a 4.7-fold increase (Table 1)^{21–24}; however, most experts believe there is no increased risk in patients with CD.

The most recent data from the TREAT registry, however, provide no evidence that infliximab therapy produces a higher risk of lymphoma (relative risk [RR]: 0.8, 95% CI: 0.22–2.99; Table 2).¹⁴ The TREAT registry also has shown no increased risk for all other cancer types (RR: 0.74, 95% CI: 0.49–1.12), although longer follow-up is needed. Recent evidence in adolescents, however, suggests that concomitant administration of biologic agents and immunomodulatory agents may be associated with the development of hepatosplenic T-cell lymphoma, a virtually incurable form of non-Hodgkin's lymphoma.²⁵ Because of the seriousness of this complication, the concomitant use of these agents has recently become discouraged until further investigation can be completed.

Mortality

Mortality rates have also been addressed in regard to the influence of biologic agents. The TREAT registry showed relatively similar mortality risks among infliximab-treated and untreated patients (0.53 vs 0.43 per 100 patient-years, respectively).¹⁴ When multivariate analysis was performed, infliximab use was not significantly associated with increased mortality risk, but prednisone use was (OR: 2.10, 95% CI: 1.15–3.83, $P=0.016$). When comparing across clinical trials, biologic agent use is associated with an approximately 1% per year mortality rate.

Other Adverse Events

Other major or serious AEs have been associated with biologic agents in CD patients, including demyelinating disorders, congestive heart failure, severe hepatic reactions, liver

Table 1. Lymphoma Risk in Crohn's Disease

| Publication | Relative incidence of lymphoma compared to general population |
|------------------------------------|---|
| Greenstein AJ et al. ²⁴ | 4.7-fold increase |
| Mellemkjaer L et al. ²³ | 1.5-fold increase |
| Lewis JD et al. ²² | 1.4-fold increase |
| Bernstein CN et al. ²¹ | 2.4-fold increase |
| Range | 1.4- to 4.7-fold increase |

Table 2. Incidence of Lymphomas in the TREAT Registry

| Treatment | Patients | Incidence per 100 Pt-Y |
|-----------------------------|----------|------------------------|
| Not treated with infliximab | 3,111 | 0.057 |
| Infliximab | 3,179 | 0.062 |

Odds ratio of lymphoma associated with infliximab: 1.09 [95% confidence interval: 0.24–4.85]

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failure, jaundice, and hepatitis. However, these all occur at relatively infrequent rates, and, in some cases, no causal relationship has been confirmed.^{26,27}

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Discussion Forum

Drs. Lichtenstein and Loftus discuss the future of research in biologic therapies for CD.

G&H As the options for biologic therapies to treat CD continue to expand, is there a need for head-to-head trials to establish advantages of specific agents in particular populations?

Dr. Edward V. Loftus, Jr In an ideal world, head-to-head trials could potentially provide useful information. However, funding for such an endeavor would be difficult to attain from any source. Further, the number of patients required to power a study with two active-treatment arms is much larger than a placebo-controlled design. Therefore, recruitment would pose an additional significant challenge.

G&H Would it be feasible to establish ground rules for the standardization of trial designs, so that comparison of results across trials of biologics can be made more effectively?

EL Over the last ten years, the design of trials of biologic therapies has been refined through a trial-and-error process, and we are now at the point where the appropriate length and population size for both induction and maintenance trials have been established. Based on what we've learned from the past, I foresee a sort of convergence, where investigators will use roughly similar designs and endpoints because they have seen which study designs are most efficient.

Dr. Gary R. Lichtenstein I agree and would also add that part of the past disparity has been due to a lack of guidance from the regulatory agencies as to how to design trials. Government regulators learn in the same manner that we learn. Looking back, there were key data regarding these

drugs that we did not initially have, and many of the things that we have since learned have led us to design trials in a different fashion. It is an ongoing educational process, but it is the agency, the US Food and Drug Administration (FDA), that provides a sort of institutional memory to inform new investigators entering into this arena. However, regulators will need to be flexible and willing to revisit guidelines as new data accrue. I believe that as we continue to learn about these drugs, the way we test them will continue to evolve. Trials five years from now will be markedly different from those we are conducting currently.

Further, complete standardization will be difficult, as trial design ultimately depends on the unique features of the molecule or molecules that are being evaluated, as well as the clinical scenario. Although the current discussion is primarily regarding anti-TNF α agents, other biologics with other mechanisms may require different designs.

EL Certain aspects common to all biologics, such as the development of antibodies, should be examined in all trials so that they can be compared. However, Dr. Lichtenstein makes an excellent point in that the learning process is continual. If trials become too standardized, we run the risk of never discovering novel methods for treating and managing patients.

GL If the FDA does mandate standardization and advances it as knowledge advances, it will require regular joint meetings of investigators, manufacturers, and regulators to set forth the pertinent information so that it is used in the best possible fashion to further our understanding of trial design, as well as the development of effective agents.

Clinical Trials in Biologic Therapy for Crohn's Disease: Comparing Designs and Data

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

1. Which clinical trial did not test the efficacy of adalimumab in CD patients?
 - a. CLASSIC I
 - b. GAIN
 - c. ACCENT II
 - d. CHARM
2. What CDAI score is generally considered to be indicative of CD remission?
 - a. <150
 - b. 150–210
 - c. 220–450
 - d. >450
3. The CHARM trial showed that patients with a shorter CD duration (<2 years) had a remission rate of _____, which was superior to patients with a longer CD duration (>5 years).
 - a. 14%
 - b. 41%
 - c. 59%
 - d. 65%
4. The prevalence of smoking among patients participating in trials of biologic therapy for CD has been similar across trials, ranging from _____ to _____.
 - a. 25%; 29%
 - b. 30%; 36%
 - c. 33%; 39%
 - d. 36%; 41%
5. True or False? Acute induction trials are generally short and designed mainly to determine efficacy of a study agent.
 - a. True
 - b. False
6. _____ by a biologic study agent is defined as a reduction in the signs and symptoms of CD that is calculated using the CDAI.
 - a. Remission
 - b. Toxicity
 - c. Safety
 - d. Response
7. A substudy of the _____ trial showed that mucosal healing revealed by endoscopic examinations correlated with infliximab-induced improvements in CD activity.
 - a. PRECiSE 1
 - b. PRECiSE 3
 - c. ACCENT I
 - d. CHARM
8. In order to detect an AE which occurs at a frequency of 0.1% with 95% confidence, a study population of _____ patients is required.
 - a. 3
 - b. 30
 - c. 300
 - d. 3,000
9. In ACCENT I, the immunogenicity rate of patients on episodic infliximab therapy was _____.
 - a. 6%
 - b. 9%
 - c. 28%
 - d. 34%
10. Recent data from the TREAT registry suggested that infliximab use did not increase the risk for lymphoma, with a relative risk of _____.
 - a. 0.5
 - b. 0.8
 - c. 1.0
 - d. 1.2

Evaluation Form: Clinical Trials in Biologic Therapy for Crohn's Disease: Comparing Designs and Data

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. Summarize historic research of the biologic options for Crohn's disease. | 1 | 2 | 3 | 4 | 5 |
| 2. Describe differences in trial design of different agents and how they may have effected outcomes. | 1 | 2 | 3 | 4 | 5 |
| 3. Compare data from different trials while weighing the effect of trial designs on efficacy and safety 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. _____

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