Induction and Maintenance Therapy With Infliximab for Children With Moderate to Severe Ulcerative Colitis

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BACKGROUND & AIMS: We evaluated the efficacy and safety of infliximab for inducing and maintaining benefit in children with moderately to severely active ulcerative colitis (UC). METHODS: Patients (6–17 years old) who had active UC (Mayo scores of 6–12; endoscopic subscores ≥2) and had not responded to or tolerated conventional treatment were given 5 mg/kg infliximab at weeks 0, 2, and 6. The primary end point was response at week 8 (decreases in Mayo scores ≥50% and ≥3 points and decreases in rectal bleeding subscores of ≥1 or an absolute subscore of ≤1). At week 8, only responders were randomly assigned to groups given infliximab every 8 or 12 weeks (q8w or q12w) and followed through week 54. Maintenance end points included pediatric UC activity index scores <10 points, defined as remission. RESULTS: At week 8, infliximab induced a response in 73.3% of patients (44 of 60) (95% confidence interval, 62.1%–84.5%; a positive result was defined by 95% confidence interval lower limit >40%). Among responders, twice as many were in remission at week 54 after q8w (8 of 21, 38.1%) than q12w (4 of 22, 18.2%; P = .146) therapy. Assuming the q8w remission rate for responders, the overall remission rate at week 54 would be 28.6%. Serious adverse events and infusion reactions occurred in similar proportions in the q8w and q12w groups. No deaths, malignancies, opportunistic infections, tuberculosis, or delayed hypersensitivity reactions were reported. CONCLUSIONS: Infliximab was safe and effective, inducing a response at week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy. The overall remission rate at week 54 for all enrolled patients was 28.6%, assuming the more effective q8w remission rate.

Keywords: Mucosal Healing; Inflammatory Bowel Disease (IBD); Clinical Trial; Pediatric Ulcerative Colitis Activity Index (PUCAI).

Ulcerative colitis (UC), an inflammatory bowel disease, can affect people of any age, although occurrence peaks in late adolescence, with 20% of all patients affected with UC presenting before the age of 20 years.¹ In adults and children, UC is believed to be similar in terms of treatment response and shared pathophysiological mechanisms, including overexpression of tumor necrosis factor alpha (TNF-α); however, disease location at presentation tends to be left-sided colitis/proctitis in adults versus pancolitis and more severe in children.²–⁴

The efficacy and safety of therapies used to treat adult UC patients have not been evaluated in controlled pediatric studies; however, treatment in children generally follows the adult paradigm.² Corticosteroids are effective for short-term treatment, but up to 45% of pediatric patients develop corticosteroid dependence in the subsequent year, which puts them at risk for corticosteroid-related side effects.⁵,⁶ In a large inception cohort of newly diagnosed children with UC starting thiopurine therapy without previous or concomitant biological or calcineurin inhibitor therapy, approximately 50% had corticosteroid-free inactive disease at 12 months.⁷

Infliximab, an anti–TNF-α monoclonal antibody, is considered safe and effective for the treatment of UC in adults on the basis of findings of 2 randomized, double-blind, placebo-controlled studies, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2), and for the treatment of children with Crohn’s disease on the basis of results of the Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF-α Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate-to-Severe Crohn’s Disease (REACH study).⁸,⁹

Small preliminary studies have indicated that response to infliximab therapy is similar in pediatric and adult UC patients.¹⁰¹¹ This phase 3, randomized, open-label, parallel-group study prospectively evaluated the safety and efficacy of infliximab in pediatric patients with moderately to severely active UC.

Abbreviations used in this paper: ACT, Active Ulcerative Colitis Trial; ANA, antinuclear antibody; 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; CI, confidence interval; IRB, institutional review board; IV, intravenous; 6-MP, 6-mercaptopurine; MTX, methotrexate; OSCI, Outcome of Steroid Therapy in Colitis Individuals study; PUCAI, Pediatric Ulcerative Colitis Activity Index; q8w, every 8 weeks; q12w, every 12 weeks; REACH, Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF-α Chimeric Monoclonal Antibody (Infliximab, REMICADE) in Pediatric Subjects With Moderate-to-Severe Crohn’s Disease; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis.

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1542-3565/$36.00
doi:10.1016/j.cgh.2011.11.026
Methods

Eligibility

Eligible patients were 6–17 years old, inclusive, with moderately to severely active UC (defined as having a baseline [ie, week 0] Mayo score of 6–12 points, including an endoscopy subscore ≥2). A UC diagnosis, confirmed by biopsy, must have been established ≥2 weeks before screening. Patients must have failed to respond to adequate treatment with or have experienced medical complications or adverse effects from 5-aminosalicylic acid (5-ASA); compounds, immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]), or oral or intravenous (IV) corticosteroids. Dosages of any current treatments or enteral feeding regimens (1 week) must have been stable and antibiotic use discontinued (2 weeks) before screening. Patients with acute severe extensive UC and those who previously used other investigational drugs or any TNF antagonist were excluded. The protocol was approved by the institutional review board (IRB) at each site. Written informed consent was obtained from all parents/legal guardians, and assent was obtained from children on the basis of IRB guidelines before the conduct of any study-related procedures.

Study Design

The first patient was enrolled on August 25, 2006, and the last assessment occurred on June 24, 2010. Eligible patients received an induction regimen of infliximab 5 mg/kg at weeks 0, 2, and 6. Infliximab (REMIcade; Janssen Biotech, Inc, Horsham, PA) was prepared by the pharmacist and administered open-label. At week 8, patients who achieved clinical response (primary end point) were randomized equally to receive infliximab 5 mg/kg every 8 weeks (q8w) (ie, at weeks 14, 22, 30, 38, and 46) or every 12 weeks (q12w) (ie, at weeks 18, 30, and 42) by using a blocked randomization schedule stratified by baseline corticosteroid use and were followed for efficacy through week 54 and safety through week 62 (http://ClinicalTrials.gov NCT00336492). Nonrandomized patients did not receive further infliximab treatment and were followed for safety through 8 weeks after their last dose.

Patients who lost response during the maintenance phase were eligible to increase their infliximab dose and/or frequency. Patients receiving infliximab 5 mg/kg q8w increased to 10 mg/kg q8w. Patients receiving infliximab 5 mg/kg q12w who lost response within 8 weeks of the previous infliximab infusion had the dose and frequency increased to 10 mg/kg infliximab q8w, whereas patients in the same group who lost response between 8 and 12 weeks after the previous infusion continued to receive 5 mg/kg infliximab but increased the frequency of infusions to q8w.

Efficacy

Evaluations. Mayo scores were determined at weeks 0, 8, and 54 (if an endoscopy was performed). At week 54, endoscopy was optional because of its invasive nature. The Mayo score (ranging from 0–12, with higher scores indicating more severe disease activity) is a composite of 4 subscores: stool frequency, rectal bleeding, Physician’s Global Assessment, and mucosal appearance at endoscopy. Each subscore was rated on a scale of 0–3 indicating normal to severe activity. The partial Mayo score (ie, Mayo score without endoscopy subscore) ranges from 0–9 and was calculated at each study visit.

The validated Pediatric Ulcerative Colitis Activity Index (PUCAI) score, a noninvasive (no endoscopy required) scoring system incorporating 6 subscores, was also measured and provided an assessment of efficacy maintenance at week 54. Subscores range from 0–10 for abdominal pain, consistency of most stools, nocturnal bowel movement, and activity level. Subscore for the number of stools per 24 hours ranges from 0–15. Rectal bleeding subscores range from 0–30. Total PUCAI scores range from 0–85, with higher scores indicating more severe disease activity.

Outcome assessments. The primary efficacy end point of clinical response at week 8 was defined by a decrease in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Secondary efficacy end points at week 8 included Mayo clinical remission as defined by a score ≤2 with no individual subscore >1, mucosal healing defined by Mayo endoscopy subscore of 0 or 1, and PUCAI clinical remission as defined by a score <10. Secondary efficacy end points also included the evaluation of clinical remission at week 54.

During the maintenance phase, loss of clinical response was defined as either (1) an increase from the week 8 partial Mayo score of ≥2 points at 2 consecutive visits at least 7 days apart or (2) an increase from the week 8 partial Mayo score of ≥3 points at any visit.

Concomitant Medications

Patients receiving UC-specific medical therapies were to be on stable doses before enrolling. Patients receiving oral or IV corticosteroids or immunomodulators were to be on stable doses before the start of the study and could taper their dose during the study if clinically indicated. Other UC-specific medical therapies were to remain stable.

Safety

Adverse events were documented at each study visit. An infusion reaction was defined as any adverse event that occurred during or within 1 hour after infliximab infusion. Tuberculosis assessments were made, and serum samples were collected for determination of routine hematology and blood chemistry parameters. Blood samples to determine the presence of antinuclear antibodies (ANA), anti–double-stranded DNA antibodies (if positive for ANA), and antibodies to infliximab were collected at weeks 0, 30, and 54. Analyses for antibodies to infliximab were performed by using a bridging immunoassay.

Statistical Methods

Descriptive statistics (eg, median, interquartile range) were used to summarize continuous variables. Categorical data were summarized by using counts and percentages.

For the primary end point of clinical response at week 8, the proportion of patients in clinical response and 95% confidence interval (CI) were determined. If the lower bound of the 95% CI was >40%, the study was to be declared positive. The criterion of >40% was based on the use of pooled data from the placebo groups in the ACT 1 and ACT 2 studies as a “historical control.” The upper limit of the 95% CI for the proportion of placebo patients in clinical response at week 8 in the pooled ACT studies was 39.1%; thus the cutoff point was set at 40%.
Although this study was not adequately powered to show a difference between the maintenance groups (ie, q8w versus q12w), PUCAI clinical remission at week 54 was compared between the maintenance groups by using the 2-sided \( \alpha = 0.05 \) \( \chi^2 \) test.

Patients who met any of the following criteria for treatment failure were considered to not have achieved their dichotomous efficacy end point (ie, clinical response, clinical remission [Mayo or PUCAI score], or mucosal healing): (1) had a colectomy (partial or full) or ostomy, (2) discontinued study drug because of unsatisfactory therapeutic effect, or (3) had a prespecified prohibited medication change. In addition, for clinical remission at week 54, patients who stepped up their treatment were considered to not have achieved the end point. Patients with missing observations were considered to not have achieved their clinical end points.

For the analysis of corticosteroid use, patients who experienced any treatment failure event had their baseline values carried forward from the time at which the event occurred, and patients with missing observations had their last observation carried forward.

The Mayo score was calculated if at least 1 subscore was available from the visit at which the Mayo score was measured. The PUCAI score was calculated only when 3 or more of the 6 subscores were available from the visit at which the PUCAI score was to be measured. For missing subscores, the last available value was carried forward to compute a full Mayo or PUCAI score. If all 4 Mayo (or \( \geq 3 \) PUCAI) subscores were missing, the Mayo (or PUCAI) score was not calculated and was considered missing for that visit, and the patient was considered to not have achieved the Mayo (or PUCAI) score-related clinical outcomes.

The partial Mayo score was calculated similar to that for the full Mayo score if data were available from at least 1 of 3 Mayo subscores that comprise this efficacy variable; if all 3 subscores were missing, the partial Mayo score was not calculated and was considered missing for that visit.

A sample size of 60 patients ensured <12% precision in estimating the true proportion of pediatric patients in clinical response at week 8 by using a 95% CI. This sample size calculation assumed a clinical response rate of 67% at week 8 on the basis of the clinical response rate of all randomized adult patients receiving infliximab 5 mg/kg in the ACT 1 and ACT 2 trials.8

Results

Patient Disposition, Baseline Characteristics, and Prior Concomitant Medication Use

Twenty-three investigative sites participated in the United States and Canada (52 of 60 patients, 86.7%) and Belgium and the Netherlands (8 of 60 patients, 13.3%).

All patients were receiving baseline UC medications (Table 1). Among enrolled patients, 53.3% (32 of 60 patients) were female, 81.7% (49 of 60 patients) were white, median age was 14.5 years, median C-reactive protein level was 0.3 mg/dL, median disease duration was 1.4 years, and 76.7% (46 of 60 patients) had extensive disease. The median Mayo score was 8.0, and the median PUCAI score was 55.0 (Table 1).

Demographics, baseline characteristics, and baseline concomitant medications were generally balanced between the randomized maintenance groups. However, patients receiving infliximab q8w had a greater duration of disease (1.8 vs 1.1 years) and duration of UC symptoms (5.5 vs 2.0 months) compared with those receiving infliximab q12w.

Among 60 enrolled patients, 45 were randomized by an Interactive Voice Response System at week 8 to receive infliximab q8w (n = 22) or q12w (n = 23) (Figure 1).

Overall, 50.0% of patients (30 of 60) permanently discontinued infliximab treatment. Fifteen patients discontinued before week 8 and were followed for 8 weeks after their last dose for safety. Fifteen randomized patients, including 11 who stepped up their infliximab dose, discontinued maintenance treatment (4 of 22 patients, 18.2% q8w and 11 of 23 patients, 47.8% q12w; Figure 1). More patients randomized to q12w (4 of 23, 17.4%) than q8w (1 of 22, 4.5%) maintenance therapy discontinued because of unsatisfactory therapeutic effect (Supplementary Figure 1). There were no differences in baseline corticosteroid or immunomodulator use between patients who discontinued before or after week 8.

Of 45 randomized patients, 23 stepped up therapy (Figure 1). More patients stepped up in the q12w than q8w group (60.9% vs 40.9%). Of 14 patients in the q12w group who stepped up, 8 stepped up to 10 mg/kg q8w and 6 to 5 mg/kg q8w. Most patients stepped up by week 22 (18 [78.3%]). Among those who stepped up, 7 (30.4%) discontinued treatment because of an adverse event, 3 (13.0%) for unsatisfactory therapeutic effect, and 1 (4.3%) for other reasons.

Efficacy

Primary efficacy end point. At week 8, clinical response was achieved by 44 of 60 infliximab-treated pediatric patients (73.3%; 95% CI, 62.1%–84.5%). Because the lower limit of the 95% CI for the proportion of pediatric patients in clinical response at week 8 in this study was 62.1%, the protocol-specified criterion for declaring a positive study was met. Note that the number of patients randomized at week 8 does not equal the number of patients in clinical response at week 8 because (1) 1 responder was considered a nonresponder because of treatment failure, (2) 1 nonresponder was incorrectly randomized as a responder, and (3) 1 responder was not randomized and discontinued from the study by the sponsor for administrative reasons.

Other efficacy end points. After induction therapy, clinical remission at week 8 was achieved by 24 of 60 (40.0% Mayo score) patients and 17 of 51 (33.3% PUCAI score) evaluable patients.

Mucosal healing was achieved at week 8 in 41 of 60 (68.3%) infliximab-treated children.

Among randomized patients, improvement from the baseline partial Mayo score of 6.0 was observed as early as week 2; the median reduction from baseline at week 8 was 4.0. During the maintenance phase, the median reduction in partial Mayo score was maintained in the q8w group but increased to near baseline values in the q12w group at week 54 (Figure 2A).

Twenty-three of 30 patients who discontinued therapy were evaluable for PUCAI at their last visit. Disease activity was more severe at the last visit for patients who discontinued after week 8 (no disease, 1 of 10 [10%]; mild, 1 of 10 [10%]; moderate, 6 of 10 [60%]; severe, 2 of 10 [20%]) than for patients who discontinued before week 8 (mild, 4 of 13 [30.8%]; moderate, 4 of 13 [30.8%]; and severe disease, 5 of 13 [38.5%]).

When comparing maintenance treatment regimens, the PUCAI clinical remission rate was numerically greater for pa-
patients randomized to the infliximab q8w group relative to those in the infliximab q12w group at week 30 (8 of 20, 40.0% vs 4 of 21, 19.0%; \( P = .141 \)) and week 54 (8 of 21, 38.1% vs 4 of 22, 18.2%; \( P = .146 \)) (Figure 2B).

Among patients randomized at week 8 to a maintenance regimen, 28 of 45 (14 in each group) were taking corticosteroids at baseline, 0.54 mg/kg/d in the q8w group and 0.49 mg/kg/d in the q12w group. A substantial reduction in median corticosteroid use was seen by week 8 after induction therapy. The median value in the q8w group was maintained at 0 from week 8 until a slight increase at week 54 (0.04 mg/kg/d). The median value in the q12w group reached its minimum value (0.15 mg/kg/d) by week 8 but returned to baseline levels at week 54 (Figure 2C).

More patients receiving corticosteroids at baseline were in corticosteroid-free PUCAI clinical remission at week 30 (5 of 12, 41.7% vs 1 of 13, 7.7%), week 54 (5 of 13, 38.5% vs 0 of 13), and both weeks 30 and 54 (5 of 13, 38.5% vs 0 of 13) in the q8w than q12w group, although the sample sizes were small (Figure 2D).

### Efficacy after step-up.

Among step-up patients who remained in the study and had data at week 54, 9 of 10 (90.0%) demonstrated improvement in disease activity (defined as a decrease of 2 points in their partial Mayo score). Notably, these results are based on a small number of patients who also might have altered their concomitant UC medications.

### Efficacy by subgroup.

On the basis of the results of subgroup analyses, there do not seem to be any variables that indicate which patients would be responders. The variables that were analyzed include sex, age (≤15 years, >15 years), race (white, non-white), weight (≤50.8 kg, >50.8 kg), baseline Mayo score (≥10, <10), baseline PUCAI score (≥64, ≤64), duration of disease (≤1 year, >1 year), extent of disease (limited to left side of colon, extensive), baseline concomitant medications, concomitant medication history, baseline C-reactive protein.
(<0.6 mg/dL, ≥0.6 mg/dL), and region (North America, Europe) (data not shown).

Additional subgroup analyses were performed for age group and baseline use of immunomodulators (Table 2). Analyses comparing patients receiving concomitant immunomodulators (ie, 6-MP, AZA, or methotrexate [MTX]) with those receiving infliximab monotherapy revealed no differences in any efficacy end points, and analyses based on the age groups of 6–11 and 12–17 years old revealed no consistent pattern indicating greater efficacy in one age group over the other.

**Safety**

All 60 treated patients were included in the safety assessments (Table 3). Patients randomized to maintenance treatment at week 8 experienced at least 1 adverse event during an average of 47.5 weeks of patient follow-up. Among patients who were not randomized at week 8 and thus discontinued from the study, 12 of 15 patients (80%) experienced at least 1 adverse event during an average of 9.8 weeks of patient follow-up. Although the overall infliximab safety profile was similar between the infliximab q8w and q12w maintenance groups, worsening of UC occurred in 15 of 23 patients (65.2%) receiving infliximab q12w compared with 8 of 22 patients (36.4%) receiving infliximab q8w.

Proportions of patients experiencing 1 or more serious adverse events were similar between patients receiving infliximab q8w (4 of 22, 18.2%) and q12w (5 of 23, 21.7%) but greater among patients not randomized at week 8 (5 of 15, 33.3%), including one report of severe neutropenia (Table 3). Worsening of UC was the only serious adverse event occurring in more than 1 patient in either group. No patient died or developed a malignancy, demyelinating disorder, optic neuritis, or seizure during the study.

Through week 54, a greater proportion of patients discontinued infliximab q12w because of at least 1 adverse event (6 of 23, 26.1%) compared with patients receiving infliximab q8w (3 of 22, 13.6%). Worsening of UC was the reason for discontinuation for the 6 patients receiving infliximab q12w and for 1 receiving infliximab q8w. Other reasons for infliximab discontinuation in the q8w group were alopecia in 1 patient and both cyanosis and dyspnea in 1 patient.

Proportions of patients who developed at least 1 infection (13 of 22, 59.1% and 14 of 23, 60.9%, respectively) or serious infection (3 of 22, 13.6% and 3 of 23, 13.0%, respectively) were similar between infliximab q8w and q12w maintenance groups (Table 3). Serious infections included pneumonia in 1 nonrandomized patient, 1 patient each with infection of unknown origin, viral infection, and facial cellulitis in the q8w group; and 1 patient each with pharyngitis, worsening UC, and urinary tract infection in the q12w group.

Infusion reactions were documented in 1 of 15 (6.7%) nonrandomized patients, 4 of 22 (18.2%) patients receiving infliximab q8w, and 3 of 23 (13.0%) patients receiving infliximab q12w. Overall, 17 of 340 (5.0%) infusions were associated with an infusion reaction: 1 of 40 (2.5%) nonrandomized patients, 13 of 165 (7.9%) patients receiving infliximab q8w, and 3 of 135 (2.2%) patients receiving infliximab q12w (Table 3).
There were no new reports of autoimmune disease, possible delayed hypersensitivity reactions, or anaphylactic reactions through week 54. One patient receiving infliximab q8w experienced a serious adverse event of lupus erythematosus syndrome after week 54.

Overall, 5 of 60 patients required a colectomy within the 54-week period after their baseline infusion (2 of 15 nonrandomized patients [13.3%], 1 of 22 patients [4.5%] in the q8w group, and 2 of 23 patients [8.7%] in the q12w group).

Four of 52 evaluable patients (7.7%) were positive for antibodies to infliximab. Two patients (1 not randomized and 1 in the q8w group) received immunomodulators, and 2 patients (1 in the q8w and 1 in the q8w group who stepped up to infliximab 10 mg/kg) did not receive immunomodulators. Newly positive ANA (≥1:160) and anti–double-stranded DNA antibodies at any time were detected in 33.3% (6 of 18) and 10.5% (2 of 19), respectively, of patients receiving infliximab q8w, compared with 15.0% (3 of 20) and 0.0% (0 of 20), respectively, of patients receiving infliximab q12w.

**Discussion**

Our study achieved the primary efficacy end point of clinical response at week 8. Infliximab induced clinical response in 73.3% of patients. The criterion for a positive study was met because the lower limit of the 95% CI for the proportion of patients in clinical response was 62.1%, which is greater than the protocol-specified limit of 40%.

Efficacy was also demonstrated by multiple other measures and end points. Infliximab induced Mayo and PUCAI clinical remission in at least one-third of patients. Mucosal healing at week 8 was achieved in more than two-thirds of pediatric UC patients. Although all Mayo subscores were improved at week 8 compared with baseline, it was possible for patients with mucosal healing and mild UC symptoms to have not met the definition for Mayo clinical remission. With maintenance therapy, a numerically greater proportion of patients randomized as responders achieved PUCAI clinical remission in the q8w group (38.1%) than q12w group (18.2%) at week 54. This difference was not statistically significant, but the study was not powered specifically for this outcome variable. If the remission rate from the more effective q8w therapy is used to calculate the overall remission rate of all 60 patients enrolled, 28.6% of patients were considered to be in remission at week 54. It is possible that better disease control might arise from infliximab dosage adjustments, because in an analysis mimicking real-world clinical practice by allowing for step-up therapy, clinical remission at week 54 was achieved by 42.8% of patients (assuming the remission rate at week 54 in the q8w group of 57.1%).

A direct comparison of remission at week 54 with adult patients from ACT 1 is not available because the full Mayo score was not obtained at this time point in our study. Endoscopy, a component of the full Mayo score, was optional at week 54 because repeated endoscopies in pediatric patients are unacceptable. An indirect comparison of remission at week 54 can be made on the basis of (1) the similarity between week 8 PUCAI and Mayo remission in our study when considering the high correlation between these variables, (2) the consistency of week 8 Mayo remission at week 8 in our study compared with ACT 1 (47 of 121, 38.8%) and ACT 2 (41 of 121, 33.9%), (3) the consistency of partial Mayo scores through week 54 between our study and ACT 1, and (4) the similarity of adult and pediatric disease. At week 54, 34.6% of infliximab-treated patients in ACT 1 were in Mayo clinical remission; in our study, 38.1% of patients receiving infliximab q8w were in Mayo clinical remission.
Patients in remission (PUCAI score) at week 8

Patients in clinical response at week 8

Therapy in Colitis Individuals (OSCI) study,16 128 children have evaluated infliximab for the management of corticosteroid-refractory or corticosteroid-dependent pediatric UC patients.5 Currently, infliximab is the only biologic agent approved for the treatment of UC in adults only. All patients in the current study were receiving concomitant UC medication; almost two-thirds received corticosteroids and approximately one-half received 6-MP, AZA, or 5-ASA. Thus, there is a need for an efficacious treatment for pediatric patients with this disease.

Recently, large, multicenter, prospective observational studies have evaluated infliximab for the management of corticosteroid-refractory or corticosteroid-dependent pediatric UC patients. In the prospective multicenter Outcome of Steroid Therapy in Colitis Individuals (OSCI) study,15,16 128 children hospitalized with acute severe colitis were evaluated for short-term corticosteroid response rates (defined as no colectomy, or infliximab or calcineurin inhibitor use before hospital discharge) and response rates to treatments administered during 1 year after hospital discharge. Second-line treatment (ie, colectomy, infliximab or calcineurin inhibitor) in corticosteroid-refractory patients was administered at the discretion of the gastroenterologist. Among corticosteroid-treated children, 91 (71.1%) responded to corticosteroid therapy, and 37 (28.9%) failed to respond and required salvage therapy. Among corticosteroid-refractory patients receiving infliximab, 25 of 33 (75.8%) had a short-term response, and 18 of 33 (54.5%) had sustained response during 1 year of follow-up.

In another recent prospective multicenter pediatric study,17 clinical outcomes were reported from 52 infliximab-treated UC patients treated according to local clinical practice (ie, allowance for UC therapy dose modifications for waning efficacy) from the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. During 24 months of follow-up, approximately 35% of patients reported inactive or mildly active disease (on the basis of the Physician’s Global Assessment) without corticosteroid therapy.

Although the present study was small, the safety profile during 1 year of maintenance infliximab therapy appears to be consistent with that reported in other inflammatory bowel disease studies of infliximab, including the treatment of pediatric UC patients.11,12,17 No deaths, malignancies, serious neurologic events, opportunistic infections including tuberculosis, or congestive heart failure were reported during the study. The overall postmarketing safety review of adverse events reported for infliximab-exposed pediatric patients supports the conclusion that the safety profile of infliximab in the pediatric population is consistent with that seen in the adult population and consistent with current labeling.15 Although no new safety concerns were observed in our study, prescribers should be aware of warnings in the product label regarding the risk of
Table 3. Summary of Infliximab Safety Through Week 54

<table>
<thead>
<tr>
<th>No. of treated patientsa</th>
<th>Patients not randomized at week 8</th>
<th>Patients randomized at week 8 to maintenance infliximab 5 mg/kg</th>
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<td></td>
<td>q8w</td>
<td>q12w</td>
<td>Combined</td>
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<tr>
<td>No. of treated patientsa</td>
<td>15</td>
<td>22</td>
<td>45</td>
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<tr>
<td>Mean duration of follow-up (wk)</td>
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<td>Mean exposure to infliximab (wk)</td>
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<td>Patients with ≥1 AE</td>
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<td>22 (100.0)</td>
<td>23 (100.0)</td>
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<td>Patients with ≥1 SAE</td>
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<td>3 (13.6)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Patients with ≥1 infection</td>
<td>4 (26.7)</td>
<td>13 (59.1)</td>
<td>14 (60.9)</td>
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<tr>
<td>Patients with ≥1 infusion reaction</td>
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<td>4 (18.2)</td>
<td>3 (13.0)</td>
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<td>135</td>
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<tr>
<td>Infusion with reactions</td>
<td>1 (2.5)</td>
<td>13 (7.9)</td>
<td>3 (2.2)</td>
</tr>
</tbody>
</table>

NOTE. Data presented are number (%) of patients unless otherwise specified.
AE, adverse event; SAE, serious adverse event.
A 7-year-old boy with a normal screening neutrophil count (4.61 \times 10^9/L [normal range, 1.5–8 \times 10^9/L]) was hospitalized for severe neutropenia (0.03 \times 10^9/L) 2 weeks after his first infliximab dose. This patient was receiving concomitant corticosteroid and sulfasalazine. Infliximab and sulfasalazine were discontinued. Sulfasalazine toxicity and infection were excluded, and antibody-mediated neutropenia was suspected. The severe neutropenia resolved during the next 2 months.

Appendix: Contributing Investigative Sites

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at doi:10.1016/j.cgh.2011.11.026.
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References


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Acknowledgements

Editorial and writing support was provided by James P. Barrett, an employee of the Medical Affairs Publications Group, Janssen Biotech, Inc. Members of the T72 Study Group are listed in the Appendix.

Conflicts of interest

The authors disclose the following: Jeffrey Hyams, Harland S. Winter, Subra Kugathasan, Stanley Cohen, James Markowitz, Johanna Escher, Gigi Veereman-Wauters, Wallace Crandall, Robert Baldassano, and Anne Griffiths received research funding in conjunction with the conduct of this study. Jeffrey Hyams, James Markowitz, and Anne Griffiths received research funding in conjunction with other studies sponsored by Janssen Research & Development, LLC. Jeffry Hyams, Harland S. Winter, Subra Kugathasan, James Markowitz, Wallace Crandall, Robert Baldassano, and Anne Griffiths served as Consultants to Janssen Research & Development, LLC. Marion Blank, Lakshmi Damaraju, Jewel Johanns, and Cynthia Guzzo are employees of Janssen Research & Development, LLC. Subra Kugathasan, James Markowitz, and Wallace Crandall received honoraria from Janssen Research & Development, LLC. Stanley Cohen received other research grants from and chaired conferences sponsored by Janssen Research & Development, LLC.

Funding

Janssen Research & Development, LLC, provided support for this study.
CONSORT 2010 Flow Diagram for Pediatric Ulcerative Colitis Trial

Enrollment

Assessed for eligibility (not reported)

Treated (n=60)

Infliximab 5 mg/kg Week 0, 2, 6

Not randomized (n=15)

Discontinued:

Adverse event (n=4)

Lack of efficacy (n=6)

Other (n=5)

Clinical responders at Week 8 based on IVRS

Randomized (n=45)

Allocation

Infliximab 5 mg/kg q8w

• Received allocated intervention (n=22)

• Did not receive allocated intervention (n=0)

Infliximab 5 mg/kg q12w

• Received allocated intervention (n=23)

• Did not receive allocated intervention (n=0)

Follow-Up

Discontinued intervention and completed follow-up (n=2)

Discontinued intervention (n=4)

Adverse event (n=3)

Lack of efficacy (n=1)

Discontinued intervention and completed follow-up (n=5)

Discontinued intervention (n=11)

Adverse event (n=8)

Lack of efficacy (n=4)

Other (n=1)

Analyses

Efficacy

Induction (n=60): Week 8

Mayo clinical remission

PUCAI clinical remission

Mucosal healing

Maintenance q8w (n=22); Week 30, Week 54

PUCAI clinical remission,

Corticosteroid-free clinical remission (n=14)

Maintenance q12w (n=23); Week 30, Week 54

PUCAI clinical remission,

Corticosteroid-free clinical remission (n=14)

Safety

Patients not Randomized (n=15), q8w (n=22), q12w (n=23), Combined (n=45), Total (n=60)

Supplementary Figure 1. CONSORT flow diagram. IVRS, interactive voice response system.