

## Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children

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**Background & Aims:** The REACH study evaluated the safety and efficacy of infliximab in children with moderately to severely active Crohn's disease. **Methods:** Patients (n = 112) with a Pediatric Crohn's Disease Activity Index (PCDAI) score >30 received infliximab 5 mg/kg at weeks 0, 2, and 6. Patients responding to treatment at week 10 were randomized to infliximab 5 mg/kg every 8 or 12 weeks through week 46. A concurrent immunomodulator was required. Clinical response (decrease from baseline in the PCDAI score  $\geq 15$  points; total score  $\leq 30$ ) and clinical remission (PCDAI score  $\leq 10$  points) were evaluated at weeks 10, 30, and 54. **Results:** At week 10, 99 of 112 (88.4%) patients responded to infliximab (95% confidence interval: [82.5%, 94.3%]) and 66 of 112 (58.9%) patients achieved clinical remission (95% confidence interval: [49.8%, 68.0%]). At week 54, 33 of 52 (63.5%) and 29 of 52 (55.8%) patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively, compared with 17 of 51 (33.3%) and 12 of 51 (23.5%) patients receiving treatment every 12 weeks ( $P = .002$  and  $P < .001$ , respectively). **Conclusions:** Pediatric patients responding to an induction regimen of infliximab were more likely to be in clinical response and remission at week 54 without dose adjustment when their maintenance therapy was given every 8 weeks rather than every 12 weeks. Allowing for dose intensification in the case of relapse, remission rates, but not response rates, at week 54 were superior with every 8-week dosing compared with every 12-week dosing.

The true incidence of Crohn's disease (CD) in the pediatric population is unknown, but 25% of new diagnoses of inflammatory bowel disease occur in patients younger than 20 years of age.<sup>1</sup> In children, both the

disease and its treatment, which can include corticosteroids and immunomodulatory agents, can often result in significant long-term effects that include growth failure, osteopenia, and pathologic fractures.<sup>2,3</sup> Corticosteroid dependency and resistance are common in the pediatric population.<sup>4</sup>

The presentation of CD in children is similar to that in adults, suggesting that the same pathophysiologic mechanisms involving tumor necrosis factor alpha (TNF $\alpha$ ) are involved. The efficacy and safety of infliximab, a monoclonal antibody that binds with high affinity and specificity to TNF $\alpha$ ,<sup>5</sup> in the treatment of adult patients with moderately to severely active CD is well documented.<sup>6-9</sup> In particular, 58% of adult patients with CD in the ACCENT I study responded to a single infusion of infliximab 5 mg/kg within 2 weeks of initiating therapy.<sup>7</sup> Open-label studies and case reports suggest that a response to infliximab in CD is comparable in children and adults.<sup>10-13</sup>

We conducted a multicenter, randomized, open-label study of infliximab in pediatric patients with moderately to severely active CD. The study was entitled "A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF $\alpha$  chimeric monoclonal antibody (infliximab, REMICADE, Malvern, PA) in pediatric subjects with moderate-to-severe Crohn's disease" or the "REACH" study. In the REACH study, the efficacy of a 3-dose induction regimen of infliximab in reducing signs and symptoms of CD in children was evaluated. We also compared the efficacy and safety through 54 weeks of maintenance therapy given every 8 weeks with that given every 12 weeks.

**Abbreviations used in this paper:** CD, Crohn's disease; CDAI, Crohn's disease activity index; PCDAI, Pediatric Crohn's Disease Activity Index; REACH, A randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF $\alpha$  chimeric monoclonal antibody (infliximab, REMICADE<sup>®</sup>) in pediatric subjects with moderate-to-severe Crohn's disease; TNF $\alpha$ , tumor necrosis factor alpha.

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## Materials and Methods

### Patients

This multicenter, randomized, open-label study was conducted at 34 sites in North America (73.2% of patients), Western Europe (22.3% of patients), and Israel (4.5% of patients). Patients were enrolled from February 24, 2003, to March 31, 2004. The institutional review boards at participating sites approved the protocol. Written informed consent was obtained from all parents/legal guardians, and assent was obtained from children based on individual Institutional Review Board guidelines.

Eligible patients were 6 to 17 years of age, inclusive, and had a Pediatric Crohn's Disease Activity Index (PCDAI)<sup>14,15</sup> >30 at baseline. The diagnosis of CD, which was confirmed by endoscopy and biopsy, was made at least 3 months before screening. Patients also were required to have initiated treatment with an immunomodulator (ie, azathioprine, 6-mercaptopurine, or methotrexate) at least 8 weeks before screening, and were to have been receiving a stable dose for at least the previous 2 weeks. Patients receiving the following concomitant treatments were eligible to participate: aminosalicylates (if the dose was stable at least 2 weeks before screening), oral corticosteroids at the equivalent of 60 mg/day of prednisone or less (stable dose for 1 week), enteral nutrition (stable regimen for 2 weeks), or antibiotics (stable dose for at least 1 week before week 0). Rectal or parenteral corticosteroids were not permitted and had to be discontinued at least 2 weeks prior to screening. Patients were excluded from the study if they had received previous treatment with infliximab or any other agent targeted at reducing TNF.

### Study Design

Eligible patients received an induction regimen of infliximab 5 mg/kg at weeks 0, 2, and 6. Four weeks later (at week 10), patients were evaluated for a clinical response to treatment as defined as a decrease from baseline in the PCDAI score of at least 15 points, with a total score of 30 or less. Patients who met these criteria, as assessed by the principal investigators, were randomized in a 1:1 ratio to receive subsequent infusions of infliximab 5 mg/kg every 8 weeks at weeks 14, 22, 30, 38, and 46, or every 12 weeks at weeks 18, 30, and 42. Patients who did not respond to the induction regimen at week 10 received no further treatment with infliximab and were discontinued from the study.

The objectives of the REACH study were to assess the efficacy of a 3-dose induction regimen of infliximab in reducing signs and symptoms of pediatric CD, and to examine clinical response and clinical remission at week 54, and changes from baseline to week 54 in corticosteroid use and patient height.

Patient allocation to treatment group was performed using an adaptive, stratified design with investigational

site as the strata. The pharmacist prepared the infusion (infliximab, REMICADE<sup>®</sup>, Centocor, Inc., Malvern, PA), which was administered in an open-label manner.

### Efficacy Evaluations

Patients were assessed at weeks 0, 2, 6, and 10. Patients who received infliximab every 8 weeks had additional visits at weeks 14, 22, 30, 38, 46, and 54, while those who received infliximab every 12 weeks had additional visits at weeks 18, 30, 42, and 54. At each visit, the components of the PCDAI score were measured. The PCDAI is a validated multi-item measure of severity of illness that, in contrast to the adult-derived Crohn's Disease Activity Index (CDAI), includes linear growth and places less emphasis on subjectively reported symptoms and more on laboratory parameters of intestinal inflammation.<sup>14,16</sup> For a subset of patients, health-related quality of life was assessed by the IMPACT III Questionnaire, which was administered at weeks 0, 10, 30, and 54. The IMPACT III Questionnaire was specifically developed to assess quality of life in pediatric patients with inflammatory bowel disease. The questionnaire is validated only in patients ranging in age from 10 to 17 years in North America.<sup>17,18</sup> However, 5 of the 76 patients who completed an IMPACT III questionnaire were 9 years old or younger; these patients were included in the analysis. The IMPACT III scores range from 35 to 175, with higher scores indicating better quality of life.

Patients who lost clinical response were eligible to cross over one time during the study to receive treatment more frequently and/or at a higher dose. The treatment regimen to which patients crossed over was based on the length of time between the previous infusion and loss of clinical response. If clinical response was lost prior to 8 weeks from the previous infliximab infusion, for both the every-8-weeks and every-12-weeks groups, patients were eligible to cross over to infliximab 10 mg/kg every 8 weeks. Patients receiving infliximab every 12 weeks who lost clinical response within the period from week 8 to week 12 following the previous infusion were eligible to cross over to infliximab 5 mg/kg every 8 weeks. Loss of clinical response was defined by: (1) an increase in the PCDAI of at least 15 points from the reference PCDAI score at week 10 at 2 consecutive visits at least 7 days apart, or (2) the overall PCDAI score was higher than 30 points at any scheduled or unscheduled visit. Patients who lost response and crossed over were considered non-responders in the analyses (treatment failures) for the remainder of the study.

### Serum Infliximab Concentrations

Blood samples for measurement of infliximab concentrations were collected at several time points during the study, including immediately before each infusion and at 60 minutes following infusion at weeks 0, 2, 6, and 42 (for patients receiving infliximab every

12 weeks) or 46 (for patients receiving infliximab every 8 weeks).

### **Concomitant Medications**

Patients receiving corticosteroids were to maintain a stable dose until week 2, after which a defined tapering schedule was initiated if the patient's condition had improved. A patient entering the study, who was receiving corticosteroid doses of at least 20 mg/day prednisone equivalent, tapered at a maximum rate of 10 mg/day per week. Patients entering the study receiving at least 10 but <20 mg/day tapered at a maximum rate of 5 mg/day per week; the maximum rate for patients receiving <10 mg/day prednisone equivalent was 2.5 mg/day per week. Aminosalicylates and immunomodulators were to be maintained at a constant dose for the duration of the study.

### **Safety Evaluations**

Data for all of the 112 study participants are included in the safety analyses. At each visit, adverse events were documented, and blood samples for clinical laboratory evaluations were obtained. Blood samples were also collected to determine the presence of antinuclear antibodies at weeks 0, 30, and 54. Samples positive for antinuclear antibodies were tested for antidouble-stranded DNA antibodies. The criterion for a positive antidouble-stranded DNA antibodies result was the presence of an antinuclear antibodies  $\geq 1:40$  and a positive Crithidia assay test. Blood samples for measurement of antibodies to infliximab were collected at weeks 0, 30, and 54.

### **Statistical Methods**

The proportion of patients in clinical response at week 10 was assessed, and corresponding 95% confidence intervals were determined. Patients who met any of the following criteria for treatment failure between week 0 and week 10 were considered nonresponders in the analysis of clinical response at week 10: (1) had protocol-prohibited concomitant medication changes, (2) had CD-related surgery (drainage of abscess or seton placement acceptable), or (3) discontinued study participation. Patients who had insufficient data to assess their clinical response status at week 10 were also considered nonresponders. The proportion of patients in clinical remission (PCDAI score  $\leq 10$  points) at week 10 was also assessed. The proportions of patients in clinical response and in clinical remission at week 54, as well as the changes from baseline to week 54 in daily corticosteroid use, were compared between the maintenance regimens, that is, every 8 weeks versus every 12 weeks. Patients who lost clinical response and subsequently crossed over were considered nonresponders in the analyses for the remainder of the study. The same treatment failure and missing data rules as described above for the week-10 analyses

were applied to the week-54 analyses. To assess patient clinical status at week 54 independent of whether patients required dose modification or changes in concomitant medications, clinical response and remission were evaluated, ignoring whether or not patients crossed over and suspending the treatment failure rules.

Change from baseline in patient height status was assessed using the height z-score, which is a measure of the deviation of the patient's height from the expected height of an age- and sex-matched population, in this case the 2000 Centers for Disease Control Growth Charts for the United States (<http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/zscore/zscore.htm>). The z-score was calculated as the (observed height - reference population mean) divided by the standard deviation of the reference population. Patients with a 1-year delay in bone age, as assessed by radiograph of the wrist, had z-scores calculated at baseline and weeks 30 and 54.

All analyses were based on an intent-to-treat principle. Analyses comparing the 2 maintenance regimens were performed using the  $\chi^2$  test for dichotomous variables and using analysis of variance on the van der Waerden normal scores for continuous variables. To test for an overall effect of infliximab on a variable, regardless of dose or dosing interval, paired *t*-tests were used to compare baseline and postbaseline measurements. All statistical testing was 2 sided and utilized a 0.05 level of significance.

The power to detect a significant treatment effect between the every-8-week and every-12-week treatment regimens, using a 2-sided  $\chi^2$  test at the 0.05 level of significance and assuming that approximately 67% of the 110 patients were randomized at week 10 (or approximately 36 patients per group), was 65% (assuming 60% and 30% responses in the patients receiving infliximab every 8 weeks and every 12 weeks, respectively) and 31% (assuming 60% and 40% responses in the patients receiving infliximab every 8 weeks and every 12 weeks, respectively).

### **Role of Funding Source**

A committee comprising the REACH Steering Committee members and Centocor, Inc. staff members designed this study; all Steering Committee members are authors of this manuscript. Centocor, Inc. collected data from all clinical sites to create the clinical database. Centocor, Inc. staff members and members of the REACH Steering Committee analyzed and interpreted the data, wrote this manuscript, and agreed to submit this manuscript for publication. The principal investigators approved the content of the manuscript before submission.

## **Results**

### **Patient Disposition, Baseline Characteristics, and Prior Concomitant Medications**

The study population comprised 66 (58.9%) males and 46 (41.1%) females with a mean age of 13.3 years

**Table 1.** Baseline Patient Characteristics

| Characteristic                           | Patients not randomized at week 10 | Patients randomized at week 10   |                                   |              | Total patients |
|--|------------------------------------|----------------------------------|-----------------------------------|--------------|----------------|
|  |                                    | Infliximab 5 mg/kg every 8 weeks | Infliximab 5 mg/kg every 12 weeks | Combined     |                |
| Number of patients                       | 9                                  | 52                               | 51                                | 103          | 112            |
|  |                                    | Number (percent) of patients:    |                                   |              |                |
| Gender                                   |                                    |                                  |                                   |              |                |
| Male                                     | 4 (44.4%)                          | 33 (63.5%)                       | 29 (56.9%)                        | 62 (60.2%)   | 66 (58.9%)     |
| Female                                   | 5 (55.6%)                          | 19 (36.5%)                       | 22 (43.1%)                        | 41 (39.8%)   | 46 (41.1%)     |
| Race                                     |                                    |                                  |                                   |              |                |
| Caucasian                                | 9 (100.0%)                         | 43 (82.7%)                       | 42 (82.4%)                        | 85 (82.5%)   | 94 (83.9%)     |
| Black                                    | 0 (0.0%)                           | 7 (13.5%)                        | 8 (15.7%)                         | 15 (14.6%)   | 15 (13.4%)     |
| Asian                                    | 0 (0.0%)                           | 1 (1.9%)                         | 0 (0.0%)                          | 1 (1.0%)     | 1 (0.9%)       |
| Other                                    | 0 (0.0%)                           | 1 (1.9%)                         | 1 (2.0%)                          | 2 (1.9%)     | 2 (1.8%)       |
| Involved GI area                         |                                    |                                  |                                   |              |                |
| Ileum                                    | 4 (44.4%)                          | 37 (71.2%)                       | 38 (74.5%)                        | 75 (72.8%)   | 79 (70.5%)     |
| Colon                                    | 7 (77.8%)                          | 48 (92.3%)                       | 41 (80.4%)                        | 89 (86.4%)   | 96 (85.7%)     |
| Upper tract                              | 3 (33.3%)                          | 20 (38.5%)                       | 17 (33.3%)                        | 37 (35.9%)   | 40 (35.7%)     |
| Concomitant medications at baseline:     |                                    |                                  |                                   |              |                |
| 6-MP/azathioprine                        | 7 (77.8%)                          | 46 (88.5%)                       | 47 (92.2%)                        | 93 (90.3%)   | 100 (89.3%)    |
| Methotrexate                             | 2 (22.2%)                          | 7 (13.5%)                        | 2 (3.9%)                          | 9 (8.7%)     | 11 (9.8%)      |
| 5-Aminosalicylates                       | 3 (33.3%)                          | 31 (59.6%)                       | 25 (49.0%)                        | 56 (54.4%)   | 59 (52.7%)     |
| Concomitant cortico-steroids at baseline |                                    |                                  |                                   |              |                |
| ≤1 mg/kg P.Eq.                           | 2 (22.2%)                          | 23 (44.2%)                       | 10 (19.6%)                        | 33 (32.0%)   | 35 (31.3%)     |
| >1 mg/kg P.Eq.                           | 1 (11.1%)                          | 1 (1.9%)                         | 2 (3.9%)                          | 3 (2.9%)     | 4 (3.6%)       |
|  |                                    | Mean (SD)                        |                                   |              |                |
| Age (years)                              | 13.7 (3.3)                         | 12.9 (2.5)                       | 13.7 (2.4)                        | 13.3 (2.5)   | 13.3 (2.5)     |
| Weight (kg)                              | 47.9 (13.2)                        | 45.0 (17.3)                      | 41.9 (11.5)                       | 43.5 (14.7)  | 43.8 (14.6)    |
| Height (cm)                              | 153.7 (18.0)                       | 153.1 (15.2)                     | 153.0 (14.6)                      | 153.1 (14.8) | 153.1 (15.0)   |
| Disease duration (years)                 | 2.4 (1.6)                          | 2.3 (1.5)                        | 1.6 (1.3)                         | 1.9 (1.4)    | 2.0 (1.4)      |
| Symptom duration (months)                | 4.6 (2.9)                          | 6.6 (7.9)                        | 8.2 (9.6)                         | 7.4 (8.8)    | 7.2 (8.5)      |
| PCDAI score                              | 41.7 (10.2)                        | 42.1 (9.2)                       | 40.1 (6.8)                        | 41.1 (8.1)   | 41.2 (8.3)     |
| ESR (mm/h)                               | 30.6 (22.4)                        | 37.3 (18.7)                      | 41.9 (26.8)                       | 39.6 (23.1)  | 38.9 (23.1)    |

6-MP, 6-mercaptopurine; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; PCDAI score, Pediatric Crohn's Disease Activity Index; P.Eq., prednisone equivalent.

(standard deviation of 2.5 years). The mean (SD) PCDAI score at baseline was 41.2 (8.3) (Table 1).

Of the 112 patients who entered the study and received an infusion of infliximab 5 mg/kg at week 0, 103 (92.0%) were randomized to maintenance treatment at week 10 (Figure 1). These 103 patients were randomized to receive infliximab every 8 weeks (52 patients) or every 12 weeks (51 patients). Two patients who did not meet the PCDAI criteria for clinical response at week 10 were randomized by the investigator in error; these patients were considered nonresponders for these analyses. One patient who met the clinical response criteria at week 10 was mistakenly not randomized; this patient was considered a responder in the clinical response at the week-10 analysis. Beyond these errors in randomization, 3 patients who were considered by the investigator to be in clinical response based on the PCDAI score had received prohibited concomitant medications before the week-10 evaluations. These 3 patients were considered to be nonresponders in

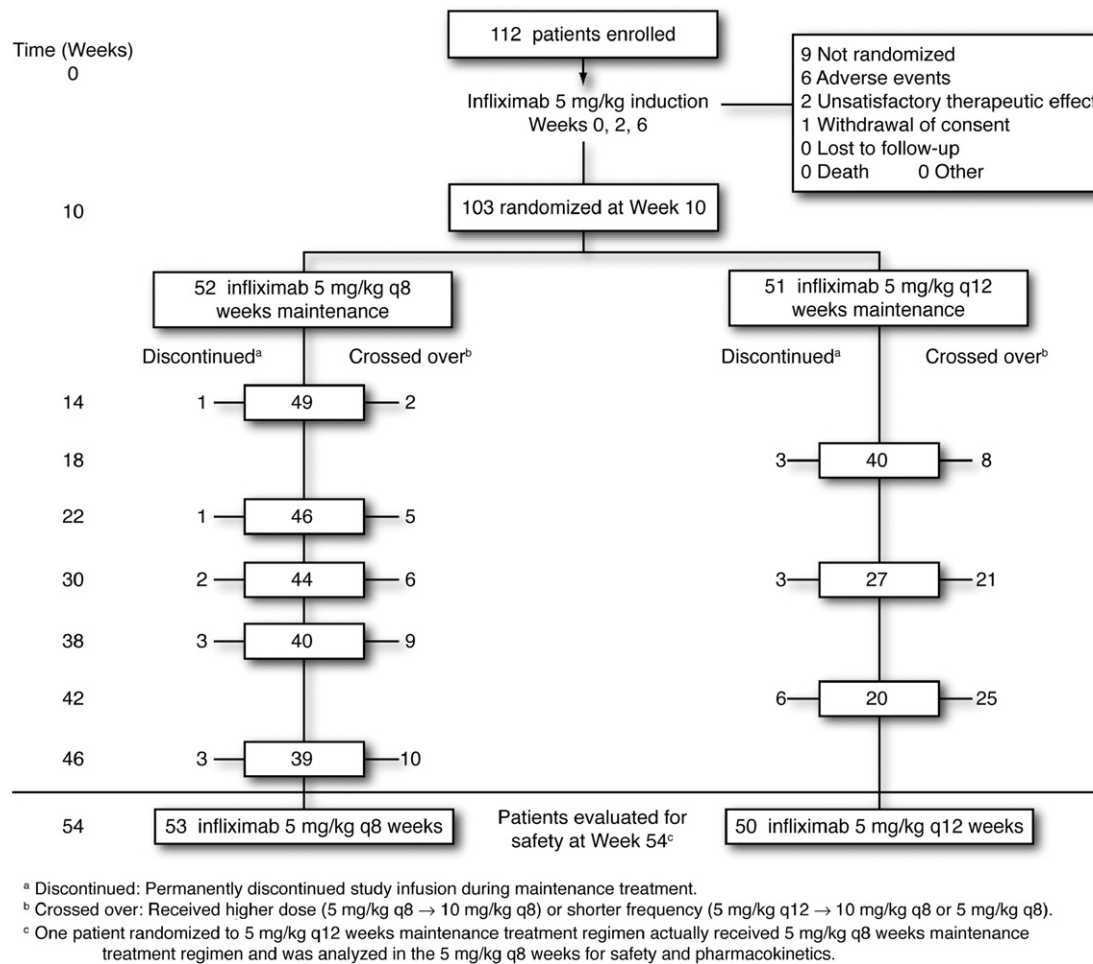
the clinical response at week-10 analysis. Thus, 99 patients were considered to have achieved clinical response at week 10 (see *Efficacy* results).

Twenty-four (21.4%) of the 112 patients who entered the study discontinued the study through week 54; 9 discontinued before or at week 10, and 15 discontinued following randomization at week 10 (with 6 of these patients discontinuing after crossover). A greater proportion of patients receiving infliximab every 12 weeks discontinued therapy due to an adverse event (4 of 51 patients or 7.8%) or due to unsatisfactory therapeutic effect (4 of 51 patients or 7.8%) than patients receiving infliximab every 8 weeks (2 of 52 patients or 3.8% for each of these discontinuation reasons).

### *Efficacy*

**Clinical response and remission.** Ninety-nine of the 112 (88.4%) treated patients responded to an induction regimen of infliximab 5 mg/kg at week 10; the





**Figure 1.** Status of pediatric patients with Crohn's disease through week 54. Note that the number of patients discontinuing and crossing over are cumulative over visits, and that patients who discontinued after crossover are not included in this figure.

corresponding 95% confidence interval was (82.5%, 94.3%). Sixty-six of 112 (58.9%) treated patients were in clinical remission following the induction regimen of infliximab 5 mg/kg at week 10; the corresponding 95% confidence interval was 49.8%, 68.0%.

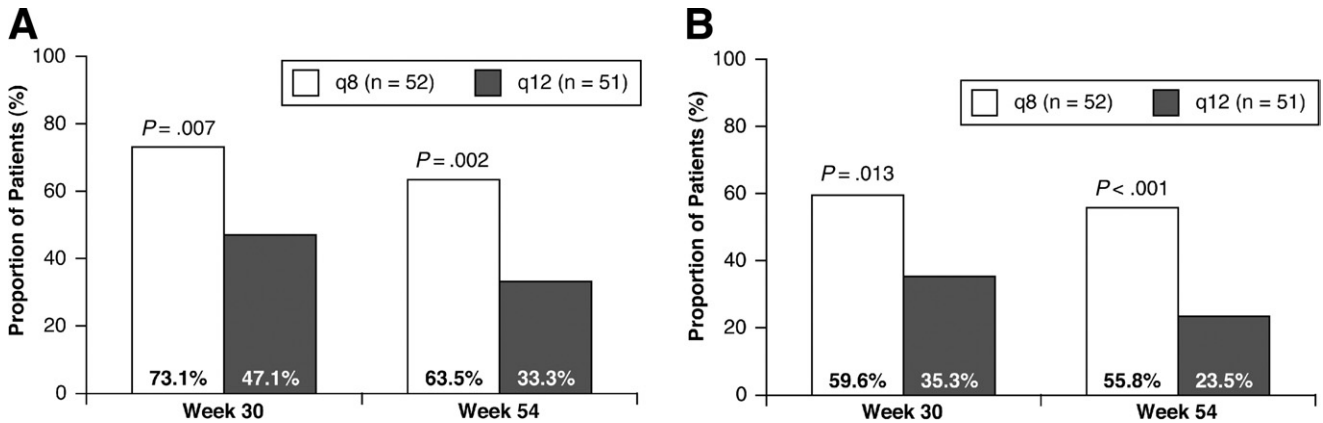
Among all randomized patients, 33 of 52 (63.5%) and 29 of 52 (55.8%) patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission at week 54, respectively, compared with 17 of 51 (33.3%) and 12 of 51 (23.5%) patients receiving treatment every 12 weeks ( $P = .002$  and  $P < .001$ , respectively; Figure 2A and B). Note that in this analysis, according to the protocol treatment failure rules, all patients who crossed over were considered nonresponders.

The mean PCDAI score decreased by 31.3 points from baseline (mean of 41.1) to week 10 (Figure 3A). The improvement in PCDAI score was evident as early as 2 weeks following the first infusion of infliximab. Similar significant improvements in the PCDAI score were noted at weeks 30 and 54 (Figure 3A).

At week 10, the mean changes from baseline in PCDAI, as well as the proportion of patients in clinical remission, were similar for patients randomized to receive infliximab every 8 weeks (−33.2 and 65.4, respectively) and those randomized to receive infliximab every 12 weeks (−29.4% and 62.7%, respectively).

**Quality of life.** As shown in Figure 3B, the mean IMPACT III score at week 10 had improved significantly from baseline (mean increase of 23.9,  $P < .001$ ). Similarly, the mean IMPACT III scores at weeks 30 and 54 had improved significantly from baseline ( $P < .001$  for both comparisons). When mean changes from baseline were compared between the maintenance regimens, patients receiving infliximab every 8 weeks showed slightly more improvement than those receiving infliximab every 12 weeks at both week 30 (mean changes of 24.7 and 18.3, respectively;  $P = .165$ ) and week 54 (mean changes of 26.5 and 22.5, respectively;  $P = .236$ ), although in neither case was the observed difference statistically significant.

**Corticosteroid use.** Average daily corticosteroid use for the combined infliximab maintenance groups



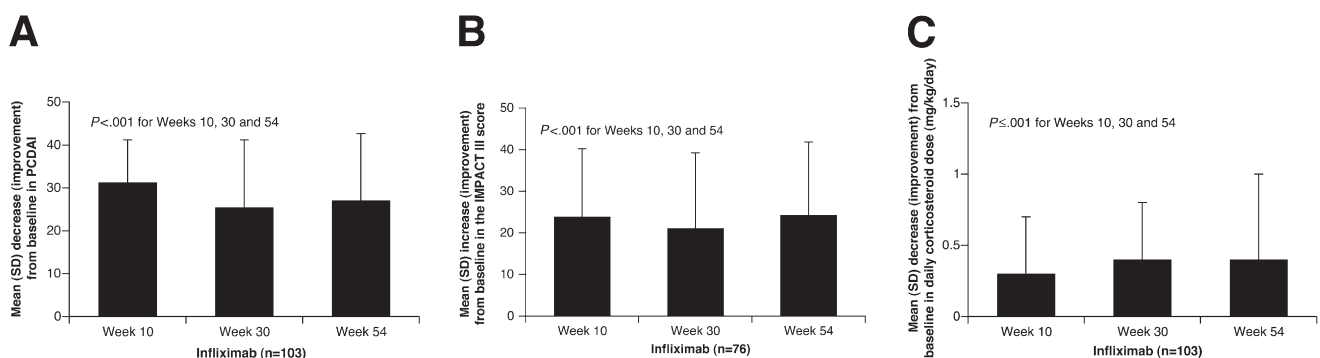
**Figure 2.** Clinical response (decrease from baseline to week 10 in the total PCDAI score of at least 15 points and a total PCDAI score of no more than 30 points (A) and clinical remission (PCDAI score of 10 points or lower; (B) for week 10 responders at weeks 30 and 54. All randomized patients.

decreased significantly ( $P < .001$ ) from baseline to week 10 (mean decrease of 0.3 mg/kg per day). Significant decreases in corticosteroid use were also observed at weeks 30 and 54 (Figure 3C). At week 10, 15 of the 36 patients on corticosteroids at baseline had discontinued corticosteroids (12 of 24 and 3 of 12 patients in the every-8-weeks and every-12-weeks groups, respectively). By week 54, 10 of the 12 patients on corticosteroids at week 10 in the every-8-weeks group, compared with 5 of the 9 patients in the every-12-weeks group, had discontinued corticosteroids (Figure 4). When clinical remission was evaluated in patients discontinuing corticosteroid use, a difference was noted in favor of the group receiving maintenance treatment every 8 weeks (see below).

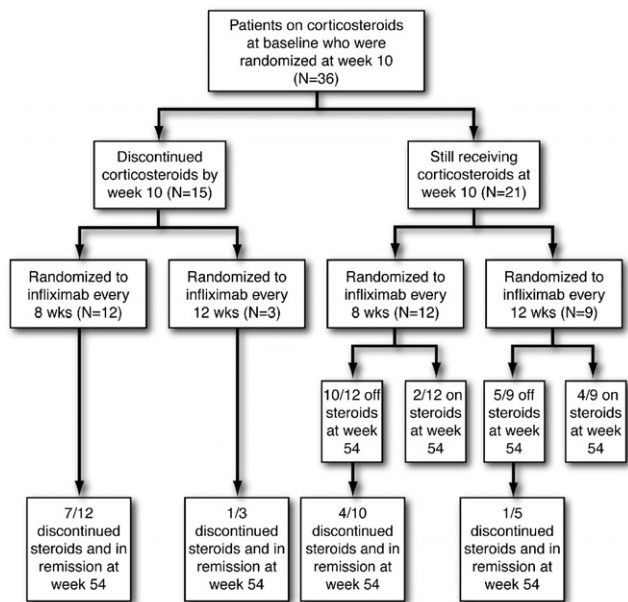
By the time of the first maintenance dose, 19 of 24 patients receiving infliximab every 8 weeks and 7 of 12 patients receiving infliximab every 12 weeks had discontinued corticosteroid use. Note that the first maintenance dose corresponded to week 14 for patients receiving infliximab every 8 weeks and to week 18 for those

receiving infliximab every 12 weeks. Among the 36 patients who were using corticosteroids at baseline, 13 (36.1%) were in clinical remission at week 54 and were no longer using corticosteroids from weeks 30 through 54: 11 (45.8%) patients receiving infliximab every 8 weeks and 2 (16.7%) patients receiving infliximab every 12 weeks. Of the 21 patients on corticosteroids at week 10, 5 (23.8%) were in clinical remission and no longer using corticosteroids at week 54 (4 of 12 [33.3%] patients receiving infliximab every 8 weeks and 1 of 9 [11.1%] patients receiving infliximab every 12 weeks; Figure 4).

**Height status.** The height status of patients with at least a 1-year delay in bone age was assessed, and the patient's height  $z$ -score was calculated. The height  $z$ -score is a measure of the deviation of the patient's height from the expected height of an age- and sex-matched population. The mean baseline  $z$ -score of these patients was  $-1.5$ . The scores for these patients improved significantly at both week 30 (mean improvement in  $z$ -score of 0.3;  $P < .001$ ) and week 54 (mean improvement in  $z$ -score of 0.5;  $P < .001$ ).



**Figure 3.** Summary of mean improvement from baseline for the pediatric Crohn's disease activity index (PCDAI) score (A), IMPACT III questionnaire score (B), and daily corticosteroid (prednisone equivalent) dose (C). All randomized patients. Patients who discontinued the study or had insufficient data had their last nonmissing PCDAI score/average daily corticosteroid value carried forward. Patients who had a prohibited CD-related surgery or had a prohibited concomitant medication change had their last nonmissing PCDAI score/average daily corticosteroid value prior to the event carried forward to all subsequent visits. Patients who crossed over prior to week 30 had the IMPACT III score from the first crossover visit carried forward for the week-30 analysis.



**Figure 4.** Flowchart of patient corticosteroid use for those who were on corticosteroids at baseline and who were randomized at week 10. Patients who had a prohibited CD-related surgery or had a prohibited concomitant medication change were considered to not be in clinical remission at week 54. Likewise, patients who had a dose adjustment were considered not to be in clinical remission. Patients who discontinued the study or had insufficient data to assess their clinical remission status at week 54 were considered to not be in clinical remission. Patients with missing data for corticosteroid use had their last corticosteroid dose carried forward in the analysis.

**Clinical response following crossover.** Of the 35 patients who crossed over, 32 satisfied the criteria for being evaluable in the analysis of regained response. Evaluable patients were those who were in clinical response at some point during their maintenance phase and subsequently lost response, thus warranting crossover; patients who were in clinical response at the time of crossover were excluded. Of the 32 patients evaluated, 24 (75.0%) regained response after crossing over, including 5 of 9 (55.6%) patients who initially received infliximab

5 mg/kg every 8 weeks and subsequently crossed over to infliximab 10 mg/kg every 8 weeks and 19 of 23 (82.6%) patients who initially received infliximab 5 mg/kg every 12 weeks and subsequently crossed over to receive either infliximab 10 mg/kg (12/13, 92.3%) or 5 mg/kg (7/10, 70.0%) every 8 weeks.

**Clinical status with suspension of treatment failure rules.** Clinical status was also assessed by suspending treatment failure rules, ignoring whether or not patients crossed over, and without imputing data for patients who discontinued. In these post hoc analyses, a greater proportion of patients were in clinical remission at week 54 in the every-8-weeks group (71%, 35 of 49) than in the every-12-weeks group (47%, 21 of 45;  $P = .02$ ). Although a similar proportion of patients in each group were in clinical response at week 54 (84%, 41 of 49 and 80%, 36 of 45, respectively), 49% (25 of 51) of patients in the every-12-weeks group lost response during the 54-week follow-up in contrast to 19% (10 of 52) of patients in the every-8-weeks group.

**Antibodies to Infliximab**

Through week 54, 105 patients were evaluated for the presence of antibodies to infliximab (see Table 2). The presence of infliximab in the serum of patients is known to interfere with the interpretation of the analyses for antibodies to infliximab. Therefore, patients who were not positive for antibodies to infliximab but had detectable concentrations of infliximab following their last infusion, which could compete for the detection of antibodies to infliximab in the immunoassay used, were classified as inconclusive. In this evaluation, 3 of 105 (2.9%) patients developed antibodies to infliximab: 1 who was not randomized at week 10 (at week 16, titer of 1:40), 1 receiving infliximab every 8 weeks (at week 54, titer of 1:10), and 1 receiving infliximab every 12 weeks (week 22, titer of 1:10). The majority (77.1%, 81 of 105) of patients had inconclusive test results for antibodies to infliximab, and 20.0% (21 of 105) of patients had negative findings.

**Table 2.** Incidence of Infusion Reactions by Antibody to Infliximab Status Through Week 54 (Treated Patients)

|   | Positive <sup>a</sup> | Negative <sup>b</sup> | Inconclusive <sup>c</sup> | All patients  |
|---|-----------------------|-----------------------|---------------------------|---------------|
| Evaluable patients with appropriate samples <sup>d</sup>        | 3/105 (2.9%)          | 21/105 (20.0%)        | 81/105 (77.1%)            | 105           |
| No. (percent) of patients with infusion reactions <sup>e</sup>  | 1/3 (33.3%)           | 6/21 (28.6%)          | 10/81 (12.3%)             | 17 (16.2%)    |
| No. (percent) of infusions with infusion reactions <sup>e</sup> | 1/13 (7.7%)           | 8/108 (7.4%)          | 12/492 (2.4%)             | 21/613 (3.4%) |

<sup>a</sup>Includes values for all patients with appropriate samples who had at least 1 positive sample at any time.  
<sup>b</sup>Includes values for all patients with appropriate samples who had a negative sample after the last evaluation, excluding patients who were positive.  
<sup>c</sup>Includes values for all patients with appropriate samples who had an inconclusive sample (sample with detectable infliximab concentration) after the last evaluation, excluding those who were positive.  
<sup>d</sup>Patients with appropriate samples either had antibodies to infliximab at some time point following their first infusion or had 1 or more samples obtained after their last infusion.  
<sup>e</sup>Adverse event data for patients who crossed over were excluded from the point of crossover.

**Table 3.** Summary of Safety Findings for All Patients (n = 112) Through Week 54

| Safety parameter                                 | Patients not randomized at week 10 | Patients randomized at week 10   |                                   |            | Total patients |
|--|------------------------------------|----------------------------------|-----------------------------------|------------|----------------|
|  |                                    | Infliximab 5 mg/kg every 8 weeks | Infliximab 5 mg/kg every 12 weeks | Combined   |                |
| Patients treated                                 | 9                                  | 53                               | 50                                | 103        | 112            |
| Average weeks of:                                |                                    |                                  |                                   |            |                |
| Follow-up  | 8.8                                | 51.5                             | 49.6                              | 50.6       | 47.2           |
| Exposure   | 3.9                                | 44.0                             | 40.6                              | 42.3       | 39.2           |
| Infliximab exposure over 54 weeks (mean/patient) |                                    |                                  |                                   |            |                |
| No. of infusions                                 | 21                                 | 409                              | 319                               | 29         | 31             |
| Total mg/kg                                      | 11.0                               | 40.0                             | 31.1                              | 40.0       | 39.9           |
| Patients (n, percent) with:                      |                                    |                                  |                                   |            |                |
| Adverse events                                   | 9 (100.0%)                         | 51 (96.2%)                       | 46 (92.0%)                        | 97 (94.2%) | 106 (94.6%)    |
| Adverse events leading to discontinuation        | 6 (66.7%)                          | 2 (3.8%) <sup>a</sup>            | 4 (8.0%) <sup>b</sup>             | 6 (5.8%)   | 12 (10.7%)     |
| Serious adverse events <sup>c</sup>              | 7 (77.8%)                          | 8 (15.1%)                        | 7 (14.0%)                         | 15 (14.6%) | 22 (19.6%)     |
| Infection  | 3 (33.3%)                          | 39 (73.6%)                       | 19 (38.0%)                        | 58 (56.3%) | 61 (54.5%)     |
| Serious infection <sup>d</sup>                   | 2 (22.2%)                          | 3 (5.7%)                         | 4 (8.0%)                          | 7 (6.8%)   | 9 (8.0%)       |
| Intestinal stenosis                              | 2 (22.2%)                          | 1 (1.9%)                         | 0 (0.0%)                          | 1 (1.0%)   | 3 (2.7%)       |
| Infusion reactions <sup>e</sup>                  | 1 (11.1%)                          | 9 (17.0%)                        | 9 (18.0%)                         | 18 (17.5%) | 19 (17.0%)     |
| Pneumonia  | 0 (0.0%)                           | 2 (3.8%)                         | 1 (2.0%)                          | 3 (2.9%)   | 3 (2.7%)       |
| Herpes zoster                                    | 0 (0.0%)                           | 2 (3.8%)                         | 0 (0.0%)                          | 2 (1.9%)   | 2 (1.8%)       |

NOTE. Data for patients who crossed over are included according to the initial randomized treatment assignment and represent the safety profile from week 0 through week 54.

<sup>a</sup> Two patients discontinued from every-8-weeks dosing due to worsening Crohn's disease (CD) in 1 patient and bacterial infection in the other.

<sup>b</sup> Four patients discontinued from every-12-weeks dosing due to intestinal obstruction (2 patients), worsening CD (third patient), and worsening CD/enterocolitis (fourth patient).

<sup>c</sup> The most frequently occurring serious adverse events among randomized patients were related to the gastrointestinal system, including CD in 7 patients and abscess in 2 patients overall.

<sup>d</sup> The serious infections included sepsis and fever among 2 patients not randomized at week 10; colitis, pneumonia, and furunculosis/adenitis/abscess in 3 patients receiving infliximab every 8 weeks; and abscess, abdominal pain/fever/vomiting, worsening of CD, and enterocolitis in 4 patients receiving treatment every 12 weeks.

<sup>e</sup> An infusion reaction was defined as any adverse experience that occurred during or within 1 hour following the infusion. Infusion reactions occurring in 2 or more patients included flushing (8 patients); injection site infiltration and dyspnea (4 patients each); and sweating, urticaria, chest pain, vomiting, hypotension, and paresthesias (each in 2 patients).

## Safety

Safety data for all 112 treated patients are reported according to the actual treatment received. Total exposure to infliximab is presented in Table 3. Of note, as a result of more patients who received infliximab every 12 weeks discontinuing from the study, patients receiving infliximab every 8 weeks were followed an average of 1.9 weeks (or 3.7%) longer than those receiving infliximab every 12 weeks.

The proportions of patients reporting adverse events and serious adverse events were similar between the 2 maintenance treatment regimens. With regard to adverse events of interest, similar proportions of patients in these maintenance groups also had upper respiratory tract infection (19 of 53 [35.8%] patients receiving infliximab every 8 weeks and 16 of 50 [32.0%] patients receiving infliximab every 12 weeks) and anemia (6 of 53 [11.3%] patients receiving infliximab every 8 weeks and 5 of 50 [10.0%] patients receiving infliximab every 12 weeks). Notable infections included pneumonia in 3 patients (2 receiving infliximab every 8 weeks and 1 receiving infliximab every 12 weeks), herpes zoster in 2 patients receiving

infliximab every 8 weeks, and abscess in 5 patients (4 patients receiving infliximab every 8 weeks and 1 patient receiving infliximab every 12 weeks).

Although the incidence of adverse events noted by the investigator to be infections was higher among patients receiving infliximab every 8 weeks (39 of 53 patients or 73.6%) than for those receiving treatment every 12 weeks (19 of 50 patients or 38.0%), the incidence of serious infections was similar between patients receiving infliximab every 8 weeks (3 of 53 patients or 5.7%) and those receiving treatment every 12 weeks (4 of 50 patients or 8.0%; Table 3). Only 1 of the patients with serious infections had an infection that was not related to CD. This patient, who received infliximab every 8 weeks and was hospitalized for pneumonia 50 days after the week-30 infusion, was treated with antibiotics (overnight) and recovered. Adverse events reported by the investigator as infections were subsequently examined by time of occurrence. Through week 14, during which time all patients received identical treatment, 39.6% (21 of 53) and 22.0% (11 of 50) of patients subsequently randomized to receive infliximab every 8 weeks and every 12 weeks, respectively,



had infections ( $P = .059$ ). A similar trend was observed for events reported as infections after week 14, when infliximab was administered either every 8 weeks (56.6% or 30 of 53) or every 12 weeks (36.0% or 18 of 50;  $P = .048$ ). There were no deaths, malignancies, central nervous system demyelinating disorders, optic neuritis, or seizures during the study.

The proportions of patients with infusion reactions were similar between the 2 maintenance treatment regimens (9 of 53 [17.0%] patients receiving infliximab every 8 weeks and 9 of 50 [18.0%] patients receiving infliximab every 12 weeks; Table 3). When assessed as the proportion of infusions with infusion reactions, a slightly lower incidence was observed with infusions given every 8 weeks (12 of 409 infusions or 2.9%) than with those administered every 12 weeks (17 of 319 infusions or 5.3%); however, this difference was not statistically significant ( $P = .126$ ; based on Fisher exact test). Only 1 infusion reaction, occurring at week 6 in a patient who was subsequently not randomized at week 10 for this reason, led to discontinuation of infliximab therapy. Among the 105 patients with evaluable samples for detection of antibodies to infliximab, 7.7% (1 of 13) of infusions resulted in infusion reactions among patients positive for antibodies to infliximab, compared with 7.4% (8 of 108) and 2.4% (12 of 492) in patients negative for antibodies to infliximab and with inconclusive status, respectively (Tables 2 and 3).

There were no cases of serum sickness-like reactions or possible delayed hypersensitivity reactions. Two patients had possible anaphylactic reactions. One patient who was not randomized at week 10 had a nonserious reaction of anaphylaxis at the week-6 infusion and 1 receiving infliximab every 8 weeks had flushing, edema, dyspnea, and urticaria as part of a nonserious anaphylactic reaction at the week-14 infusion. The latter patient received prophylactic medication before subsequent infusions without any further reaction.

Newly positive antinuclear antibodies ( $\geq 1:40$  titer) at any time were detected in 11 of 48 (22.9%) patients receiving infliximab every 8 weeks and in 12 of 43 (27.9%) patients treated every 12 weeks. Similarly, newly positive antidouble-stranded DNA antibodies at any time was detected in 3 of 51 (5.9%) patients receiving infliximab every 8 weeks and in 4 of 48 (8.3%) patients treated every 12 weeks. There were no new reports of autoimmune disease.

Three (6.0%) patients receiving infliximab every 12 weeks had a markedly elevated alanine aminotransferase (defined as at least a 100% increase from baseline and a value of at least 150 U/L). These marked elevations occurred during the induction phase of infliximab dosing and were limited to 1 or 2 occurrences that returned to normal despite continued treatment with infliximab. None of these patients had a concurrent markedly abnormal bilirubin elevation. No patient had a marked

elevation in aspartate aminotransferase. One patient receiving infliximab every 8 weeks had a marked elevation in total bilirubin that returned to normal while still receiving infliximab therapy.

## Discussion

Results of this prospective, multicenter, randomized, open-label study show that infliximab is effective in the treatment of moderately to severely active CD in children. The proportions of pediatric patients in clinical response (88.4%) and clinical remission (58.9%) at week 10 in this study exceeded those observed in the ACCENT I study of adult patients with CD (66.7% and 39.1%, respectively).<sup>7</sup>

In making comparisons of infliximab efficacy between studies, it is important to point out several differences between the 2 studies. In the present study, patients were required to be receiving an immunomodulator for a minimum of 8 weeks at the time infliximab therapy was started (although 1 patient did not meet this requirement), compared with only 27.5% of the adults studied. The potential confounding factor of smoking, which is associated with more active CD,<sup>19</sup> was present in 39.8% of adults but was not a factor in our pediatric population. The patients in the current study had a median disease duration of 1.6 years compared with >7 years for patients in the ACCENT I study.<sup>7</sup> Thus, the adult patients in the ACCENT I study would appear to have been patients considered harder to treat than the pediatric patients in REACH. In addition, an activity index more appropriate for a pediatric population, that is, the PCDAI, was used in the current study; whereas the CDAI was used in adults.

Although both PCDAI and CDAI reflect disease activity in pediatric CD, PCDAI is better at discriminating between levels of disease activity in children.<sup>16</sup> In addition, several studies have shown the effectiveness of the PCDAI in reflecting physician global assessment of disease activity<sup>14,20</sup> and the sensitivity of this instrument to short-term changes in clinical condition.<sup>21,22</sup> Of note, the 15-point decrease in PCDAI required to define a clinical response in our study is actually greater than the 12.5-point decrease recommended in a previous study.<sup>20</sup>

This study has also shown an important difference in the efficacy of infliximab infusions given every 8 weeks compared with every 12 weeks in maintaining clinical response. At week 54, 63.5% and 55.8% of patients receiving infliximab every 8 weeks did not require dose adjustment and were in clinical response and clinical remission, respectively. The proportions of patients in clinical response and remission were lower among children receiving infliximab treatment every 12 weeks (33.3%,  $P = .002$  and 23.5%,  $P < .001$ ) than in those receiving treatment every 8 weeks. Twice as many children receiving infliximab every 12 weeks required an intensification of their treatment schedule (eg, increased dose or shorter inter-

val) when compared with children receiving infliximab every 8 weeks (25 of 51 or 49.0% vs. 10 of 52 or 19.2%, respectively). Even when the need for dose intensification was ignored, and treatment failure rules were suspended, a significantly higher proportion of patients initially randomized to receive infliximab every 8 weeks was in clinical remission at week 54 when compared with patients randomized to receive treatment every 12 weeks (71% vs. 47%, respectively;  $P = .02$ ). Thus, patients receiving infliximab every 8 weeks were not only less likely to require more intensive therapy, but were also more likely to be in clinical remission at week 54.

Importantly, the height z-scores improved significantly from baseline to both weeks 30 and 54. The rapid response to infliximab therapy was also evident in changes observed in patient quality of life, with the mean IMPACT III score improving significantly from baseline to week 10 (mean improvement of 23.9,  $P < .001$ ); significant improvement was also observed at weeks 30 and 54.

In terms of safety findings, the proportions of patients with adverse events and serious adverse events were similar between the maintenance groups. The proportion of patients with adverse events that were considered by the investigator to be infections was higher among patients receiving infliximab every 8 weeks compared with those receiving maintenance therapy every 12 weeks, both through week 14 and after week 14. Of note, the unblinded nature of the study could have had the potential to affect adverse event data collection. Further analysis of the infections showed that upper respiratory infections accounted for the majority of cases. It is possible that the less frequent dosing interval in the every-12-weeks group was associated with an underreporting of adverse events considered to be infections. Alternatively, it is possible that the more frequent dosing interval in the every-8-weeks group was associated with a higher reporting rate, or that in fact, these children actually did have a higher likelihood of developing an intercurrent viral infection.

Three patients had pneumonia; 2 patients were receiving infliximab every 8 weeks and 1 was receiving infliximab every 12 weeks. The pneumonia was considered serious in 1 of the patients receiving infliximab every 8 weeks. All 3 patients recovered. Of note, 2 patients had herpes zoster; both patients were receiving maintenance infliximab every 8 weeks. These infections were reported on study days 75 (following 3 infliximab infusions) and 349 (following 8 infliximab infusions). Although infliximab appeared to be well tolerated in this small population of pediatric patients with Crohn's disease, patients must be monitored for the occurrence of uncommon serious adverse events such as the rare occurrence of hepatosplenic T-cell lymphoma that has been reported recently in children who have been treated with azathioprine and infliximab for CD.<sup>2,3</sup>

The proportion of patients with antibodies to infliximab seen in the REACH study was lower than that seen in the adult population.<sup>7</sup> The requirement for patients to be receiving azathioprine or 6-mercaptopurine prior to study entry may have been a factor that decreased the proportion of children with antibodies to infliximab. However, caution should be exercised in interpreting these data, as the majority of patients had inconclusive test results for antibodies to infliximab due to the detection of infliximab in the serum.

In conclusion, an impressive 88% of pediatric patients with CD achieved clinical response with infliximab therapy at week 10. Pediatric patients who responded to an induction regimen of infliximab were more likely to be in clinical response and remission at week 54 without dose adjustment when their maintenance therapy was given every 8 weeks rather than every 12 weeks. Allowing for dose intensification in the case of relapse, remission rates, but not response rates, at week 54 were superior with every-8-week dosing compared with every-12-week dosing.

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