

Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease CME

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Background: The endoscopic substudy of the ACCENT I (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) Crohn's disease trial examined the effects of infliximab on mucosal inflammation and mucosal healing, and assessed their impact on outcomes.

Design: ACCENT I was a randomized, double-blind, parallel group study.

Setting: This study took place at multiple centers in North America, Europe, and Israel.

Main Outcome Measurements: Ileocolonoscopy examinations were performed at weeks 0, 10, and 54. Complete mucosal healing was defined as the absence of all mucosal ulcerations. The end point of principal interest was the proportion of patients randomized as responders with mucosal healing at week 10. The proportion of responders who demonstrated mucosal healing at week 54 or at both weeks 10 and 54 is also summarized. Changes in Crohn's disease endoscopic index of severity (CDEIS) scores from baseline to week 10 and 54 were calculated for all patients in this substudy.

Results: Complete mucosal healing by week 10 occurred in significantly more week 2 responders who had received 3 doses of infliximab compared with a single dose (31% vs. 0%, $p = 0.010$). A significantly higher proportion of week 2 responders in the combined scheduled maintenance group had complete mucosal healing at week 54 compared with the episodic group (50% vs. 7%, $p = 0.007$). The results for all patients are consistent with those for week 2 responders only. Significantly greater improvement in the CDEIS occurred with scheduled maintenance compared with episodic treatment at week 10 ($p \leq 0.001$) and week 54 ($p = 0.026$). Notably, no strong relationship between clinical remission and complete mucosal healing was found. Overall, mucosal healing appeared to correlate with fewer hospitalizations, although these results were not statistically significant.

Conclusions: Scheduled infliximab maintenance therapy resulted in more improvement in mucosal ulceration and in higher rates of mucosal healing. There was a numerical trend for patients with better mucosal healing to have a lower rate of Crohn's disease-related hospitalizations. (Gastrointest Endosc 2006;63:433-42.)

The proinflammatory cytokine tumor necrosis factor- α (TNF α) plays an important role in the pathogenesis of Crohn's disease, a chronic inflammatory disorder of the GI tract.¹⁻⁵ Crohn's disease classically affects the terminal ileum, although multiple segments of the GI tract also may be affected. Granulomatous, transmural inflammation of the intestine occurs, and endoscopic examination

reveals the presence of ulceration. Infliximab, an anti-TNF α monoclonal antibody, binds to TNF α with high affinity, thereby neutralizing its biologic activity.⁶ The administration of infliximab to patients with moderately to severely active Crohn's disease induces clinical remission,⁷ decreases corticosteroid requirements,⁸ and promotes fistula closure.^{9,10}

The endoscopic and histologic response to short-term therapy with infliximab was investigated and previously reported by D'Haens et al.¹¹ In that multicenter, randomized, double-blind, placebo-controlled study of 30 patients with active refractory Crohn's disease, treatment

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0016-5107/\$30.00

doi:10.1016/j.gie.2005.08.011

with a single dose of infliximab produced both clinical improvement and significant healing of endoscopic lesions. In addition, histologic response data revealed that the entire mucosal layer showed the disappearance of inflammatory infiltrate after treatment with infliximab.

The ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) I study was conducted to evaluate the efficacy and the safety of repeated infusions of infliximab in patients with Crohn's disease. The primary efficacy results of the maintenance phase of the study for the subpopulation of responding patients have been reported.⁸ Safety results have been reported,⁸ with similar incidences of serious adverse events, drug-related adverse events, and Crohn's disease-related complications across treatment groups. In a recent analysis of all ACCENT I patients (both initial responders and nonresponders), Rutgeerts et al¹² reported that patients in the scheduled infliximab maintenance groups had better Crohn's disease activity index (CDAI)¹³ response and remission rates, and significantly fewer Crohn's disease-related hospitalizations and surgeries than patients in the episodic treatment group. Hospitalizations and surgeries have a major effect on the overall cost of care for patients with Crohn's disease, as illustrated by Feagan et al,¹⁴ who reported that hospitalizations account for 56% of the total cost of caring for patients with Crohn's disease. An understanding of the various manifestations of Crohn's disease that affect medical costs may lead to the development of important treatment goals, e.g., mucosal healing.

The analysis presented here compares the effects of scheduled maintenance treatment with that of episodic treatment on the attainment of complete mucosal healing as determined by endoscopic examination, and on mucosal inflammation as assessed by changes in Crohn's disease endoscopic index of severity (CDEIS)^{15,16} scores in all patients who participated in the ACCENT I endoscopy substudy. The relationship between mucosal healing and fewer Crohn's disease-related hospitalizations and surgeries is presented, and the importance of mucosal healing, including its apparent impact on overall cost of disease, is discussed.

PATIENTS AND METHODS

Patients

The ACCENT I study was a multicenter, randomized, double-blind study conducted at 55 sites in North America, Europe, and Israel. A total of 100 consecutive patients at selected study sites in North America and Europe had the opportunity to participate in this endoscopic substudy. The institutional review boards at the participating sites approved both the primary and endoscopy substudy protocols. Participation in the endoscopic substudy required written patient informed consent.

Eligible patients were those at least 18 years of age and with Crohn's disease of at least 3 months' duration, with

Capsule Summary

What is already known on this topic

- Endoscopic examination of asymptomatic patients with Crohn's disease often reveals ulcers, erosions, or strictures.
- Infliximab completely heals the mucosa in short-term Crohn's disease studies.

What this study adds to our knowledge

- Complete mucosal healing is more likely to occur with maintenance every 8 weeks than with episodic (as needed) infusions of infliximab.

colitis, ileitis, or ileocolitis confirmed by radiography or endoscopy, and with a CDAI score of 220 to 400. Allowable concomitant medications were as follows: aminosalicylates (stable dose for at least 4 weeks before trial entry); corticosteroids at less than or equal to the equivalent of 40 mg/d prednisone (stable dose for at least 3 weeks); methotrexate (stable dose for at least 6 weeks); and azathioprine (AZA), 6-mercaptopurine (6-MP), or mycophenolate mofetil (stable dose for at least 8 weeks). Dosages of each of these medications remained constant throughout the trial, with the exception of corticosteroids, which could be tapered as previously reported.⁸ Patients who had received prior treatment with any anti-TNF agent were excluded from the study.

Study design

The details of the design of the primary study (i.e., ACCENT I) have been reported.⁸ A total of 573 patients received an infusion of infliximab 5 mg/kg at week 0. Patients then were randomly assigned to either placebo infusions at weeks 2, 6, and then every 8 weeks until week 46 (episodic treatment); infliximab 5 mg/kg at the same time points as above (5 mg/kg scheduled maintenance); or infliximab 5 mg/kg at weeks 2 and 6 followed by 10 mg/kg every 8 weeks until week 46 (10 mg/kg scheduled maintenance). Patients who initially responded and then lost response were eligible at or after week 14 to receive treatment with infliximab, as needed, with a dose 5 mg/kg higher than that indicated by their randomization group.

Procedures, follow-up schedule, and evaluation

Patients were clinically assessed at weeks 0, 2, 6, 10, 14, and every 8 weeks through week 54. At each visit, adverse events were ascertained and samples for clinical laboratory evaluations and the patient's CDAI score were obtained. Surgery and hospitalization were defined as any surgery or hospitalization related to Crohn's disease with the exception of perianal abscess drainage.

Ileocolonoscopies were performed, and mucosal inflammation was scored according to an endoscopy sub-study protocol. Ileocolonoscopy examinations were performed at baseline, week 10, and week 54. The degree and the extent of mucosal ulceration (i.e., aphthoid ulceration, superficial or shallow ulceration, deep ulceration, or ulcerated stenosis) were evaluated in each segment of the colon and the ileum. Endoscopic evaluation was performed by the endoscopist at the local facility, and a videotape of the endoscopy was recorded by using standardized methods. Mucosal healing was defined as the absence of mucosal ulceration in all segments at the follow-up endoscopy in patients who had previously been identified as having ulceration in at least one segment of the colon or the ileum.

Videotapes were assessed by a central reviewer (P.R.) in a blinded fashion. This review consisted of two parts. First, the central reviewer assessed the quality of the procedure based on the availability of the recorded images and quality of the video. Second, the central reviewer independently assessed each section of the colon and the ileum for the presence and the extent of mucosal ulceration.

Because mucosal ulceration may have been observed by the local endoscopist, the central reviewer, or both, a conservative definition was adopted for use in the statistical analysis. If the central reviewer considered all videoendoscopy tapes for a given patient to be reviewable, that patient was considered to have mucosal healing at a follow-up visit if the following criteria were satisfied:

- At baseline, the patient had mucosal ulceration in at least 1 of the 5 segments as observed by the local endoscopist. If the videoendoscopy satisfied the quality assessment, the central reviewer must have confirmed that mucosal ulceration was present in at least 1 of the 5 segments of the colon and the terminal ileum.
- At follow-up, no mucosal ulceration was observed in any of the 5 segments by local endoscopy. If the videoendoscopy satisfied the quality assessment, the central reviewer must have confirmed that no mucosal ulceration was observed in any of the 5 segments of the colon and the terminal ileum.

If the central reviewer considered any videoendoscopy tape for a patient to lack quality for review, a patient was considered to have mucosal healing at a follow-up visit if the local endoscopist identified ulceration at baseline in at least one segment of the colon and the terminal ileum, and observed that there was no ulceration in these same segments at follow-up.

In addition to mucosal healing, the degree of mucosal inflammation was assessed by using the CDEIS. Endoscopic data on the rectum, the sigmoid and the left colon, the transverse colon, the right colon and the cecum, and the terminal ileum were collected, and a score was calculated for each segment. Each segment score was based on the presence and the surface area of any superficial or deep ulceration noted. CDEIS was based on the segment score

averaged over segments on which data were available, ulcerated stenosis in any segment, and nonulcerated stenosis in any segment. The CDEIS could range from 0 to 44, with higher scores indicative of greater severity of disease.

Thus, patients may be included in the analysis of CDEIS but not for mucosal healing determination if all 5 segments were not re-examined.

Statistical methods

Mucosal healing was a prespecified secondary end point in the ACCENT I protocol. The end point of principal interest in this substudy was the proportion of patients with mucosal healing at week 10 among those randomized as responders at week 2; mucosal healing at week 54 and at both weeks 10 and 54 also were summarized for these patients. Clinical response was defined as a reduction in the CDAI of 70 points or more, along with a reduction of at least 25%.

Changes in CDEIS scores from baseline to week 10 and 54, and the correlation between changes in CDEIS and CDAI scores also were assessed. Results of post hoc analyses conducted to assess the association between mucosal healing and clinical remission, and hospitalizations and surgeries also are presented. Clinical remission was defined as a CDAI score less than 150. All patients in the endoscopy substudy are included in these analyses.

Patients with baseline ulcers and at least one post-baseline colonoscopy were included in the analysis of mucosal healing. The effect of infliximab on mucosal healing was examined by comparing the proportion of patients by using the Pearson chi-square test. Patients who did or did not attain mucosal healing and also who were or were not in clinical remission are summarized.

Analysis of variance on the van der Waerden normal scores was used to compare percent change in CDEIS scores. The Spearman rank-order correlation coefficients were used to measure the association between the change in CDAI and CDEIS scores. Median percent change from baseline and correlation analyses were based on observed data, with no imputation made for missing data.

All statistical tests were two sided. Nominal *p* values are reported, with no adjustments for multiple testing.

RESULTS

Patient disposition, baseline characteristics

A summary of patient disposition for those evaluated for mucosal healing is provided in Figure 1. As shown, 99 patients were randomized and underwent endoscopic examination at week 0. Seventeen patients did not have confirmed ulceration in their colon or terminal ileum at baseline, and one patient withdrew consent. Therefore, 81 of 99 patients (82%) who were randomized demonstrated mucosal ulceration at baseline. Six patients (3

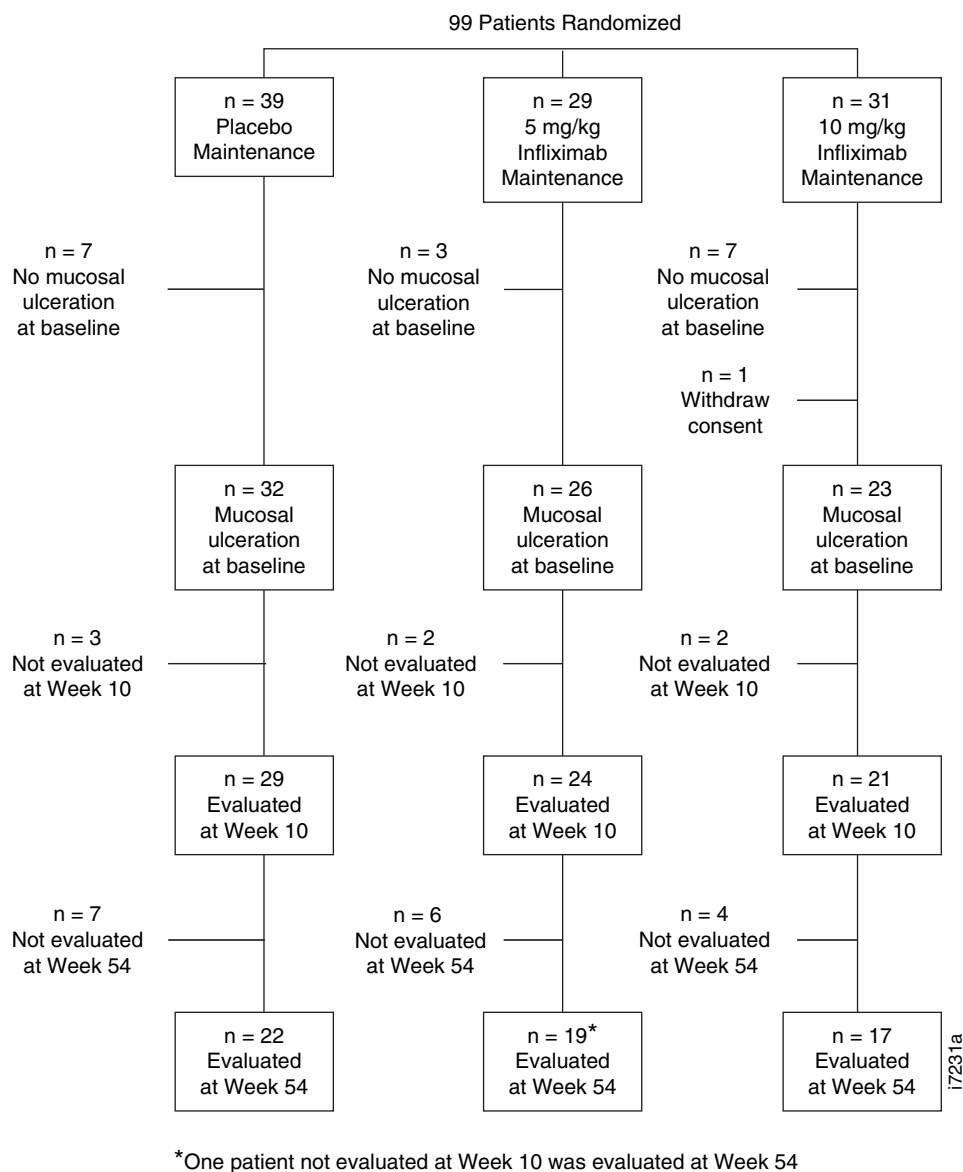


Figure 1. Summary of patient disposition from baseline through week 54 for all patients randomized to the endoscopy substudy.

episodic and infliximab maintenance therapy, each) did not have any post-baseline-endoscopy results and are not included in the analysis of mucosal healing. Seventeen patients (7 episodic and 10 infliximab maintenance therapy) had baseline and week 10 endoscopies, 1 patient (infliximab 5 mg/kg maintenance therapy) had baseline and week 54 endoscopies, and 57 patients (22 episodic and 35 infliximab maintenance therapy) had all 3 endoscopies. Thus, 75 of 81 patients (93%) were evaluated for mucosal healing.

Overall, patients who did not undergo follow-up endoscopies were evenly divided between those who did not complete the study and those who completed the study but refused follow-up endoscopy, with a similar distribution across treatment groups. As shown in Table 1, the disease characteristics of all patients in the endoscopy

substudy, all patients in the endoscopy substudy who underwent follow-up endoscopy at week 54, and all patients in the ACCENT I study were similar.

The percentages of patients who were in clinical response at week 2 were 67% (66/99) of all patients in the endoscopy substudy, 70% (40/57) of those evaluated for mucosal healing at both weeks 10 and 54, and 59% (335/573) of all randomized patients in the ACCENT I study. At week 54, the percentages of patients evaluated who were in clinical response were 61% (60/99) of all patients in the endoscopy substudy, 67% (38/57) of those evaluated for mucosal healing at both weeks 10 and 54, and 60% (345/573) of all randomized patients in the ACCENT I study. Responders who participated in this substudy were distributed among the treatment groups as follows: 24 patients in the episodic group, 19 patients in the

TABLE 1. Baseline demographic and disease characteristics of all endoscopy substudy patients, endoscopy substudy patients with mucosal healing evaluated, and all randomized patients participating in ACCENT I

Category	Variable	Description	Endoscopic substudy patients evaluated for mucosal healing at wk 54 (n = 58)	All randomized endoscopic substudy patients (n = 99)	All randomized patients (n = 573)
Demographics	Gender	Women	37 (63.8%)	60 (60.6%)	334 (58.3%)
		Men	21 (36.2%)	39 (39.4%)	239 (41.7%)
Clinical	Age, y	Median	30	35	35
		CDAI	Patients evaluated	57	98
	CDEIS	Median	304.0	308.0	297.0
		Patients evaluated	58	99	99
	IBDQ	Median	8.8	7.3	7.3
		Patients evaluated	58	99	569
	Duration of disease, y	Median	127.0	124.0	127.0
		Patients evaluated	58	99	573
	Involved intestinal area	Median	7.2	7.5	7.9
		Patients evaluated	58	98	568
Ileum only		7 (12.1%)	15 (15.3%)	137 (24.1%)	
Colon only		16 (27.6%)	28 (28.6%)	109 (19.2%)	
	Ileum and colon	35 (60.3%)	55 (56.1%)	322 (56.7%)	

ACCENT, A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen; CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; IBDQ, inflammatory bowel disease questionnaire.

5 mg/kg infliximab maintenance group, and 23 patients in the 10 mg/kg infliximab maintenance group.

Efficacy

Improvement in CDEIS. Baseline CDEIS scores were similar between treatment groups. Compared with baseline, overall CDEIS scores were improved at weeks 10 and 54 among patients in the episodic and scheduled infliximab treatment groups (Fig. 2).

At week 10, the median percent change from baseline in CDEIS score was more than twofold greater in patients who received 3 doses of infliximab than in patients who received a single dose (76% vs. 32%, $p < 0.001$) (Fig. 3A). By week 54, the median percent improvement in CDEIS score from baseline continued to be significantly greater in patients in the combined scheduled

maintenance group compared with those in the episodic treatment group (93% vs. 54%, $p = 0.026$) (Fig. 3B).

Correlation of clinical and endoscopic measures of disease activity. The correlation between the change from baseline to weeks 10 and 54 in the clinical measure of disease activity (i.e., CDAI) relative to change in the endoscopic measure of disease activity (i.e., CDEIS) was determined. There was a positive and statistically significant correlation between the change from baseline in CDAI and CDEIS at week 10 ($r = 0.33$, $p = 0.002$, $n = 85$) and week 54 ($r = 0.37$, $p = 0.003$, $n = 64$).

Mucosal healing. Patients with mucosal ulceration at baseline were evaluated at weeks 10 and 54 for mucosal healing. Representative examples of baseline mucosal ulceration followed by partial mucosal healing at week 10 and complete mucosal healing at week 54 in a patient

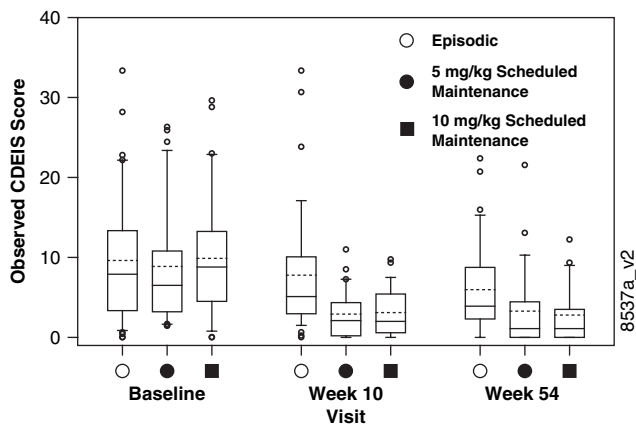


Figure 2. Box plot of CDEIS scores at baseline, week 10, and week 54. The top and the bottom of each box indicate the 25th and 75th percentiles. The *solid line* within the box denotes the median; the *dotted line* denotes the mean. The central vertical lines (*whiskers*) extend from the edge of the box to the 10th and 90th percentiles. Any value lying outside of these percentiles is represented with an *open circle*. Baseline: Episodic, n = 39; 5 mg/kg scheduled maintenance, n = 29; 10 mg/kg scheduled maintenance, n = 31. Week 10: Episodic, n = 35; 5 mg/kg scheduled maintenance, n = 28; 10 mg/kg scheduled maintenance, n = 25. Week 54: Episodic, n = 27; 5 mg/kg scheduled maintenance, n = 21; 10 mg/kg scheduled maintenance, n = 18. The median percent change from baseline in CDEIS was significantly greater in the combined scheduled maintenance group compared with that of the placebo group at week 10 ($p < 0.001$) and week 54 ($p = 0.026$).

who received 5 mg/kg scheduled maintenance therapy are shown in Figure 4A to C. Although improvement was evident by week 10, the patient whose endoscopy is shown only met the criteria for complete mucosal healing at week 54.

At week 10, complete mucosal healing was documented in 10 of 32 week 2 responders (31%) who had a 3-dose induction regimen with infliximab at weeks 0, 2, and 6 compared with 0 of 17 responders who received a single dose of infliximab at week 2 ($p = 0.010$) (Fig. 5A).

At week 54, significantly more responders in the combined scheduled treatment groups (5 and 10 mg/kg) demonstrated complete mucosal healing when compared with responders in the episodic treatment group (50% vs. 7%; $p = 0.007$) (Fig. 5B). In the 5 and 10 mg/kg maintenance treatment groups individually, there were also significantly more responders with complete mucosal healing (5 of 11 responders [46%] in the 5 mg/kg group, $p = 0.026$; and 8 of 15 responders [53%] in the 10 mg/kg group, $p = 0.007$) compared with the episodic treatment group (1 of 14 patients [7%]).

A significantly greater proportion of responders in the combined scheduled maintenance group both achieved complete mucosal healing at week 10 and continued to demonstrate complete mucosal healing at week 54. Complete mucosal healing was observed at both time points in 27% of responders in the combined scheduled infliximab maintenance group, while, in contrast, complete mucosal healing at both weeks 10 and 54 was not observed in any

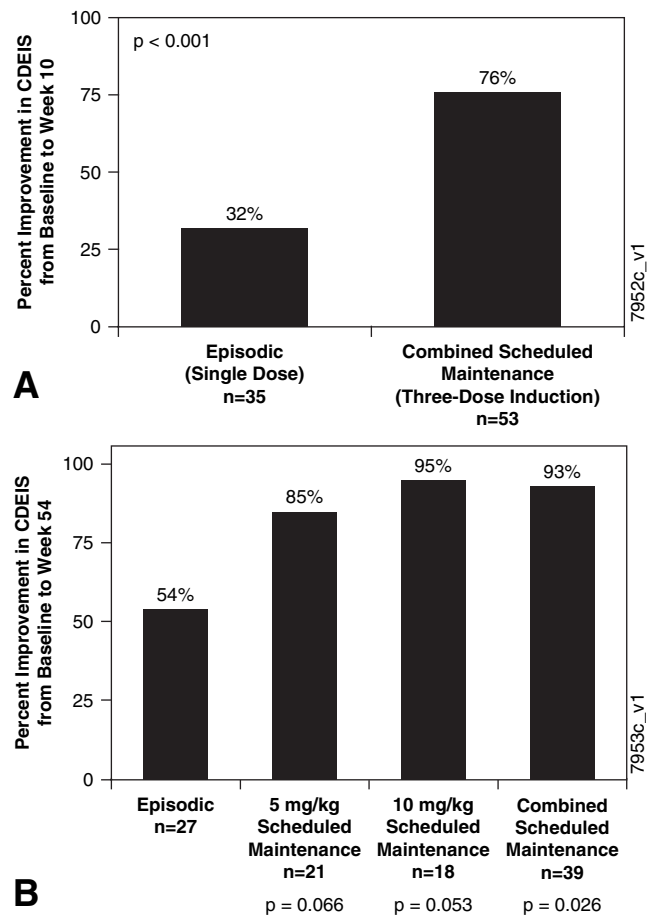


Figure 3. A, Median percent change in CDEIS from baseline to week 10: all patients in the endoscopy substudy. **B,** Median percent change in CDEIS from baseline to week 54: all patients in the endoscopy substudy.

responder who received episodic treatment ($p = 0.033$) (Fig. 5C). The benefit of maintenance infliximab therapy administered every 8 weeks in this regard also was apparent in both the individual 5 mg/kg and 10 mg/kg scheduled maintenance therapy groups (18% in the 5 mg/kg group [$p = 0.096$]; 33% in the 10 mg/kg group [$p = 0.018$]). This difference was statistically significant only for the 10 mg/kg group.

Among the cohort of week 2 responders with mucosal healing at week 10, 7 of 10 (70.0%) in the maintenance groups also had mucosal healing at week 54. Among the cohort of week 2 responders without mucosal healing at week 10, 6 of 22 patients (27.3%) in the maintenance group, and 0 of 17 patients (0%) in the episodic group had mucosal healing at week 54.

Complete mucosal healing results for all patients in the endoscopy substudy are consistent with those for responders only. At weeks 10 and 54, significantly greater ($p < 0.05$) proportions of all patients in the combined maintenance group had complete mucosal healing when compared with those in the episodic treatment group.¹² This also is true for all patients with complete mucosal healing at both weeks 10 and 54 ($p = 0.006$).

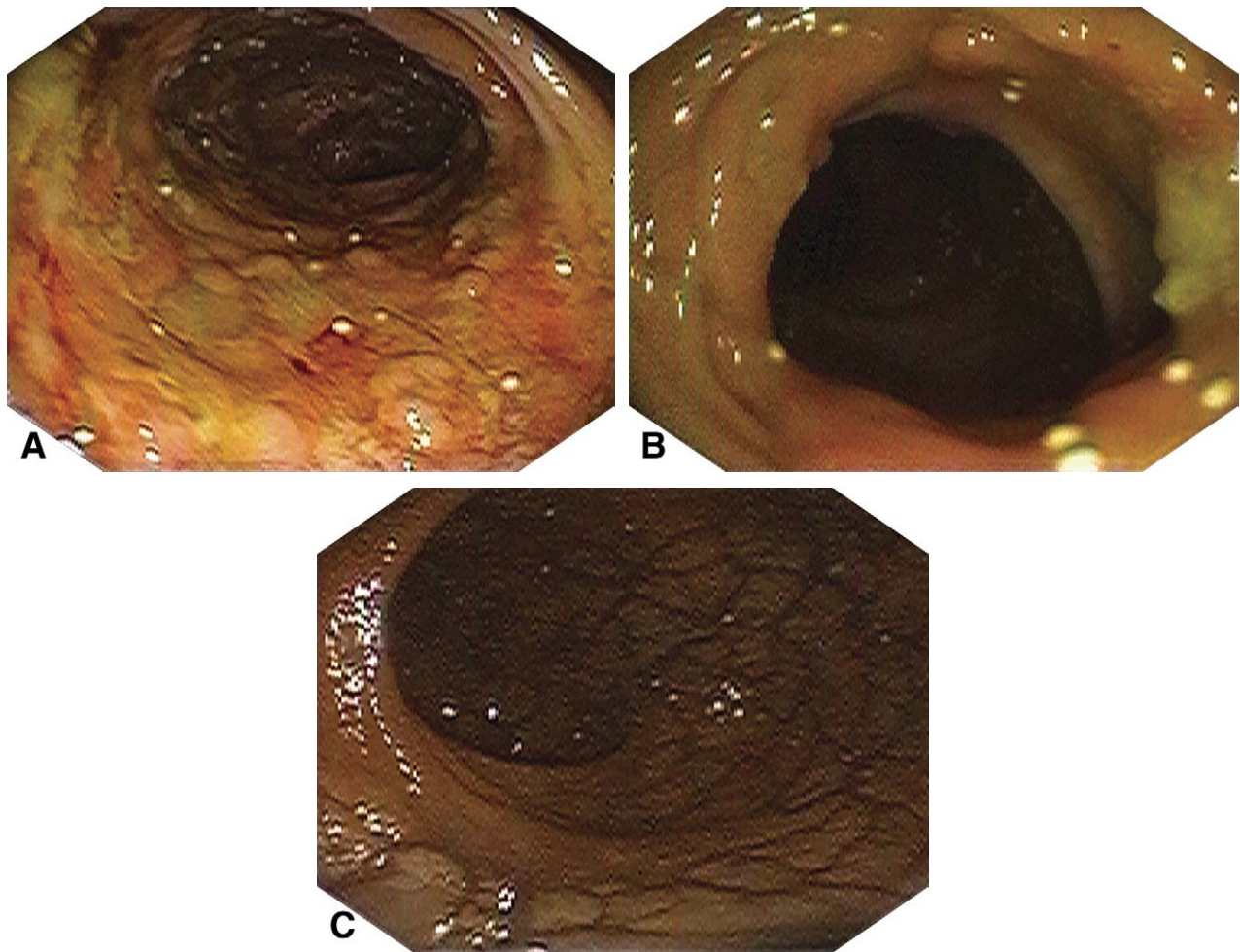


Figure 4. **A**, Mucosal ulceration at the baseline endoscopy (week 0). **B**, Partial mucosal healing observed at the week 10 endoscopy. **C**, Complete mucosal healing observed at the week 54 endoscopy.

Mucosal healing and clinical remission. There was no consistent relationship between mucosal healing and clinical remission (Table 2). Slightly more than one third of all patients with mucosal healing at week 10 were in clinical remission, while two thirds of all patients with mucosal healing at week 54 were in clinical remission.

Hospitalizations. Among all patients, 9 who had mucosal healing at both week 10 and week 54 did not require hospitalization (Table 3). Patients with mucosal healing at only one of those visits still required fewer hospitalizations (18.8%) compared with those who did not have mucosal healing at either visit (28%). These trends were consistent when episodic and maintenance groups were examined separately.

DISCUSSION

The results of this study demonstrated that scheduled maintenance therapy with infliximab was significantly

more likely than episodic treatment to induce complete mucosal healing and decrease endoscopic evidence of inflammation. By week 10, patients who received scheduled maintenance treatment had more than twice the improvement in CDEIS as that exhibited by patients in the episodic group. The greater benefit of scheduled treatment was maintained through week 54, with patients in the combined scheduled maintenance group demonstrating more than 90% improvement in CDEIS score compared with 54% improvement among those in the episodic group.

Despite the significant improvement in CDEIS and CDAI scores observed in this analysis, the correlation between these indices was weak. This is consistent with the weak correlation between CDEIS and CDAI that has been shown by others. Cellier et al¹⁷ reported a weak but significant correlation between endoscopic and clinical indices overall ($n = 121$, $r = 0.32$, $p < 0.001$) that appeared to be homogenous in subgroups (i.e., clinically quiescent or active disease, pure colonic disease, untreated patients).

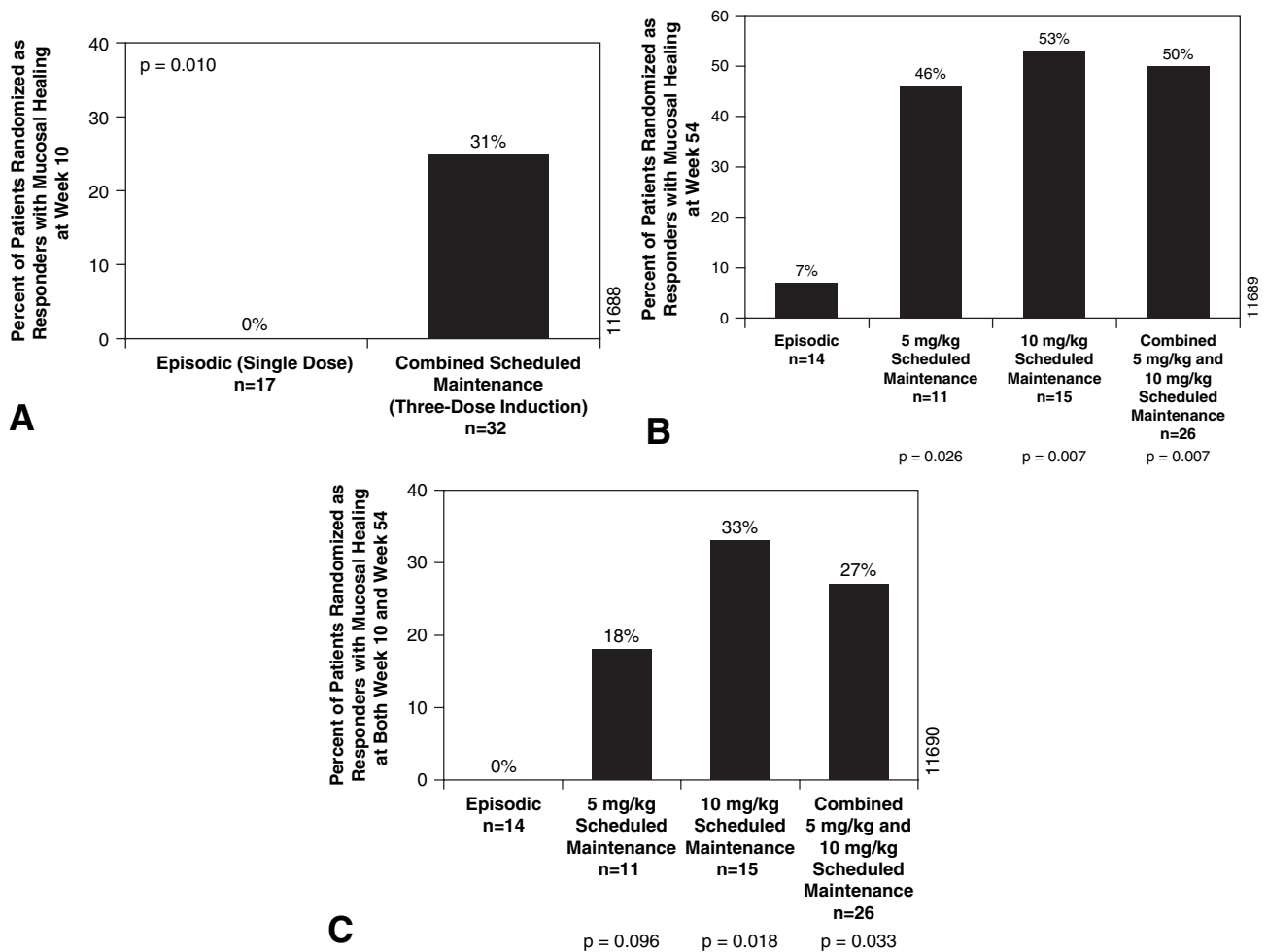


Figure 5. **A**, Proportion of responders with mucosal healing at week 10. **B**, Proportion of responders with mucosal healing at week 54. **C**, Proportion of responders with mucosal healing at both weeks 10 and 54.

Van Dullemen et al¹⁸ reported healing of ulcerations in 8 of 10 patients 4 weeks after a single infliximab infusion. A subsequent randomized, placebo-controlled study conducted by D'Haens et al¹¹ showed an improvement in CDAI and CDEIS in patients with active refractory Crohn's disease after a single infusion of infliximab. Our study provides further support of these observations in a larger population treated with infliximab for 1 year and illustrates the advantage of scheduled maintenance vs. episodic therapy.

Patients treated with corticosteroids generally showed symptomatic relief without dramatic endoscopic healing.¹⁹⁻²¹ Although studies have suggested that long-term treatment with AZA may be associated with mucosal healing, an accurate assessment of the potential impact of AZA on mucosal ulceration is hampered by study design limitations.^{22,23} More recently, Cosnes et al²⁴ assessed the effect of earlier use of immunosuppressants on Crohn's disease-related surgery in a retrospective cohort of 2575 patients distributed over 5 consecutive chronologic cohorts. No significant decrease in the need for excisional

surgery was found despite the increased use of immunosuppressants during the past 25 years.

No patients were hospitalized among those who had mucosal healing at both weeks 10 and 54. In comparison, among patients who had mucosal healing at only one of these time points, 18% were hospitalized, and, among patients who did not have mucosal healing at both time points, 28% were hospitalized. The treatment of moderate-to-severe Crohn's disease is associated with substantial costs, driven in large part by hospitalizations and surgeries. Rutgeerts et al²⁵ found that the endoscopic severity of the lesions predicted the symptomatic course of the disease and the need for future surgeries. Hence, the development of a therapy that can prevent the formation of mucosal ulceration or that can heal existing mucosal ulcerations has the potential to substantially reduce the cost of caring for patients with Crohn's disease. This reduction in cost has to be examined in context with the cost of therapy and other benefits that it may offer. Cost-effectiveness analyses are needed to examine the net cost of infliximab (cost of therapy minus the cost effects from reduced hospitalizations

TABLE 2. Summary of mucosal healing and clinical remission among all patients in the endoscopy substudy

Clinical remission*	Wk 10		Wk 54		Wk 10 and 54	
	Mucosal healing (n = 14)	No mucosal healing (n = 59)	Mucosal healing (n = 18)	No mucosal healing (n = 34)	Mucosal healing (n = 9)†	No mucosal healing (n = 66)‡
In remission, n (%)§	5 (35.7)	24 (40.7)	12 (66.7)	19 (55.9)	3 (33.3)	18 (27.3)
Not in remission, n (%)	9 (64.3)	35 (59.3)	6 (33.3)	15 (44.1)	6 (66.7)	48 (72.7)

*Clinical remission was defined as a Crohn's disease activity index score < 150 points.

†Mucosal healing was defined as mucosal healing at both wk 10 and wk 54.

‡No mucosal healing was defined as no mucosal healing at either or both time points.

§For the analysis under the "Wk 10 and wk 54" column, "In remission" includes patients who were in clinical remission at both time points.

||For the analysis under the "Wk 10 and wk 54" column, "Not in remission" includes patients who were not in clinical remission at either or both time points. Furthermore, if clinical remission status was missing, the patient was considered to not be in clinical remission at that time point.

and surgeries) in comparison with the improved patient benefit in terms of patient well-being and quality of life.

It is interesting that we did not find a strong relationship between mucosal healing and clinical remission. Among patients who were in clinical remission, a substantial proportion did not demonstrate complete mucosal healing. Conversely, there were patients who had mucosal healing but who were not in clinical remission. One possible explanation for the latter observation is that these patients may have had active mucosal disease beyond the reach of the colonoscope. However, given that clinical remission does not necessarily imply mucosal healing, the apparent relationship between mucosal healing and the important outcome of hospitalization seen here is all the more interesting. We did not have sufficient numbers of patients to determine whether lack of mucosal healing could predict the future need for hospitalization in patients who were in remission. It is possible that mucosal ulcerations are precursors to disease flare that can lead to hospitalization. It also is possible that studies in larger numbers of patients could demonstrate important differences in other outcomes, such as the need for surgery. Further research is needed to determine whether the goal of Crohn's disease therapy should be clinical remission alone or clinical remission combined with mucosal healing.

Future studies should include a prospective evaluation of the long-term importance of mucosal healing (i.e., whether patients with mucosal healing have a better outcome than those without mucosal healing). Patient outcomes that could be the subject of such future studies include relapses, hospitalizations and surgeries, and Crohn's disease-related deaths, as well as the development of perianal disease, strictures, abscesses, fistulas, cancers, extraintestinal manifestations, and dysplasia.

Clinical response in the group of patients fully able to be evaluated in the endoscopic substudy was higher than that seen in both patients in the entire endoscopic substudy and in all patients in the whole ACCENT I trial.

TABLE 3. Number of patients with Crohn's disease-related hospitalizations by mucosal healing category assessed at wk 10 and wk 54 among all patients in the endoscopy substudy

Treatment groups*	Crohn's disease-related hospitalizations		
	Healing at both visits†	Healing at 1 visit‡	No healing at either visit§
Episodic treatment (N = 29)	0 (0.0)	1/5 (20.0)	9/24 (37.5)
Combined maintenance treatment (N = 46)	0/9 (0.0)	2/11 (18.2)	5/26 (19.2)
All patients (N = 75)	0/9 (0.0)	3/16 (18.8)	14/50 (28.0)

* $p > 0.05$ (Fisher exact test) comparisons of the proportion of patients requiring hospitalization among the mucosal healing categories within each treatment regimen, and all patients.

†For the analysis under "Healing at both visits," mucosal healing was recorded at both wk 10 and wk 54.

‡For the analysis under "Healing at 1 visit," mucosal healing was recorded at either wk 10 or wk 54.

§For the analysis under "No healing at either visit," mucosal healing was recorded at neither time point. Furthermore, if mucosal healing status was missing, then the patient was considered to have no mucosal healing at that time point.

Thus, it is possible that the mucosal healing results observed in the patients able to be evaluated in the substudy may, to some extent, overstate the benefit that could be expected in the overall study population.

In summary, scheduled infliximab maintenance treatment offers a greater benefit than episodic treatment in healing mucosal lesions in patients with Crohn's disease. Scheduled infliximab maintenance therapy was associated with more improvement in mucosal ulceration and higher rates of mucosal healing. Of note was the lack of a strong

relationship between clinical remission and complete mucosal healing. Patients who had mucosal healing had better outcomes with regard to fewer Crohn's disease-related hospitalizations.

ACKNOWLEDGMENTS

The authors wish to thank Marion A. Blank, PhD, for her critical review of this manuscript and Mary Ann Thomas, RN, BSN, and Mary Whitman, PhD, for their writing and editorial assistance.

DISCLOSURE

Support was provided by Centocor, Inc.

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Received October 15, 2004. Accepted August 12, 2005.

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