

# Endoscopic and Histologic Healing in Children With Inflammatory Bowel Diseases Treated With Thalidomide

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**BACKGROUND & AIMS:** Mucosal healing, determined by endoscopic evaluation, is one of the most important prognostic markers for patients with inflammatory bowel diseases. Findings from histologic evaluation, however, could complement findings from endoscopy in assessing mucosal responses to treatment. We analyzed long-term results of children treated with thalidomide to determine the association between clinical response and histology and endoscopy findings.

**METHODS:** We collected data from 2 multicenter trials of 70 children with refractory Crohn’s disease (CD) or ulcerative colitis (UC) (2–18 years old; ileocolonic or colonic disease) given thalidomide or placebo (NCT00720538). Clinical remission and clinical response at 8 weeks were defined as a pediatric CD activity index scores 10 points or lower and a decrease of at least 50% from baseline, respectively, for patients with CD; and as a pediatric UC activity index score below 10 and a decrease of at least 20 points from baseline, respectively, for patients with UC. Patients with a clinical response to 8 weeks’ treatment with thalidomide underwent endoscopic examination with biopsy collection at study weeks 12 and 52. Severity of inflammation in patients with UC was assessed by Mayo score and in patients with CD by 4-grade system. Biopsies were assessed for signs of active inflammation, erosion or ulceration, and crypt abscesses and assigned a histologic score.

**RESULTS:** Clinical remission was observed in 42 patients (60.0%) and clinical response in 45 patients (64.2%) at Week 8. At Week 52, a total of 38 patients (54.3%) were still in clinical remission or still had a clinical response; 29 patients (41.4%) had mucosal healing, defined as complete healing of erosions or ulcerations, and 20 patients (27.7%) had histologic healing, defined as complete absence of markers of inflammation. Of patients with clinical remission or clinical response, 75.3% also had mucosal healing and 52.6% also had histologic healing. The probability of achieving mucosal healing decreased significantly with increasing values of erythrocyte sedimentation rate (adjusted odds ratio, 0.96; 95% CI, 0.93–0.98;  $P = .006$ ).

**CONCLUSIONS:** In a long-term analysis of data from 2 clinical trials of pediatric patients with CD or UC, 52 weeks’ treatment with thalidomide led to clinical remission in 54.3% of patients with ileocolonic or colonic disease; of these patients, 75.3% had mucosal healing and 52.6% also had histologic healing. Further studies are needed to determine how thalidomide therapy affects long-term progression of inflammatory bowel diseases. ([ClinicalTrials.gov](https://clinicaltrials.gov) number NCT00720538).

*Keywords:* Drug; IBD; Efficacy; Intestinal Mucosa.

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*Abbreviations used in this paper:* CD, Crohn’s disease; CI, confidence interval; IBD, inflammatory bowel diseases; PCDAI, Paediatric Crohn’s Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index; RCT, randomized controlled trials; UC, ulcerative colitis.

Mucosal healing has been identified in recent years as a key prognostic parameter for the management of inflammatory bowel diseases (IBD).<sup>1-3</sup> However, the optimal treatment goal for IBD should be the complete resolution of the inflammatory process, as confirmed by a histologic assessment. When compared with endoscopic activity alone, histologic healing has therefore been proposed as a potentially more accurate, although ambitious, therapeutic target for IBD.<sup>3-5</sup> Thalidomide has showed to be effective in inducing clinical remission in patients with Crohn's disease (CD) and ulcerative colitis (UC), in randomized controlled trials (RCT)<sup>6,7</sup> and in uncontrolled clinical studies.<sup>8</sup>

Few studies have prospectively evaluated the impact of drugs used to treat IBD on both endoscopic and histologic activity in children with IBD,<sup>1,5</sup> and none of these studies has reported on the effects of thalidomide. The objective of this study was to evaluate the endoscopic and histologic activity in children with IBD who respond to thalidomide.

## Methods

### *Patients and Study Design*

Figure 1 reports patient flow in the study. Patients were enrolled in the study as long-term prospective follow-up of 2 multicenter RCTs on thalidomide compared with placebo in children and adolescents with refractory CD or UC.<sup>6,7</sup>

Methods of the RCTs have been detailed elsewhere.<sup>6,7</sup> Briefly, children and adolescents with 2–18 years of age with a diagnosis of active CD or UC resistant/intolerant to steroids and/or other immunosuppressants (azathioprine or 6-mercaptopurine for 4 months; methotrexate for 3 months; infliximab, 5 mg/kg at 0, 2, 6 weeks; cyclosporine oral, 2 mg/kg/day for 4 weeks or intravenous 1 mg/kg/day for 1 week) were randomized to thalidomide or placebo.<sup>6,7</sup> Clinical response to thalidomide was measured for CD with the Paediatric Crohn's Disease Activity Index (PCDAI) and for children with UC with the Paediatric Ulcerative Colitis Activity Index (PUCAI).<sup>9,10</sup> Clinical remission and clinical response were defined respectively as a PCDAI  $\leq$ 10 points and as a drop in basal PCDAI of at least 50% for CD, and as a PUCAI <10 and a drop in the PUCAI score of at least 20 points for UC. Nonresponders to placebo at 8 weeks were switched to treatment with thalidomide and further followed up open-label for another 8 weeks.<sup>6,7</sup>

Overall in the primary RCTs 72 children received thalidomide; of these 70 had ileocolonic or colonic disease and were evaluated also with respect to endoscopic and histologic outcomes, with a prospective follow-up of 52 weeks (Figure 1).<sup>6,7</sup>

Patients dropping out from the study and suspending thalidomide, either because of side effects or lack of clinical efficacy, were not further followed up. Because in

the primary study number of responders to placebo was very low (Figure 1),<sup>6,7</sup> the endoscopic and histologic evaluation focused only on children responders to thalidomide and did not include responders to placebo.

### *Treatment*

Thalidomide (Thalidomide Pharmion, Boulder, CO, Thalidomide Celgene, Summit, NJ) was administered at a daily dosage of 50 mg, 100 mg, or 150 mg, respectively, for patients <30 kg, 30–60 kg, and >60 kg.<sup>6,7</sup> Six months after achieving clinical remission, the dose was tapered 25% for the following 6 months.<sup>6,7</sup> Any ongoing immunosuppressant use was suspended; steroids were not permitted during the study; any child needing steroids after the start of the study was considered a treatment failure.<sup>6,7</sup>

### *Endoscopic Evaluation*

Endoscopy was performed at enrolment, and during the study period at Week 12 and at Week 52. Results of the endoscopic evaluation were collected on a predefined data extraction sheet by the endoscopist of each clinical center.

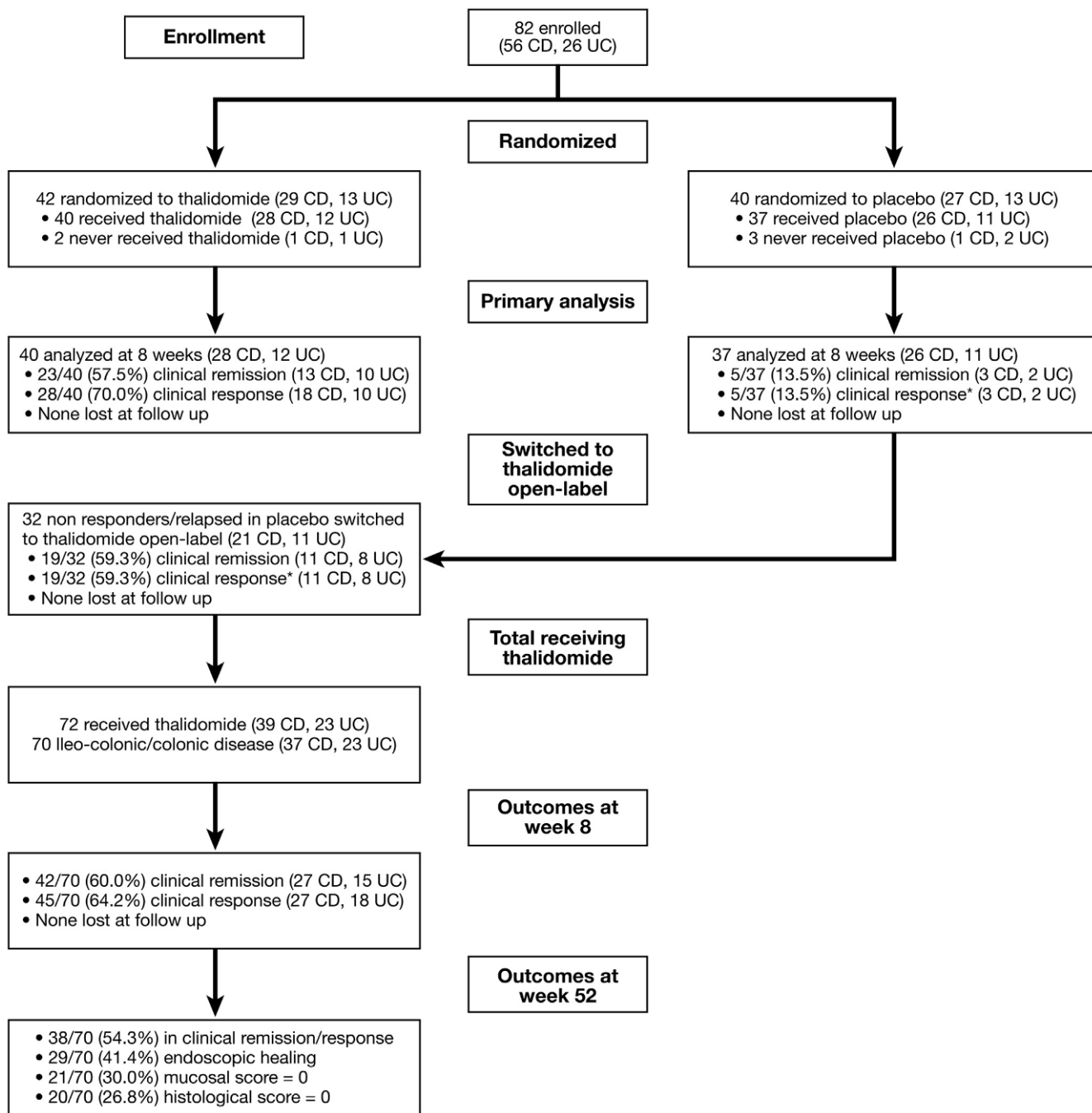
In patients with UC the Mayo score was used<sup>11</sup>: grade 0, normal mucosa; grade 1, mild disease (erythema, decreased vascular pattern, mild friability); grade 2, moderate disease (marked erythema, absent vascular pattern, friability, erosion); and grade 3, severe disease (spontaneous bleeding, ulcerations).

In patients with CD the endoscopic activity was described with a similar 4-grade system, as for Wardle et al<sup>12</sup>: grade 0, macroscopically normal; grade 1, granular mucosa and contact bleeding; grade 2, erythematous and edematous mucosa, aphthoid or superficial ulcers; and grade 3, presence of deep ulcers with slough and pseudopolyps.

Both in patients with UC and CD the most severely affected sites were considered representative for global endoscopic score.

### *Histologic Evaluation*

During each endoscopy (baseline, Week 12, Week 52) a minimum of 1 biopsy for the ileum and for each of the 5 colonic segments was taken. At least 2 biopsies were taken from the most inflamed sites. Samples were fixed in 10% neutral formalin and stained with hematoxylin and eosin. The preparation of the histologic specimen was standardized using a kit for the orientation of the gastrointestinal biopsies (Bio-Optica, Milan, Italy). The analysis of the specimens was centralized (University of Brescia). Two independent expert gastrointestinal pathologists performed the assessment in parallel. They were blinded in respect to the patient's clinical course, endoscopic findings, and treatment regimen. Findings were collected prospectively on a predefined data extraction sheet.



**Figure 1.** Flow of patients in the study.

Histologic activity was described using a predefined histologic inflammatory score (Table 1), developed for the study, in the absence of other validated scoring systems.<sup>1,4,5</sup> The score ranged from 0 (absence of inflammatory activity) to 5 (maximal inflammatory activity). The score aimed at optimizing other existing scoring systems,<sup>4,13,14</sup> and included all key elements useful for identifying active inflammation during follow-up of patients with a diagnosis of UC or CD: active inflammation, erosion or ulceration, and crypt abscesses. The most severely affected site was considered representative for the global histologic score.

### Primary and Secondary Outcomes

The primary outcome of the study was mucosal healing, defined as the absence of mucosal ulcerations or erosions (grade 0 or 1) in all segments of the gut. Other outcomes were complete endoscopic healing defined with a the Mayo or Wardle score of 0; histologic healing, defined as complete absence of inflammatory activity (histologic inflammatory score, 0). Outcomes were measured at Week 12 and Week 52. Subgroup analyses evaluated the rate of endoscopic healing by diseases type (CD, UC) and in the children with

**Table 1.** Histologic Inflammatory Score

Histologic findings	Criteria	Score
Crypt abscess	Present	1
	Absent	0
Erosions and ulcerations	Present	1
	Absent	0
Active inflammation <sup>a</sup>	Severe	3
	Moderate	2
	Mild	1
	Normal	0

NOTE. Score range, from 0 to 5 points.

<sup>a</sup>Neutrophils with or without eosinophils aggressive toward the glandular structures (ie, in phase of penetration into the glandular structure).

previous failure to infliximab (absence of clinical response or adverse events with need for treatment withdrawal).

### Statistical Analysis

Categorical variables are presented as absolute numbers, percentages, and risk ratios with 95% confidence intervals (95% CI). Unpaired categorical variables were compared using the Fisher or Yates corrected chi-square, as appropriate. Paired data were compared

using the McNemar exact test. Quantitative variables are expressed as means and standard deviations, and compared using the Student's *t* test for paired and unpaired data.

Multivariate logistic regression analysis was used to evaluate whether baseline characteristics were independently associated with the primary outcome. The relationship among disease type (CD or UC), age, sex, disease durations, "extensive disease" (defined for CD as ileocolic disease, and for UC as pancolitis), "moderate or severe disease" (defined for CD as PCDAI  $\geq 30$ , for UC as PUCAI  $\geq 65$ ), prior infliximab use, C-reactive protein, and erythrocyte sedimentation rate values with endoscopic healing was assessed using univariate logistic regression analysis. Variables associated with the outcome with a  $P < .2$  were tested in a multivariate model. Data are reported as adjusted odds ratio and 95% CI. All statistical tests were 2-sided. A  $P < .05$  was considered statistically significant.

### Ethical Considerations

All children and their parents/legal guardians were informed about the characteristics of the study, including potential side effects of thalidomide, the importance of contraception, and the risk of peripheral neuropathy. All patients enrolled in the study followed the Risk Management Program, aiming at minimizing the risk of teratogenicity. The study was approved by all the ethics

**Table 2.** Patients' Characteristics at Baseline

		CD (n = 27)	UC (n = 18)
Age, y	Mean (CI)	14.7 (13.7–15.7)	12.8 (10.9–14.6)
Male	N (%)	17 (63.0)	6 (33.3)
Female		10 (37.0)	12 (66.7)
Disease duration, y	Mean (CI)	3.4 (2.3–4.5)	3.6 (2.5–4.7)
Involved gastrointestinal areas	N (%)	Colon plus ileum, 24 (88.9) Colon only, 3 (11.1)	Pancolitis 12 (66.7)
Previous medical therapies			
Steroids	N (%)	22 (81.5)	18 (100)
6MP/azathioprine		26 (96.3)	18 (100)
Methotrexate		3 (11.1)	4 (22.2)
Cyclosporine		0 (0)	4 (22.2)
Infliximab		9 (33.3)	6 (33.3)
Antibiotics		23 (85.2)	14 (77.8)
5-Aminosalicylates		18 (66.7)	16 (88.9)
Enteral nutrition		20 (74.1)	0 (0)
Clinical activity score		PCDAI score	PUCAI score
	Mean (CI)	28.9 (24.6–33.2)	48.6 (38.0–59.1)
Laboratory indexes			
ESR, mm/h	Mean (CI)	47.5 (38.5–56.5)	55.6 (41.2–70.0)
CRP, mg/dL		2.9 (1.9–3.8)	0.9 (0.3–1.4)
Endoscopic score			
Grade 3	N (%)	16 (59.3)	9 (50)
Grade 2		11 (40.7)	8 (44.4)
Grade 1		0	1 (5.6)
Grade 0		0	0
Histologic score	Mean (range)	3.3 (2–5)	2.5 (2–5)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MP, mercaptopurine.

committees of the collaborating centers. Written informed consent was obtained from all parents/legal guardians, and assent was obtained from children. All authors had access to the study data and reviewed and approved the final manuscript.

## Results

### Patients

Seventy children with and ileocolonic/colonic disease received thalidomide. Of these, at Week 8 clinical remission was observed in 42 of 70 (60.0%) and clinical response in 45 of 70 (64.2%). All children were resistant to, intolerant to, or dependent on steroids, or on enteral nutrition (in the case of CD) or to other immunosuppressive drugs (Table 2).

As previously reported,<sup>6,7</sup> during the follow-up, 3 children with CD and 4 children with UC dropped out from the study before 52 weeks (5 children because of side effects, 2 because of a clinical relapse), leaving a sample of 38 children in clinical remission/response in thalidomide at Week 52.

### Endoscopic Findings

Figure 2 summarizes results on mucosal healing (score 0 or 1). Out of the total of children who received thalidomide, the number of those who achieved

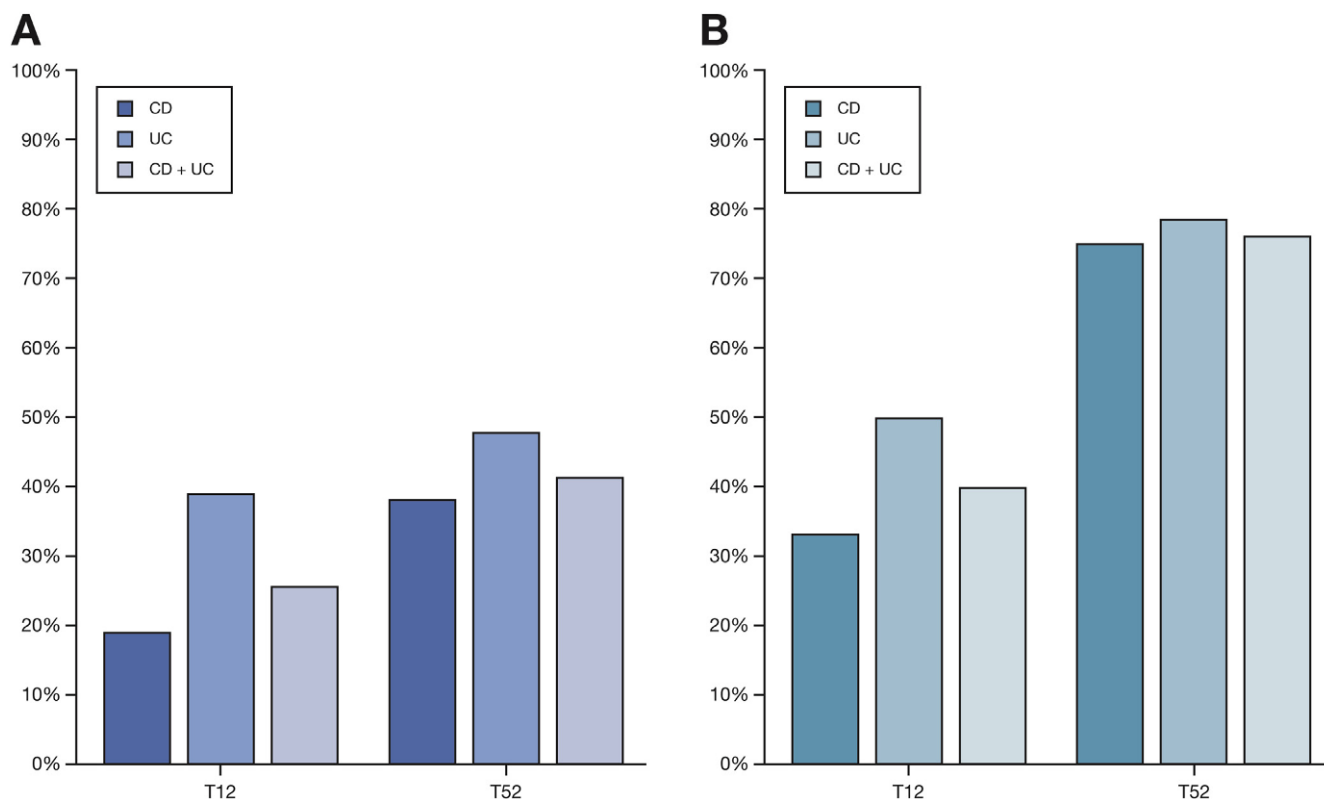
mucosal healing was 18 of 70 (25.7%) at Week 12 and 29 of 70 (41.4%) at Week 52 (Figure 2A). Among children with clinical remission/response to thalidomide, mucosal healing was achieved in 18 of 45 (40.0%) and 29 of 38 (76.3%) of children at Week 12 and Week 52, respectively (Figure 2B). A mucosal score of 0 at Week 12 and Week 52 was achieved in 8 of 70 (11.4%) and 21 of 70 (30.0%) of total children treated with thalidomide, corresponding to 8 of 45 (17.8%) and 21 of 38 (55.3%) of those in clinical remission/response.

### Histologic Findings

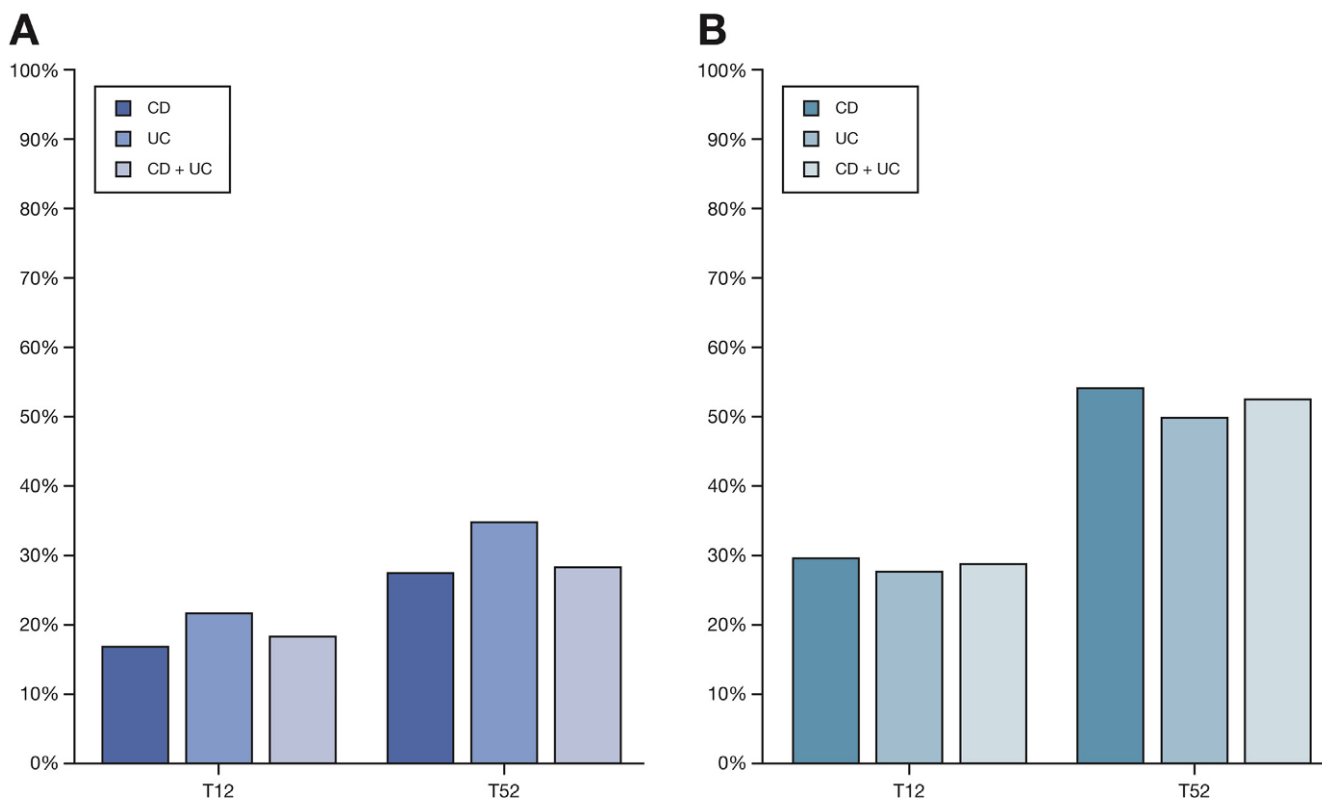
Figure 3 reports results on histologic healing. Out of all treated children, 13 of 70 (18.6%) and 20 of 70 (28.6%) had a histologic score of zero at Week 12 and Week 52 (Figure 3A), corresponding to 13 of 45 (28.9%) and 20 of 38 (52.6%) of those in clinical remission/response (Figure 3B).

### Subgroup Analyses

No statistically significant difference was detected in mucosal healing between children by diseases type (CD or UC), and by previous failure to infliximab, although there was a trend for lower response in those resistant/intolerant to infliximab (Supplementary Tables 1 and 2).



**Figure 2.** Endoscopic healing. (A) Percentage of children with mucosal healing at T12 and T52 out of those who received thalidomide. (B) Percentage of children with mucosal healing at T12 and T52 out of those in clinical response/remission.



**Figure 3.** Histologic healing. (A) Percentage of children with histologic healing (score = 0) at T12 and T52 out of those who received thalidomide. (B) Percentage of children with histologic healing (score = 0) at T12 and T52 out of those in clinical response/remission.

### Multivariate Analysis

At multivariate analysis 2 variables were independently associated with mucosal healing: erythrocyte sedimentation rate (adjusted odds ratio, 0.96; 95% CI, 0.93–0.98;  $P = .006$ ), and extensive disease (adjusted odds ratio, 6.98; 95% CI, 1.04–46.8;  $P = .045$ ). No other significant associations were identified.

### Discussion

This is the first study reporting on the effect of thalidomide on both endoscopic and histologic outcomes in patients with IBD. The rate of children with mucosal and histologic healing during thalidomide treatment significantly increased over time from Week 12 to Week 52 of treatment. At Week 52, out of all children initially treated with thalidomide, 54.3% maintained clinical remission/response, 41.4% achieved mucosal healing, and 28.6% achieved histologic healing. The corresponding rates of mucosal and histologic healing in those in clinical remission/response were of 76.3% and 52.6%, respectively.

Findings from this study on the effect of thalidomide on the endoscopic and histologic activity of IBD may explain the previously reported clinical effect of thalidomide in maintaining clinical remission in the

long-term.<sup>6,7</sup> In 2 RCTs steroid-free clinical remission was maintained with low-dose thalidomide for 181.1 weeks (95% CI, 144.53–217.76) in CD and 135.0 weeks (95% CI, 32–238) in UC.<sup>6,7</sup>

A review of previous literature<sup>8</sup> reports a rate of mucosal healing in patients with IBD treated with thalidomide of 64% (27 of 42 patients), a result in line with the findings of the present study. Besides CD and UC,<sup>15–24</sup> thalidomide was also effective in several other inflammatory diseases affecting the skin and the intestinal mucosa.<sup>25–30</sup> Although the mechanisms of action of thalidomide are not yet entirely clear, its benefit has primarily been ascribed to its roles as an anti-tumor necrosis factor- $\alpha$  agent.<sup>31–36</sup> Thalidomide also has an independent antiangiogenic effect on the vascular endothelial growth factor and on the basic fibroblastic growth factor.<sup>31,34</sup> This complementary mechanism of action may explain why thalidomide has been shown to be particularly effective in different types of inflammatory diseases involving the skin and the intestinal mucosa,<sup>6–8,15–30</sup> even after failure of biologic anti-tumor necrosis factor- $\alpha$  drugs.<sup>6–8,21</sup>

Findings from this study suggest that thalidomide may be an important alternative to other immunosuppressives, inducing high rates of clinical remission,<sup>6,7</sup> mucosal and histologic healing at Week 52, even in patients with resistance or intolerance to other anti-tumor necrosis factor agents. Existing literature on

infliximab reports that mucosal healing was maintained at Week 52 in only 30% of patients with CD<sup>37,38</sup> and 46% of patients with UC.<sup>39</sup> Studies on adalimumab report a rate of mucosal healing at 52 weeks of just 24% for CD<sup>40</sup> and 25% in UC.<sup>41</sup>

The main strengths of the study include the fact that the endoscopic and histologic evaluations were based on pre-defined transparent criteria, the histologic evaluation was blinded and centralized, the evaluation of endoscopic and histologic healing was based on conservative definitions, and the scoring systems used were mostly based on dichotomous items to reduce subjectivity in the evaluation.

The main limitation is that the endoscopic evaluation was not performed in blind, and photographic or video documentation of the endoscopic healing was not available in all collaborating centers at the time of study start. However, prospectively filling out endoscopic disease activity on a data sheet constituted acceptable “standard of documentation” at the time this study was performed. Other studies did not blind the endoscopic evaluation, especially when the study implied a long-term follow-up.<sup>42</sup> Additionally, in our study, procedures for biopsies were predefined, and we aimed at standardizing as far as possible the number and site of biopsies. Both for endoscopic and histologic scoring, the most severely affected site was considered representative for the final score. This should have limited the risk of bias, especially the overestimation of the effects of thalidomide treatment.

The finding at the multivariate analysis that the probability to achieve mucosal healing decreases with increasing values of erythrocyte sedimentation rate (every point increase in erythrocyte sedimentation rate is significantly associated with a decrease in the probability of achieving mucosal healing of 0.04 times) is not surprising. The finding of extensive disease being significantly associated with mucosal healing is probably caused by chance and by the very low number of children without extensive disease. These results, together with subgroup analyses, need to be confirmed in larger studies.

The side effects of thalidomide in children with IBD enrolled in this study have been detailed elsewhere.<sup>6,7</sup> The most frequent side effects associated with treatment suspension on the long term were peripheral neuropathy and amenorrhea.<sup>6,7</sup> Although still limited data are available, published literature<sup>6-8</sup> suggests that the safety of thalidomide in children with IBD may be acceptable when compared with the safety of other immunosuppressive drugs currently used to treat IBD. Further larger studies are needed to confirm safety of thalidomide in children.

## Conclusions

Thalidomide induces mucosal healing and complete remission of histologic inflammatory activity in a

considerable percentage of children with clinical response at Week 52. Results of this study suggest that thalidomide, for its role on the gut mucosa, may be a promising therapy for maintaining long-term remission in patients with IBD. Future studies should investigate the role of thalidomide in managing patients with IBD in the long term and its potential in changing the natural course of IBD.

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#### Conflicts of interest

The authors disclose no conflicts.

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**Supplementary Table 1.** Subgroup Analysis: Endoscopic Healing in Children Responders to Thalidomide by Disease Type

	CD N (%)	UC N (%)
Mucosal score $\leq 1$ at Week 12	9/27 (33.3)	9/18 (50.0)
Mucosal score $\leq 1$ at Week 52	18/24 (75.0)	11/14 (79.0)

*P* > .05 for all outcomes.

**Supplementary Table 2.** Subgroup Analysis: Endoscopic Healing in Children Responders to Thalidomide by Previous Failure to Infliximab

	Previous failure to infliximab N (%)	Previous failure to infliximab N (%)
Mucosal score $\leq 1$ at Week 12	3/15 (20.0)	15/30 (50.0)
Mucosal score $\leq 1$ at Week 52	9/14 (64.3)	20/24 (83.3)

*P* > .05 for all outcomes.