Effect of Thalidomide on Clinical Remission in Children and Adolescents with Ulcerative Colitis Refractory to Other Immunosuppressives: Pilot Randomized Clinical Trial

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Background: In a randomized controlled trial, thalidomide has shown to be effective in refractory Crohn's disease in children. This pilot study aimed at evaluating thalidomide in refractory pediatric ulcerative colitis (UC).

Methods: Double-blind, placebo-controlled randomized clinical trial on thalidomide 1.5 to 2.5 mg/kg/day in children with active UC despite multiple immunosuppressive treatments. In an open-label extension, nonresponders to placebo received thalidomide for an additional 8 weeks; all responders were followed up for a minimum of 52 weeks.

Results: Twenty-six children with refractory UC were randomized to thalidomide or placebo. Clinical remission at week 8 was achieved by significantly more children treated with thalidomide {10/12 (83.3%) versus 2/11 (18.8%); risk ratio, 4.5 (95% confidence interval [CI], 1.2–16.4); $P = 0.005$; number needed to treat, 1.5}. Of the nonresponders to placebo who were switched to thalidomide, 8 of 11 (72.7%) subsequently reached remission at week 8 (risk ratio, 4.0 [95% CI, 1.1–14.7]; number needed to treat, 2.45; $P = 0.01$). Clinical remission in the thalidomide group was 135.0 weeks (95% CI, 32–238), compared with 8.0 weeks (95% CI, 2.4–13.6) in the placebo group ($P < 0.0001$). Cumulative incidence of severe adverse events was 3.1 per 1000 patient-weeks. Peripheral neuropathy and amenorrhea were the most frequent adverse events.

Conclusions: In this pilot randomized controlled trial on cases of UC refractory to immunosuppressive therapy, thalidomide compared with placebo resulted in improved clinical remission at 8 weeks of treatment and in longer term maintenance of remission. These findings require replication in larger clinical studies evaluating both thalidomide efficacy and safety.

Key Words: randomized clinical trial, thalidomide, children, ulcerative colitis

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It is estimated that about 1.5 million people in Europe and nearly 600,000 people in the United States are affected by ulcerative colitis (UC).[1–3] Its incidence is increasing globally, both in adults and in children, and currently, about a quarter of total new cases have an onset during the pediatric age ranges.[2,3]

Cases of UC with an onset in childhood are generally more severe than adult-onset cases. Severe disease with total colonic involvement (pancolitis) and lack of response to available medical treatment is more common in children than in adults.[4–9] Risk of colectomy is also higher with a 30% to 40% colectomy rate at 10 years in children, as compared with 20% in adults,[6,7,9] although lower rates have been reported in some pediatric studies.[5,6] Although it is true that surgery can ultimately cure UC, it may also result in complications, such as anastomotic strictures, infections, intestinal obstruction, sexual dysfunction, and female infertility.[4,6] New options for medical treatment of UC are needed. However, as yet very few drugs have been adequately tested with randomized controlled trials (RCTs) in children.[6,10]

Thalidomide is a small molecule with anti–tumor necrosis factor α, immunomodulatory, and antiangiogenic properties.[11,12] In an RCT, thalidomide was shown to be effective in treating refractory Crohn's disease[13]; however, only very limited data are available on the effect of thalidomide in patients with UC.[14–17] Based on the experience gathered with the previous RCT in children with Crohn's disease,[13] we conducted a pilot trial to evaluate the effect of thalidomide in inducing and maintaining clinical remission in children and adolescents with UC refractory/intolerant to other immunosuppressive treatments.

MATERIALS AND METHODS

Patients

Children and adolescents aged from 2 to 18 years were eligible for enrollment if they had active UC despite other immunosuppressant treatments or if they had experienced adverse events with these drugs that prevented them from continuing the treatment. Resistance to immunosuppressants was defined as active disease despite prednisone 2 mg/kg/day (maximum 60 mg/d) or equivalent for 8 weeks and/or another immunosuppressive drug such as azathioprine or 6-mercaptopurine for 4 months; methotrexate for 3 months; infliximab 5 mg/kg at 0, 2, and 6 weeks; cyclosporine: oral, 2 mg/kg/day for 4 weeks or intravenous, 1 mg/kg/day for 1 week. Children with steroid dependency could be enrolled in the study if matching the above described criteria (i.e., resistance to other immunosuppressives). The exclusion criteria were disease requiring immediate surgery, ongoing pregnancy, neuropathy, HIV, tumors, transplanted organs, ongoing major infections or noncontrolled major diseases, participation in other experimental studies, or infliximab in the previous 8 weeks. The diagnosis of UC was established before inclusion using the Porto criteria.[18]

Clinical activity was measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI).[19,20] The PUCAI score ranges from 0 to 85 (Table, Supplemental Digital Content 1, http://links.lww.com/IBD/A896), a score of 10 or more indicating active disease, a score of 35 or more indicating moderate-to-severe disease, a score of 65 or more indicating acute severe UC.[19,20]

Study Design, Randomization, and Masking

This was a double-blind, placebo-controlled randomized clinical trial. Children were randomized to thalidomide or placebo and followed up for 8 weeks. Additionally, children in the placebo group who at 8 weeks were not in clinical remission or did not have a reduction from baseline clinical activity index of at least 75% or who at any time during the study significantly worsened their condition were switched to thalidomide and followed up in an open-label extension for an additional 8 weeks to verify whether they responded to thalidomide after failure to respond to placebo.

After the evaluation of the primary outcome (clinical remission) at 8 weeks, all responders to either thalidomide or placebo were further followed up prospectively for a minimum of an additional 52 weeks to document long-term efficacy and adverse events.

Children were randomized to receive thalidomide or placebo with a computer-generated randomization list of blocks of 4, centrally created by an independent team of researchers. Thalidomide and placebo were prepared by an independent pharmacy in a priori sequentially numbered drug containers of identical appearance in identical capsules of 50 mg so that the 2 formulations were indistinguishable. Both the clinicians who administered the study treatment and evaluated the outcomes and the children and their families were blinded to study treatment for the RCT phase (8 wk). Subsequently, the study continued open-label.

Study Treatment

Thalidomide was administered at a daily dosage of 50, 100, or 150 mg to patients weighing <30 kg, from 30 to 60 kg, and >60 kg, respectively. Any ongoing immunosuppressant was suspended. Steroids were not permitted during the study, with the exception of children who were enrolled because of a relapse during steroid treatment (i.e., nonresponders to steroids) and children with severe acute UC (PUCAI score ≥ 65), for which steroids were formally indicated.[6,21] Children starting steroids after enrollment were accounted for as a failure to treatment.

During the long-term follow-up, thalidomide could be tapered 6 months after the achievement of remission with a suggested reduction scheme of about 25% less every 6 months. This scheme could be adjusted in case of signs of clinical relapse (by increasing the daily dose of thalidomide) or in case suspect of clinical neuropathy (by decreasing the dose of thalidomide).

Thalidomide (Thalidomide Pharmion, PHARMION, Boulder, CO; Thalidomide Celgene, Celgene Corporation, Summit, NJ) use is regulated by a compulsory distribution system that aims at minimizing the risk of teratogenicity. Patients enrolled in the study followed the Pharmion Risk Management Programs and subsequently, when Pharmion was acquired by Celgene (2009), the Celgene Pregnancy Prevention Program.

Evaluation of Efficacy and Safety

At weeks 0, 4, and 8, the children were examined, diary data (i.e., general patient condition, frequency and type of abdominal pain, stool characteristics, any other complaint) and laboratory samples (hematocrit, ferritin, erythrocyte sedimentation rate, C-reactive protein, electrolytes, and others as needed according to the patient's condition) were collected, the indexes of clinical activity and the nutritional indicators were calculated, and adverse events were recorded. Disease severity was evaluated with the PUCAI.[19,20] Nutritional status was measured by body mass index and weight-for-age, compared with a validated reference national population.[22] To further complementing PUCAI and capturing the physician's global assessment of the patients' overall health status, we used a simple score developed for this trial, with a range from 1 to 10, with 10 indicating excellent health.

Evaluation of adverse events was conducted at each visit and included a detailed history, vital signs, physical examination, and laboratory analysis. Because peripheral neuropathy is a possible adverse event related to the use of thalidomide, a complete neurological examination, with special attention to any signs and symptoms of involvement of the peripheral and autonomic nervous system, was performed, using a standardized evaluation form. Electromyography (EMG) was performed at weeks 8 to 12 in all patients, as well as in cases of clinically suspected peripheral neuropathy. The EMG included motor nerve conduction velocity in the median and external sciaticus popliteus nerves and sensory nerve conduction velocity in the median and sural nerves and was performed with conventional surface recordings (no needle were placed in muscles) with silver chloride electrodes. We used a reference scale with age-related pediatric parameters. According to the study protocol, children with peripheral neuropathy, defined as the concomitant presence of clinical signs or symptoms plus EMG alterations, had to cease receiving thalidomide. Children with isolated clinical signs or symptoms, isolated EMG alterations, or a combination of uncertain clinical manifestation and EMG alterations were closely monitored. Any child experiencing an adverse event was followed up to evaluate whether the alteration was persisting.

Primary and Secondary Outcomes

The primary efficacy outcome was clinical remission at week 8, measured with the PUCAI (defined as PUCAI < 10). Secondary

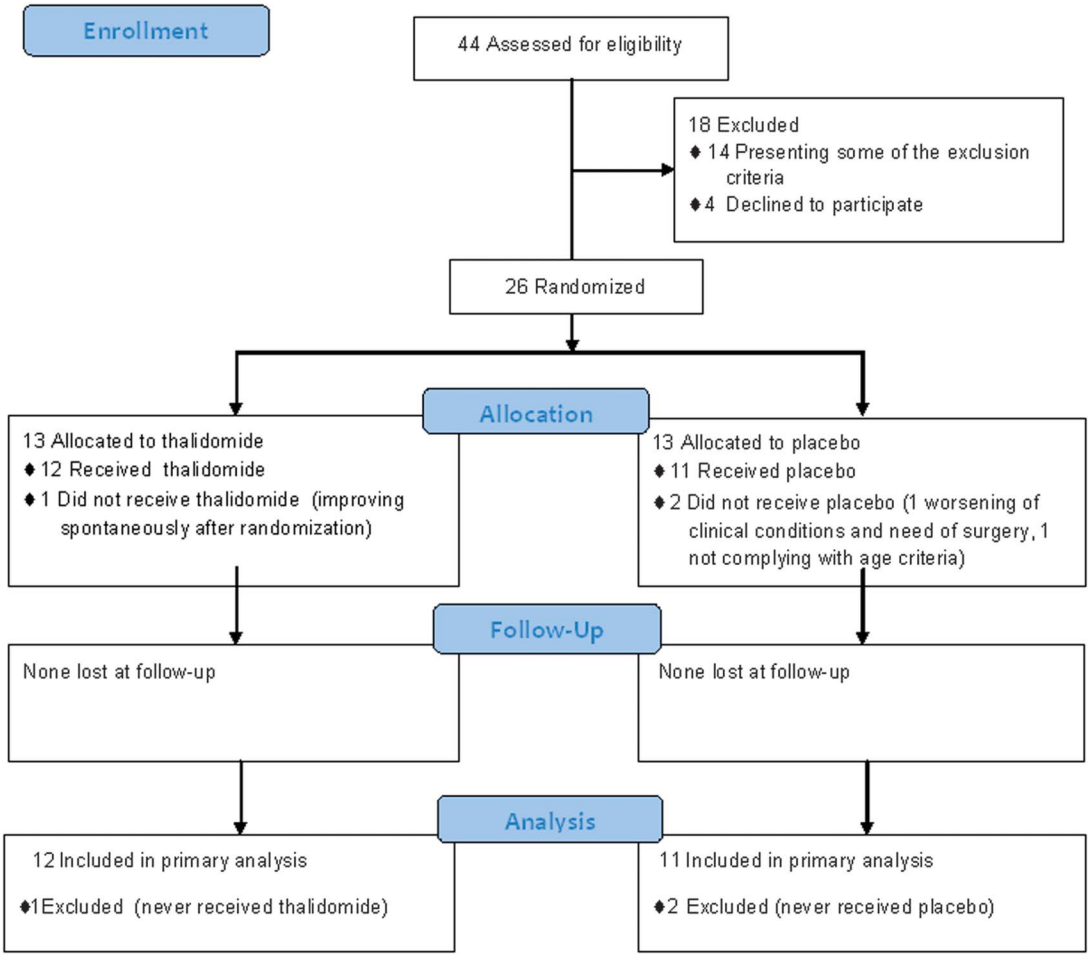

FIGURE 1. CONSORT flow diagram. Flow of patients in the RCT.

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients

	Thalidomide (N = 12)	Placebo (N = 11)	Switched to Thalidomide After Failure to Placebo (N = 11)[a]
Age, mean (CI), yr	11.7 (9.1 to 14.4)	12.9 (10.0 to 15.8)	13.1 (10.2 to 16.0)
Female gender, N (%)	7 (58.3)	8 (72.7)	8 (72.7)
Disease duration, mean (CI), yr	3.8 (2.3 to 5.8)	4.1 (2.4 to 5.7)	4.1 (2.4 to 5.7)
Children with pancolitis, N (%)	10 (83.3)	9 (81.8)	9 (81.8)
Previous medical therapies, N (%)			
Steroids	12 (100)	11 (100)	11 (100)
6-MP/azathioprine	12 (100)	11 (100)	11 (100)
Methotrexate	3 (25)	1 (9.1)	1 (9.1)
Cyclosporine	3 (25)	4 (36.4)	4 (36.4)
Infliximab	5 (41.7)	3 (27.3)	3 (27.3)
Antibiotics	10 (83.3)	7 (63.6)	7 (63.6)
5-aminosalicylates	12 (100)	10 (91)	10 (91)
Clinical activity, mean (CI)			
PUCAI score	51.6 (39.3 to 63.9)	47.0 (34.2 to 59.8)	32.5 (20.5 to 44.5)
Laboratory indexes, mean (CI)			
ESR, mm/h	49.1 (22.7 to 66.5)	39.8 (22.9 to 56.8)	54.2 (37.8 to 70.6)
CRP, mg/dL	0.90 (0.18 to 1.62)	0.65 (0.0 to 1.45)	0.79 (0.23 to 1.32)
Nutritional indicators, mean (CI)			
Weight-for-age zeta score	−0.45 (−0.79 to 1.69)	−0.06 (−1.32 to 1.20)	−0.07 (−1.24 to 1.10)
Height-for-age zeta score	−0.22 (−0.63 to 1.07)	−0.56 (−1.45 to 0.33)	−0.52 (−1.47 to 0.43)
BMI zeta score	−0.36 (−0.84 to 1.56)	0.20 (−1.11 to 1.51)	0.21 (−0.94 to 1.36)
Physician's global assessment score, mean (CI)[b]	5.4 (4.7 to 6.2)	5.7 (5.3 to 6.2)	5.9 (5.2 to 6.6)
Children with extraintestinal manifestation, N (%)[c]	3 (25)	0	0
Steroids, mean (CI)			
Mean dose, mg/kg	0.8 (0.6 to 1.1)	0.7 (0.4 to 0.9)	0.8 (0.5 to 1.1)

Unpaired categorical variables were compared using the Fisher's exact test or Yates' corrected chi-square, as appropriate; paired data were compared using the McNemar's exact test. Quantitative variables were not normally distributed, and therefore, we used nonparametrical methods: the Wilcoxon's 2-sample test for unpaired data and the Wilcoxon's matched-pair signed rank test for paired data. All statistical tests were 2-sided.

[a]Baseline characteristics of children who crossed over to thalidomide after placebo refer to the characteristic at the moment of starting thalidomide treatment.

[b]The physician's global assessment score could range from 0 to 10, with 10 indicating "excellent health status."

[c]In the thalidomide group, there were 3 children with arthritis; one of these also had cutaneous vasculitis.

MP, mercaptopurine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BMI, body mass index.

outcomes evaluated included clinical response at 4 and 8 weeks (defined as a change in the PUCAI score of at least 20 points), mean PUCAI score, C-reactive protein, erythrocyte sedimentation rate, body mass index, weight-for-age, the physician's global assessment score, steroid dosage, and incidence of adverse effects.

As exploratory outcomes, we evaluated the remission rate in the subgroup of children with previous failure or intolerance to infliximab.

Longer Term Follow-up

After the RCT phase, all responders to thalidomide (whether initially randomized or switched from placebo) were followed up prospectively for a minimum of 52 weeks to document longer term efficacy and adverse events related to use of thalidomide. Outcomes were evaluated at 12, 16, 26, and 52 weeks. Patients continuing the follow-up after the 52 weeks were assessed by a gastroenterologist every 26 weeks or whenever needed according to clinical complaints. Adverse events were monitored at each visit, and neurological examination plus EMGs were repeated every 3 months.

The primary efficacy outcome during the long-term follow-up was clinical remission. Secondary outcomes included mucosal healing, variations in clinical disease activity index (PUCAI score), steroid suspension, and thalidomide dose. We also assessed in all responders to thalidomide whether thalidomide induced mucosal healing. Endoscopic findings were assessed at weeks 12 and 52 using the Mayo Score[23]: 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); grade 3, severe disease

(spontaneous bleeding, ulcerations). The most severely affected sites was considered representative for global endoscopic score. Mucosal healing was defined as the absence of mucosal ulcerations (Mayo grade, 0–1) in patients with ulcerations at baseline (Mayo grade, 2–3),[24] and it was assessed at weeks 12 and 52.

Statistical Analysis

Based on the very limited available data existing on the efficacy of on thalidomide in treating patients with UC,[14–17] and Crohn's disease,[13–15,25–29] our a priori hypothesis was that the remission rate at 8 weeks would be 55% in the thalidomide group, compared with 20% in the placebo group. Additionally, because of major uncertainty around this estimate and the risk associated with conducting a placebo-controlled trial (e.g., possible disease progression due to placebo assignment), we predefined stopping rules to guide the final sample size; 3 interim analyses were anticipated, and cutoffs of statistical significance were predefined according to Peto group sequential stopping method, which preserve both an alpha level of 0.05 and a power of at least 80%.[30]

All children who received the study treatment were included in the analysis (intention to treat). Patients who exited the study because of treatment failure or any adverse events were considered treatment failures. For patients with treatment failure before a given time, continuous outcomes were analyzed with the value at treatment failure.

Patients who began receiving thalidomide after placebo were analyzed separately from those randomized to thalidomide. The results from the group randomized to thalidomide were compared with those of the group who later began receiving thalidomide, with statistical tests for unpaired data, whereas the results from the group who later began receiving thalidomide were compared with those from the placebo group, using tests for paired data.

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

TABLE 2. Efficacy Data

	Randomized to Thalidomide (N = 12)	Randomized to Placebo (N = 11)	Switched to Thalidomide After Placebo Failure (N = 11)	*P*: RCT Phase[a]	*P*: Open-label Phase[b]
Outcomes at week 8					
Clinical remission, N (%)[c]	10 (83.3)	2 (18.2)	8 (72.7)	0.005	0.03
Clinical response, N (%)[c]	8 (83.3)	2 (18.2)	7 (63.6)	0.03	0.04
PUCAI score, mean (CI)	12.9 (−1.4 to 27.3)	33.2 (21.1 to 45.3)	12.3 (5.7 to 18.8)	0.001	0.008
Change in ESR, mean (CI), mm/h	−18.6 (−36.4 to −0.8)	14.4 (5.6 to 23.1)	−22.0 (−34.6 to −9.4)	<0.001	0.003
Change in CRP, mean (CI), mg/dL	−0.2 (−0.9 to 0.6)	0.2 (−0.3 to 0.6)	−0.2 (−0.6 to 0.2)	0.1	0.08
Change in WAZ, mean (CI)	0.50 (0.19 to 0.81)	−0.01 (−0.22 to 0.20)	0.11 (0.01 to 0.21)	<0.001	0.2
Change in BMI z-score, mean (CI)	0.64 (0.24 to 1.04)	0.01 (−0.25 to 0.27)	0.12 (0.01 to 0.24)	<0.001	0.3
Change in physician's global assessment score, mean (CI)[d]	1.7 (1.0 to 2.4)	0.2 (−0.7 to 1.1)	1.6 (0.7 to 2.7)	<0.001	0.02
Steroids[e]					
Mean dose, mean (CI), mg/kg	0.3 (0.3 to 0.3)	0.4 (0.2 to 0.5)	0.3 (0.0 to 0.7)	0.03	0.06
Outcomes at week 4					
Clinical response, N (%)[c]	7 (58.3)	4 (36.3)	5 (45.4)	0.5	0.9
PUCAI score, mean (CI)	20.4 (6.6 to 34.2)	27.3 (15.6 to 38.9)	12.7 (6.1 to 19.4)	0.2	0.06
Change in ESR, mean (CI), mm/h	−15.2 (−34.7 to −4.3)	0.7 (−9.7 to 11.1)	−19.3 (−32.4 to −6.2)	0.02	0.06
Change in CRP, mean (CI), mg/dL	−0.1 (−0.9 to 0.7)	0.2 (−0.4 to 0.7)	−0.2 (−1.0 to 0.6)	0.6	0.2
Change in WAZ, mean (CI)	0.40 (0.09 to 0.71)	−0.01 (−0.19 to 0.17)	0.03 (−0.08 to 0.14)	0.001	0.2
Change in BMI z-score, mean (CI)	0.53 (0.13 to 0.93)	0.01 (−0.20 to 0.22)	0.06 (−0.08 to 0.21)	0.001	0.4
Change in physician's global assessment score, mean (CI)[d]	0.7 (−0.5 to 1.9)	0.9 (−0.2 to 2.0)	1.5 (0.7 to 2.2)	0.6	0.2
Steroids					
Mean dose, mean (CI), mg/kg	0.6 (0.2 to 0.9)	0.4 (0.1 to 0.6)	0.5 (0.1 to 0.8)	0.6	0.2

[a]*P*-values were calculated comparing the results in children randomized to thalidomide with the results in children randomized to placebo.
[b]*P*-values were calculated comparing the results in children randomized to placebo with the results in children switched to thalidomide after placebo failure.
[c]Clinical remission was defined as PUCAI <10. Clinical response measured with the PUCAI was defined as a change in the PUCAI score compared with baseline of at least 20 points.
[d]The physician's global assessment score could range from 0 to 10, with 10 indicating "excellent health status."
ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BMI, body mass index; WAZ, weight-for-age z-score.

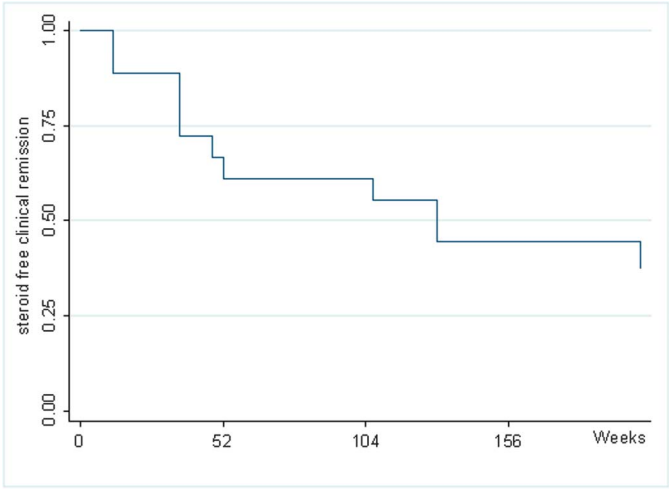

FIGURE 2. Kaplan–Meier curve of "steroid-free" duration of clinical remission. The graph represents the duration of steroid-free clinical remission (in wk) in all patients who achieved remission at week 8 in treatment with thalidomide. Mean duration of clinical remission in thalidomide was 135 (95% CI, 32–238) weeks.

Quantitative variables are expressed as mean and SD values and compared using the *t*-test for paired and unpaired data. When the distribution of the dependent variable was not normal, we applied the Wilcoxon's 2-sample test (for unpaired data) and the Wilcoxon's matched-pair signed rank test (for paired data) as nonparametric methods.

All statistical tests were 2-sided. A *P*-value <0.05 was considered statistically significant. We did not use a method of correction for multiple comparisons because all secondary outcomes were potentially correlated. Instead, results were interpreted looking both at the level of statistical significance and at biological plausibility and consistency of results across different outcomes.

We analyzed maintenance of clinical remission over time using Kaplan–Meier curves, and we used log-rank test to compare the differences between Kaplan–Meier curves. Data for adverse events are reported as absolute incidence for the RCT phase and as cumulative incidence (number of events per patient-weeks) for the long-term follow-up. Data were analyzed with OpenEpi (version 2.3.1) and with Stata 12.

ETHICAL CONSIDERATIONS

The study protocol was approved by the ethics committees of every participating center. All children and their parents or legal guardians were informed about the design of the study, including the random allocation to treatment, the meaning of the word "placebo," and the importance of blinding, as well about possible adverse effects of thalidomide. These included information on peripheral neuropathy, other neurological side effects, skin reactions, gastroenterological side effects, hematological side effects, and other possible side effects such as amenorrhea. Great emphasis was given on the importance of effective contraception, as for the Celgene Pregnancy Prevention Program. All patients and their legal guardians were clearly informed about their right to refuse participation in the study and about their right to withdraw consent from participating at any time, without reprisal. According to the study protocol, in case of significant worsening of clinical conditions, patients could be switched from placebo to active treatment (thalidomide) at any time (and in this case, according to the protocol, they were to be considered "treatment failure"). Written informed consent was obtained from all parents or legal guardians, and assent was obtained from the children.

RESULTS

Patients

Twenty-six children with active UC were randomized to either thalidomide or placebo. One child in the thalidomide group and 2 children in the placebo group never received the study treatment (Fig. 1) and were excluded from the analysis.

Table 1 shows the baseline characteristics of children allocated to thalidomide or placebo and the characteristics of those who began receiving thalidomide after failure with placebo at initiation of thalidomide. Baseline characteristics were similar among groups and by site of enrollment.

All children enrolled in this study were resistant, intolerant, or dependant on steroids; all were resistant/intolerant to azathioprine; about one-third had attempted infliximab, and about one-third had attempted cyclosporine (Fig., Supplemental Digital Content 2, http://links.lww.com/IBD/A897). Over 80% of children had pancolitis. Nearly 40% of children had severe acute UC (PUCAI score $\geq$ 65).

Efficacy

Outcomes Within 8 Weeks

At week 4, only few selected secondary outcomes were significantly different between the thalidomide group and the placebo group, while at week 8, thalidomide consistently showed a benefit over placebo. In the thalidomide group, 10 of 12 children (83.3%) reached clinical remission versus 2 of 11 (18.2%) in the placebo group (RR, 4.5 [95% CI, 1.2–16.4]; $P = 0.005$; number needed to treat [NNT], 1.5 [95% CI, 1.1–4.0]). Clinical response was also significantly better at week 8 in the thalidomide versus placebo group: 8/12 (66.6%) versus 2/11 (18.2%) (RR, 3.7 [95% CI, 1.0–13.7]; $P = 0.03$; NNT, 1.5 [95% CI, 1.18–8.14]). Mean PUCAI score, erythrocyte sedimentation rate, weight-for-age, body mass index, and physician's global assessment scores were all significantly improved in the thalidomide versus placebo group at week 8 (Table 2).

Results in the group of patients who began to receive thalidomide open-label after placebo failure were as follows: all

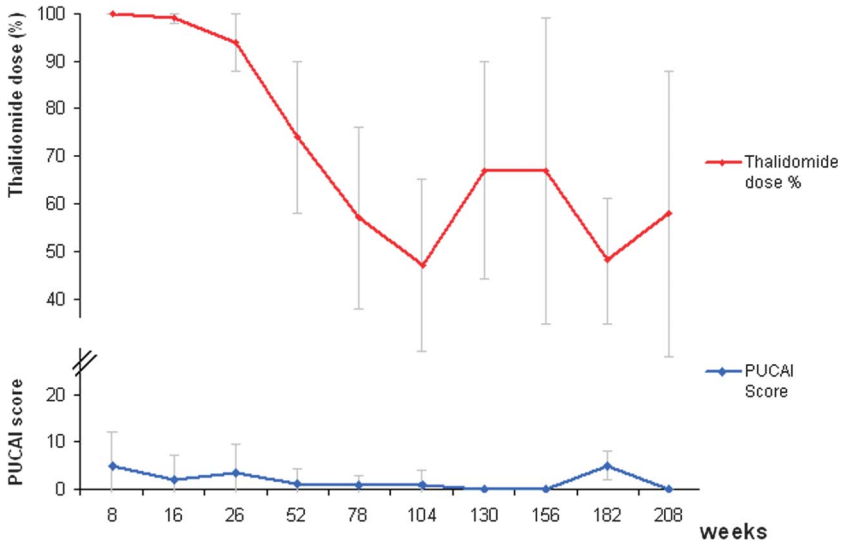

FIGURE 3. Thalidomide daily dose and clinical scores over time. The graph shows the thalidomide mean daily dose and PUCAI score over time (in wk). Thalidomide mean daily dose is expressed as a percentage of the initial dose (mean ± SD). PUCAI score is expressed as an absolute value.

patients initially treated with placebo were switched to thalidomide (9 due to placebo failure at 8 wk, 2 for clinical relapse after 1 and 3 mo, respectively); of these, 8 of 11 (72.7%) subsequently reached clinical remission at week 8 under thalidomide treatment (RR, 4 [95% CI, 1.1–14.7]; NNT, 1.8 [95% CI, 1.1–8.1]; $P = 0.03$); other secondary outcomes were overall similar to the results observed in the RCT phase (Table 2).

The exploratory analysis of the subgroup of children with failure to respond or intolerance to infliximab showed that thalidomide induced clinical remission at 8 weeks in 6 of 8 (75.0%) compared with 0 of 3 receiving placebo (RR undefined, $P = 0.03$).

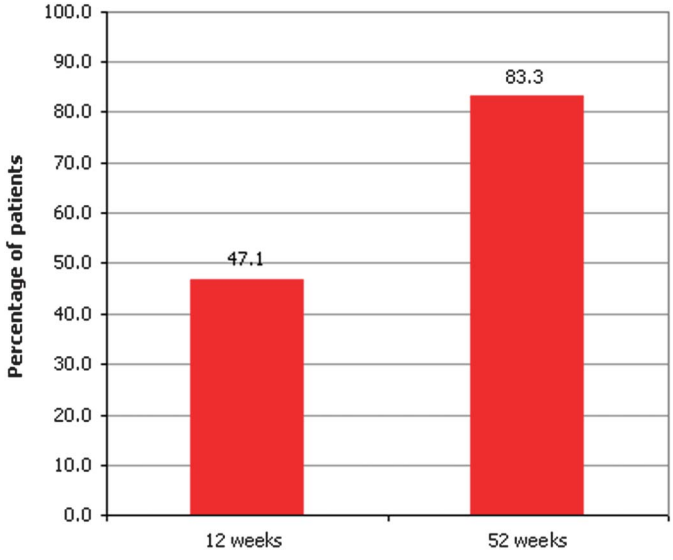

FIGURE 4. Mucosal healing. The graph depicts the percentage of responders to thalidomide reaching mucosal healing at weeks 12 and 52.

Long-term Open-label Follow-up

All responders were followed up for a minimum of 52 weeks, with none lost at follow-up. Among responders to thalidomide, the mean duration of steroid-free clinical remission (Fig. 2) was 135 weeks (95% CI, 32–238), compared with 8.0 weeks (95% CI, 2.4–13.6) in the placebo group (Chi-square log-rank test: $P < 0.0001$). During the long-term follow-up, the main reason for stopping thalidomide was the occurrence of adverse effects (6 clinical neuropathy; 2 amenorrhea), rather than clinical relapse (3 cases).

The thalidomide daily dose was progressively decreased during the follow-up, according to the reduction scheme, with maintenance of clinical remission (Fig. 3).

Of the 18 patients achieving clinical remission with thalidomide, all but one had macroscopical ulcerations at baseline. Mucosal healing was achieved in 8 of 17 patients (47%) at week 12 and in 10 of 12 patients (83.3%) at week 52 (Fig. 4).

Safety

Outcomes Within 8 Weeks

Overall, in the first 8 weeks (RCT phase), among patients treated with thalidomide, 13 of 23 (56%) reported an adverse effect versus 2 of 11 (18%) in the placebo group (RR, 3.1 [95% CI, 0.8–11.4]). No severe adverse effect was observed in the first 8 weeks of treatment (Table, Supplemental Digital Content 3, http://links.lww.com/IBD/A898).

Long-term Open-label Follow-up

Cumulative duration of follow-up in patients treated with thalidomide was 2527 patient-weeks (Table 3). Eight adverse events requiring treatment suspension occurred, for a cumulative incidence of 3.1 per 1000 patient-weeks (95% CI, 1.5–6.0).

TABLE 3. Adverse Effects

	Treated with Thalidomide (N = 23)[a]	Incidence Rate Per 1000 Patient-weeks
Duration of exposure, wk		
Mean ± SD	109.9 ± 108.7	
Median (IQR)	130 (39–213)	
Total patient-weeks of follow-up, N	2527	
Patients with any adverse events, N	19	7.5/1000
Adverse events leading to discontinuation of treatment, N		
Peripheral neuropathy	6	2.3/1000
Amenorrhea[b]	2	0.8/1000
Serious adverse events not leading to discontinuation of treatment, N		
Optic neuritis[c]	1	0.4/1000
Other adverse events, N		
Neurological[d]		
Mild EMG alterations + mild symptoms[e]	4	1.6
Isolated EMG alterations (no clinical symptoms)	2	0.8
Isolated symptoms (no EMG alterations)	1	0.4
Headache	4	1.6
Somnolence	4	1.6
Asthenia	2	0.8
Vertigo	1	0.4
Difficulty in concentrating	1	0.4
Drowsiness	1	0.4
Anxious state	1	0.4
Cutaneous		
Dermatitis	7	2.8
Urticaria	1	0.4
Acne	1	0.4
Gastrointestinal		
Constipation	5	2.0
Nausea	1	0.4
Anorexia	1	0.4
Cardiological		
Bradycardia	1	0.4
Lipotimia[f]	1	0.4
Hematological		
Leukocytopenia	1	0.4
Gynecological		
Amenorrhea[b]	3	1.2
Ocular		
Conjunctivitis	1	0.4
Photophobia	1	0.4
Others		
Myalgia	1	0.4
Perimalleolar edema	1	0.4
Total of other adverse events	47	18.8
Total of adverse events, N	56	22.1/1000

[a]All children treated with thalidomide are accounted for in the table, for the whole duration of thalidomide treatment. Overall, 23 children were treated with thalidomide; 18 were responders to thalidomide and received it in the long term.
[b]Cases of amenorrhea: case 1: she presented with amenorrhea at 32 weeks during therapy with thalidomide 100 mg/d; thalidomide was withdrawn at week 48, and regular menses reappeared 12 weeks after. Case 2: she complained of irregular menstrual cycles since week 16 while treated with thalidomide 100 mg/d; amenorrhea began at week 188 while in treatment with thalidomide 50 mg/d; thalidomide was withdrawn at week 214, and regular menses reappeared 8 weeks after. Case 3: she had irregular menstrual cycles even before the start of thalidomide, with family and personal history of irregular menstrual cycles. Regular menses reappear when estroprogestinic treatment was given. Thalidomide was continued for a total of about 5 years and eventually suspended because of peripheral neuropathy. After thalidomide suspension, she had some menstrual cycles (follow-up time after thalidomide suspension is too short to evaluate whether menses are regular). Case 4: this case was refractory to all previous treatments, while after the start of thalidomide, remission was achieved and maintained for more than 5 years; amenorrhea appeared at week 312 (thalidomide daily dose, 50 mg/d); upon decision of the patient and her family, thalidomide was not withdrawn. Case 5: she presented with amenorrhea after 78 weeks on thalidomide (dose, 75 mg/d); thalidomide daily dose was tapered, and the patient is now considering either drug suspension or start of estroprogestinic treatment.
[c]Case of optic neuritis: at week 16, while in treatment with thalidomide 100 mg/d, a girl presented with strabismus, visual obscurations (inability to see in a particular part of the visual field), and papilledema (optic disc swelling). No pathological findings were observed by nuclear magnetic resonance and angio-nuclear magnetic resonance of the brain and encephalic trunk. Thalidomide was tapered to 75 mg/d, and after 8 weeks, all symptoms were no longer apparent. She continued thalidomide till week 104 when the drug was discontinued because of the onset of clinical neuropathy.
[d]All the neurological events were short-lasting.
[e]Mild EMG alterations plus mild clinical signs/symptoms: there were cases not directly interpretable as neuropathy, such as mild tremors, occasional tingling, and unconfirmed reduction in the deep tendon reflexes.
[f]Electrocardiogram within the normal ranges, no evidence of cardiomyopathy.

Peripheral neuropathy was the most frequent severe adverse event. Clinical neuropathy was observed with a minimum cumulative dose of 332 mg/kg (equivalent to 36 wk of thalidomide therapy). Most patients reached very high cumulative doses of thalidomide (corresponding to several weeks of treatment) without developing clinical neuropathy (Table 4).

Cases not directly interpretable as neuropathy (i.e., mild EMG alterations accompanied by mild clinical signs or symptoms) occurred with a cumulative incidence of 1.6 per 1000 patient-weeks (95% CI, 0.5–3.8). Isolated EMG alterations (i.e., without clinical manifestations of peripheral neuropathy) and isolated clinical manifestations (without EMG alterations) had an incidence of 0.8 per 1000 patient-weeks (95% CI, 0.2–2.7) and 0.4 per 1000 patient-weeks (95% CI, 0.01–1.9), respectively.

TABLE 4. Thalidomide Cumulative Dose and Treatment Time

Patients	Total Weeks of Treatment	Cumulative Thalidomide Dose, mg/kg
Case 1	312	2595
Case 2	218	2071
Case 3	364	1981
Case 4	168	1714
Case 5	234	1663
Case 6[a]	234	1606
Case 7[a]	104	1398
Case 8	130	1386
Case 9	234	1362
Case 10	164	1212
Case 11[a]	130	911
Case 12	48	672
Case 13	36	540
Case 14[a]	52	470
Case 15[a]	36	396
Case 16[a]	36	332
Case 17	12	189
Case 18	12	147

[a]Cases with clinical neuropathy.

During the long-term follow-up, 5 girls reported amenorrhea, for an overall incidence of amenorrhea of 2 per 1000 patient-weeks (95% CI, 0.6–4); 1 girl had a transient episode of optic neuritis (Table 3). Nonsevere adverse events were mostly neurological, cutaneous, and gastrointestinal and were observed with a total cumulative incidence of 18.8 cases per 1000 patient-weeks (95% CI, 15.5–25.6). Adverse effects were all reversible after thalidomide discontinuation.

DISCUSSION

To our knowledge, this is the first randomized clinical trial of thalidomide in patients with UC. The pilot trial aimed to gain preliminary information on the efficacy of thalidomide for children with UC refractory or intolerant to other immunosuppressive treatments. Thalidomide was highly effective compared with placebo in inducing clinical remission in children with previous failure/intolerance to other immunosuppressants (RR, 4.5; 95% CI, 1.2–16.4; NNT, 1.5; $P = 0.005$).

It should be emphasized that the population enrolled in this study was extremely selected; all children enrolled in this study were steroid-resistant/intolerant or dependant; all were resistant to thiopurines (azathioprine), and most had already attempted treatment with other immunosuppressives, such as cyclosporine and infliximab. Currently, for this category of children, there is no medical treatment with a proven efficacy in the long term.[6,21,31] Placebo was chosen as a comparator for this reason and to measure the possible placebo effect that may potentially occur during any treatment,[32,33] including in UC.[34,35] This pilot study on extremely severe cases refractory to immunosuppressive therapy, although requiring further confirmation of results in future studies, suggests that a medical treatment such as thalidomide may be effective for long-term treatment of refractory UC cases in children. The low response rate in the placebo group, with quick relapses in all patients who initially responded to placebo, further proves that the effect of thalidomide is real.

This study confirms previous findings from a similar RCT in children with Crohn's disease.[13] First, both studies showed that the effect of thalidomide may not be evident at 4 weeks. However, lack of a substantial clinical effect at 4 weeks did not preclude a major clinical benefit at 8 weeks.[13] At 4 weeks, an initial effect of thalidomide may be suggested by a decrease in ESR values. Of note, in both studies, there was also a significant improvement in nutritional outcomes at both 4 and 8 weeks, which may be explained both by an increase in body mass and by an improvement in the hydration status of patients (reduction of watery stools and better appetite).

Second, both in Crohn's disease[13] and in UC, remission was maintained with thalidomide as a sole treatment. This is an important finding because few drug therapies are available for the maintenance of remission in patients with UC. The main reason for drug suspension during maintenance therapy seems to be the occurrence of adverse effects (neuropathy, amenorrhea), rather than resistance to treatment.

Third, both in Crohn's disease[13] and in UC, thalidomide was effective at low doses (1.5–2.5 mg/kg/d), and the daily dosage could be further tapered after the achievement of remission, down to about 0.7 to 1 mg/kg/day.

Fourth, both in Crohn's disease[13,29] and in UC, thalidomide was effective even in children with previous failure or intolerance to infliximab. This supports the hypothesis that although both thalidomide and infliximab have an anti–tumor necrosis factor α effect, their action is mediated by different mechanisms.[11,12,15,36] Future, studies should seek to explain the mechanism of action of thalidomide in inflammatory bowel diseases.

Fifth, this study confirmed that peripheral neuropathy is the most frequent adverse event associated with the use of thalidomide. However, the incidence of neuropathy was lower in children with inflammatory bowel diseases than the level observed in other studies using thalidomide in adults with multiple myeloma (i.e., the primary indication for use of thalidomide).[37–39]

As a new finding, we reported in this study the rate of mucosal healing in responders to thalidomide. Although these results need confirmation in further studies, the observed high rate (83%) of mucosal healing at 52 weeks in patients responders to thalidomide further supports the hypothesis that this drug may be highly effective in treating UC in the long term.[40]

This study, together with previous study in Crohn's disease,[13] suggests that amenorrhea may be a relatively common

adverse effect of thalidomide in the young population affected by inflammatory bowel diseases (pooled incidence in Crohn's disease[13] and UC = 1.5 per 1000 patient-weeks). Such an adverse event was previously described as a relatively uncommon event in the overall population of woman treated with thalidomide.[39] Cases of amenorrhea observed during thalidomide treatment were generally characterized by ovarian failure with hypergonadotropic hypogonadism and were usually reversed a few months after drug suspension.[41–43] Currently, it is not known how thalidomide induces amenorrhea and whether the risk of amenorrhea during thalidomide treatment is higher in patients with inflammatory diseases compared with other diseases.[41] We recommend that all female patients treated with thalidomide should be monitored for the occurrence of amenorrhea, and dose reduction or discontinuation of thalidomide should be considered.

All immunosuppressants used for treating inflammatory bowel diseases present a risk of severe adverse events, some of which may be even irreversible (e.g., growth failure and osteoporosis associated with the use of steroids; and tuberculosis, other severe infections, autoimmunity, and neoplastic diseases associated with the use of biological agents).[44–46] Although still limited data are available, published literature[13–17,25–29] suggests that the safety of thalidomide in children with inflammatory bowel diseases may be acceptable if compared with the safety of other immunosuppressive drugs currently used to treat inflammatory bowel diseases. Further studies are needed to better explore the safety and effectiveness of thalidomide in comparison with other immunosupprevise drugs.

CONCLUSIONS

In this pilot RCT on extremely severe cases refractory to immunosuppressive therapy, the use of thalidomide versus placebo in children and adolescents resulted in improved clinical remission at 8 weeks of treatment and long-term maintenance of remission with an open-label follow-up. More studies on thalidomide in patients with inflammatory bowel diseases should be conducted to definitively determine efficacy and safety of this treatment.

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Author contributions: The study was conceived and designed by M. Lazzerini, A. Ventura, and S. Martelossi and further discussed with contributions from the rest of the team. M. Lazzerini, A. Ventura, and S. Martelossi drafted this report. S. Manenti, G. Magazzu, S. Pellegrino, M. C. Lucanto, A. Barabino, A. Calvi, S. Arrigo, P. Lionetti, M. Lorusso, F. Mangiantini, M. Fontana, G. Zuin, G. Palla, and G. Maggiore were study investigators, help in interpreting data, and gave critical inputs to finalize the study report. M. Bramuzzo, M. C. Pellegrin, and M. Montico performed the data analysis, under the supervision of M. Lazzerini. V. Villanacci, and S. Manenti performed all histological evaluations. R. Paparazzo coordinated the drug distribution. M. Montico helped in the statistical analysis. M. Bramuzzo and M. C. Pellegrin have full access to all of the data in the study and take responsibility for integrity of the data and accuracy of the data analysis.

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