Original Investigation

Effect of Thalidomide on Clinical Remission in Children and Adolescents With Refractory Crohn Disease
A Randomized Clinical Trial

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IMPORTANCE Pediatric-onset Crohn disease is more aggressive than adult-onset disease, has high rates of resistance to existing drugs, and can lead to permanent impairments. Few trials have evaluated new drugs for refractory Crohn disease in children.

OBJECTIVE To determine whether thalidomide is effective in inducing remission in refractory pediatric Crohn disease.

DESIGN, SETTING, AND PATIENTS Multicenter, double-blind, placebo-controlled, randomized clinical trial of 56 children with active Crohn disease despite immunosuppressive treatment, conducted August 2008–September 2012 in 6 pediatric tertiary care centers in Italy.

INTERVENTIONS Thalidomide, 1.5 to 2.5 mg/kg per day, or placebo once daily for 8 weeks. In an open-label extension, nonresponders to placebo received thalidomide for an additional 8 weeks. All responders continued to receive thalidomide for an additional minimum 52 weeks.

MAIN OUTCOMES AND MEASURES Primary outcomes were clinical remission at week 8, measured by Pediatric Crohn Disease Activity Index (PCDAI) score and reduction in PCDAI by ≥25% or ≥75% at weeks 4 and 8. Primary outcomes during the open-label follow-up were clinical remission and 75% response.

RESULTS Twenty-eight children were randomized to thalidomide and 26 to placebo. Clinical remission was achieved by significantly more children treated with thalidomide (13/28 [46.4%] vs 3/26 [11.5%]; risk ratio [RR], 4.0 [95% CI, 1.2-12.5]; $P = .01$; number needed to treat [NNT], 2.86). Responses were not different at 4 weeks, but greater improvement was observed at 8 weeks in the thalidomide group (75% response, 13/28 [46.4%] vs 3/26 [11.5%]; RR, 4.0 [95% CI, 1.2-12.5]; NNT = 2.86; $P = .01$; and 25% response, 18/28 [64.2%] vs 8/26 [30.8%]; RR, 2.1 [95% CI, 1.1-3.9]; NNT = 2.99; $P = .01$). Of the nonresponders to placebo who began receiving thalidomide, 11 of 21 (52.4%) subsequently reached remission at week 8 (RR, 4.5 [95% CI, 1.4-14.1]; NNT = 2.45; $P = .01$). Overall, 31 of 49 children treated with thalidomide (63.3%) achieved clinical remission, and 32 of 49 (65.3%) achieved 75% response. Mean duration of clinical remission in the thalidomide group was 181.1 weeks (95% CI, 144.53-217.76) vs 6.3 weeks (95% CI, 3.51-9.15) in the placebo group ($P < .001$). Cumulative incidence of severe adverse events was 2.1 per 1000 patient-weeks, with peripheral neuropathy the most frequent severe adverse event.

CONCLUSIONS AND RELEVANCE In children and adolescents with refractory Crohn disease, thalidomide compared with placebo resulted in improved clinical remission at 8 weeks of treatment and longer-term maintenance of remission in an open-label follow-up. These findings require replication to definitively determine clinical utility of this treatment.

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As many as 1.2 million people in Europe and more than half a million in the United States are estimated to have Crohn disease. Its incidence is increasing globally,[1-3] and its prevalence is particularly high in North America and Europe (319 to 322 per 100 000 persons).[2] About 25% of people with Crohn disease develop symptoms as children, and these cases are generally more severe than adult-onset cases. Resistance or intolerance to therapy is common in children with Crohn disease, with up to approximately 18% of cases requiring surgery within 5 years from disease onset. If not adequately treated, children with Crohn disease may have permanent impairments (eg, growth failure, osteoporosis, delayed sexual development, psychological disorders, failure to achieve full educational and career potential).[4-8]

Few randomized trials have evaluated the efficacy and safety of second- and third-line drugs (ie, after failure of steroids or enteral nutrition) in children with Crohn disease.[9-13] Thalidomide is a small molecule with anti–tumor necrosis factor α, immunomodulatory, and antiangiogenic properties.[14,15] It has been used since the 1960s to treat patients with erythema nodosum leprosum (an immunologic complication of leprosy) and, more recently, several other inflammatory diseases of the skin and mucous membranes (aphthous stomatitis, Behçet syndrome, mouth and esophageal ulcers in human immunodeficiency virus, mucocutaneous graft-vs-host disease, and cutaneous manifestations of systemic lupus erythematosus).[14,15] Observational studies on thalidomide in patients with Crohn disease have reported encouraging results, with remission rates ranging from 40% to 70%.[14,15] We evaluated the efficacy and adverse effects of thalidomide in inducing clinical remission in children and adolescents with refractory Crohn disease in a multicenter, double-blind, placebo-controlled, randomized controlled trial.

Methods

Patients

Patients were recruited in 6 pediatric tertiary care centers in Italy between August 2008 and September 2012. The study protocol was approved by the ethics committee of every center and the IRCCS BURLO ethical review board. Children and adolescents aged 2 to 18 years were eligible for enrollment if they had active Crohn disease despite other immunosuppressant treatments or if they had experienced adverse events with these drugs that prevented them from continuing the treatment. The diagnosis of Crohn disease was established before inclusion with the Porto criteria.[16]

Clinical activity was measured by the Pediatric Crohn Disease Activity Index (PCDAI), a validated internationally used index.[16,17] The PCDAI score ranges from 0 to 95, with a score greater than 10 indicating active disease and a score of 30 or more indicating moderate to severe disease.[16,17] A PCDAI score of 15 or greater was required for inclusion. Resistance to immunosuppressants was defined as active disease despite receiving prednisone, 2 mg/kg per day (maximum, 60 mg/d), or the equivalent for 8 weeks or an immunosuppressive drug of proven efficacy in Crohn disease, such as azathioprine or mercaptopurine for 4 months; methotrexate for 3 months; infliximab, 5 mg/kg at 0, 2, and 6 weeks; or cyclosporine, oral 2 mg/kg per day for 4 weeks or intravenously 1 mg/kg per day for 1 week.

The exclusion criteria were disease requiring immediate surgery, ongoing pregnancy, neuropathy, human immunodeficiency virus, tumors, transplanted organs, ongoing major infections or uncontrolled major diseases, participation in other experimental studies, or infliximab in the previous 8 weeks.

Study Design

This was a multicenter, 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 PCDAI score of at least 75% began receiving thalidomide and were followed up in an open-label extension for an additional 8 weeks to verify whether they responded to thalidomide after failure with placebo.

After the randomized controlled trial phase, all responders to thalidomide were further followed up prospectively for a minimum of an additional 52 weeks to document long-term efficacy and adverse events related to thalidomide.

Randomization and Masking

Children were randomized to receive thalidomide or placebo with a computer-generated randomization list with 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 randomized controlled trial phase (8 weeks). Subsequently, the study continued open label.

Study Treatment

Thalidomide was administered at a daily dosage of 50, 100, or 150 mg to patients weighing less than 30 kg, 30 to 60 kg, and greater than 60 kg, respectively. An individualized dose in the usual packaging was prepared for 2 small children (2 mg/kg/d). To minimize the sedative effect of thalidomide, we recommended patients take a single dose of the study drug in the evening. Any ongoing immunosuppressant use was suspended. Steroid receipt was not permitted during the study, with the exception of children who were tapering steroids because of a relapse.

Thalidomide use is regulated by a compulsory distribution system that aims at minimizing the risk of teratogenicity. Patients enrolled in the study followed Pharmion's (the manufacturer) risk management programs. When Pharmion was acquired by Celgene (2009), patients followed Celgene's pregnancy prevention program. All children and their parents or legal guardians were informed about the adverse effects of thalidomide, with emphasis on the importance of effective contraception and the risk of peripheral neuropathy. Written in-

formed consent was obtained from all parents or legal guardians, and assent was obtained from children. Thalidomide dose could be tapered after achievement of clinical remission.

Evaluation of Efficacy and Adverse Events

At weeks 0, 4 and 8, the children were examined, diary data (ie, general patient condition, frequency and type of abdominal pain, stool characteristics, and any other complaint) and laboratory samples (for hematocrit, ferritin, erythrocyte sedimentation rate, C-reactive protein, albumin, electrolytes, and other laboratory values as needed according to the patient's condition) were collected, the PCDAI and nutritional indicators were calculated, and adverse events were recorded. Disease severity was evaluated with the PCDAI.[16,17] Nutritional status was measured by body mass index and weight for age compared with a validated reference national population.[18] To capture the physician's global assessment of the patients' overall health status in the absence of other validated scores for children, we used a simple score developed for this study, 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 use of thalidomide, a complete neurologic 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 for 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 nerve and sensory-nerve conduction velocity in the median and sural nerves and was performed with conventional surface recordings 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.

Primary and Secondary End Points

The primary efficacy endpoints were clinical remission at week 8, measured with the PCDAI and defined by a PCDAI score of 10 or less[16,17] and a reduction in PCDAI score of 25% or greater or 75% or greater, measured at weeks 4 and 8.

Secondary outcomes measured at weeks 4 and 8 included mean PCDAI score, C-reactive protein level, erythrocyte sedimentation rate, body mass index, weight for age, the Physician Global Assessment score, and incidence of adverse effects. As exploratory outcomes, we evaluated the reduction in PCDAI score of 50% or greater, steroid dosage, and the remission rate in the subgroup of children with previous failure or intolerance to infliximab.

Longer-term Follow-up

After the randomized controlled trial phase, all responders to thalidomide (whether initially randomized or originally receiving placebo) were followed 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 and every 26 weeks thereafter. Primary efficacy outcomes were clinical remission and clinical response 75%. Secondary outcomes included mean time to reach remission, mean PCDAI score, steroid suspension, and thalidomide dose. Adverse events were monitored at each visit, and EMGs were repeated every 3 months during the follow-up.

Statistical Analysis

According to previous open-label studies on thalidomide in Crohn disease,[19-31] our a priori hypothesis was that the remission rate at 8 weeks in the thalidomide group would be 60% compared with 20% in the placebo group; it was estimated that 56 children were needed to detect a significant difference with a power of 80% and significance of .05%.

All children who received the study treatment were included in the primary analysis and analyzed by intention to treat. Patients who exited the study because of treatment failure or adverse events were considered to have failed treatment. 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.

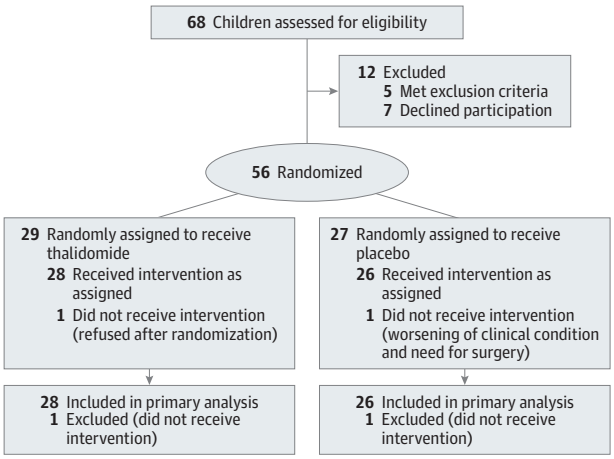
Categorical variables are presented as absolute numbers, percentages, and risk ratios (RRs) with 95% CIs. Unpaired categorical variables were compared with the Fisher exact test or Yates corrected χ^2, as appropriate. Paired data were compared with the McNemar exact test.

Quantitative variables are expressed as means and standard deviations and compared with the *t* test for paired and unpaired data. When the distribution of the dependent variable was not normal, we applied the Wilcoxon 2-sample test (for unpaired data) and the Wilcoxon matched-pairs signed rank test (for paired data) as nonparametric methods.

Multivariable logistic regression analysis was used to evaluate whether baseline characteristics were associated with the primary outcome (clinical remission) and to correct for imbalances. A stepwise approach retaining only significant variables was chosen. Data are reported as adjusted RR and 95% CI.

All statistical tests were 2-sided. $P < .05$ 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 by ex-

Figure 1. Flow of Patients Through the Trial



amining both the level of statistical significance and the biological plausibility and consistency of results across different outcomes.

We analyzed maintenance of clinical remission over time by using Kaplan-Meier curves, and we used the log-rank test to compare differences between them. Data for adverse events are reported as incidence for the randomized controlled trial phase and as cumulative incidence (number of events/patient-weeks) for the long-term follow-up. Data were analyzed with OpenEpi version 2.3.1 and with Stata version 11.

Results

Patients

Fifty-six children with active Crohn disease were randomized to either thalidomide or placebo. One child in each group never received the study treatment; these 2 children were excluded from the analysis (**Figure 1**).

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, except for the mean erythrocyte sedimentation rate value, which was higher in patients randomized to thalidomide. There were no significant differences in patients' characteristics by site of enrollment.

The detailed patients' medical histories in relation to other immunosuppressive treatments are reported in eFigure 1 in the Supplement. Eighteen children (33.3%) were enrolled during a flare-up while receiving steroid tapering. Only these children were receiving steroids at baseline.

Efficacy

Primary End Point

At week 8, 13 of 28 children receiving thalidomide (46.4%) compared with 3 of 26 of those receiving placebo (11.5%) reached clinical remission (RR, 4.0 [95% CI, 1.2-12.5]; $P = .01$; number needed to treat, 2.86 [95% CI, 1.18-9.14]).

At week 4, 25% and 75% responses were not different between groups, but at week 8, the thalidomide group had a better response (25% response, 64.2% vs 30.8%; RR, 2.1 [95% CI, 1.1-3.9]; number needed to treat, 2.99 [95% CI, 1.79-15.01]; 75% response, 46.4% vs 11.5%; RR, 4.0 [95% CI, 1.2-12.5]; number needed to treat, 2.86 [95% CI, 1.18-9.14])($P = .01$ for both).

Other Efficacy End Points and Exploratory Analyses

At week 8, thalidomide consistently showed a benefit over placebo. Mean PCDAI score, erythrocyte sedimentation rate, weight for age, and physician global assessment scores were all significantly higher in the thalidomide group compared with the placebo group (**Table 2**). By week 4, thalidomide had induced a significant decrease in erythrocyte sedimentation rate values compared with placebo and decreased the number of children with undernutrition when measured with weight-for-age *z* score less than −1 SD, but there were no other significant differences in the secondary outcomes between treatment groups. Individual PCDAI scores at baseline, week 4, and week 8 are reported in **Figure 2**.

For exploratory outcomes, at week 8, 50% response was significantly better in the thalidomide vs placebo group. Five children in the thalidomide group vs 6 in the placebo group were receiving low doses of steroids at week 8 (0.34 vs 0.35 mg/kg; 95% CI, 0.17-0.51 vs 0.20-0.50 mg/kg; $P = .10$), confirming that the protocol (steroid tapering) was followed. The exploratory analysis of the subgroup of children with failure to respond or intolerance to infliximab showed that thalidomide induced clinical remission by 8 weeks in 8 of 17 (47.7%) compared with 0 of 11 receiving placebo (RR, 2.1 [95% CI, 1.1-4.0]; number needed to treat = 2.09 [95% CI, 1.44-6.18]; $P = .01$).

Multivariable logistic regression analysis identified as independent predictors of treatment failure the following baseline characteristics: previous therapy with infliximab (adjusted RR, 0.01; 95% CI, 0.001-0.31), PCDAI score greater than 30 (adjusted RR, 0.02; 95% CI, 0.001-0.37), weight-for-age *z* score less than −1 SD (adjusted RR, 0.06; 95% CI, 0.05-0.65), and extraintestinal manifestations (adjusted RR, 0.04; 95% CI, 0.002-0.73). Baseline differences in erythrocyte sedimentation rate values did not significantly affect the probability of remission.

In the open-label extension, of the 23 nonresponders to placebo, 2 needed surgery, whereas 21 began receiving thalidomide. Of these, 11 of 21 (52.4%) subsequently reached clinical remission at week 8 (RR, 4.5 [95% CI, 1.4-14.1]; number needed to treat = 2.45 [95% CI, 1.58-6.79]; $P = .01$). Results of other outcomes comparing those crossed over to begin receiving thalidomide with the placebo group were similar to the outcomes of the randomized controlled trial (eTable 1 in the Supplement).

Longer-term Follow-up

Overall remission rate in children treated with thalidomide was 63.3% (31/49). Overall, 32 children (65.3%) achieved 75% response. Mean time to reach remission was 10.1 weeks (SD, 4.9).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	No. (%)[a]		
	Thalidomide (n = 28)	Placebo (n = 26)	Thalidomide After Placebo (n = 21)
Age, mean (SD), y	14.0 (3.5)	15.0 (3.0)	15.1 (2.0)
Male	15 (53.5)	17 (65.4)	13 (61.9)
Female	13 (46.4)	9 (34.6)	8 (30.1)
Disease duration, mean (SD), y	3.0 (2.2)	4.3 (3.3)	4.0 (3.1)
Median (IQR)	2 (15)	3 (2-5.7)	3 (2-5)
Involved areas			
Only ileum	3 (10.7)	2 (7.6)	1 (4.7)
Only colon	3 (10.7)	8 (30.7)	5 (23.8)
Ileum and colon	22 (78.5)	16 (61.5)	15 (71.4)
Concomitant upper tract	8 (28.5)	10 (38.4)	8 (38.1)
Concomitant perianal disease	6 (21.4)	7 (26.9)	6 (28.5)
Disease behavior			
Nonstricturing/nonpenetrating	15 (53.5)	18 (69.2)	15 (71.4)
Stricturing	10 (42.8)	7 (26.9)	5 (23.8)
Patients with fistulas[b]	3 (10.7)	2 (7.6)	2 (9.5)
Extraintestinal manifestations[c]	11 (39.2)	14 (53.8)	8 (38.1)
Previous medical therapies			
Steroids	24 (85.7)	24 (92.3)	18 (85.7)
Enteral nutrition	26 (92.8)	18 (69.2)	14 (66.7)[d]
Mercaptopurine/azathioprine	28 (100)	25 (96.1)	20 (95.2)
Methotrexate	2 (7.1)	5 (19.2)	3 (14.3)
Infliximab	9 (32.1)	11 (42.3)	8 (38.1)
Antibiotics	22 (78.5)	23 (88.4)	18 (85.7)
5-Aminosalicylates	17 (60.7)	18 (69.2)	13 (62.0)
Enrolled while receiving treatment with steroids[e]	11 (39.2)	9 (34.6)	4 (19.0)
Previous segmental resections	1 (3.5)	1 (3.8)	1 (4.5)
PCDAI score, mean (SD)[f]	30.3 (12.6)	30.0 (10.5)	27.4 (11.7)
PCDAI score ≥30	15 (53.6)	15 (57.7)	10 (47.6)
Laboratory indexes			
C-reactive protein, mean (SD), mg/dL	3.1 (2.8)	3.0 (2.8)	3.1 (2.9)
Erythrocyte sedimentation rate, mean (SD), mm/h	54.6 (27.9)[g]	41.1 (20.9)	42.7 (17.1)
C-reactive protein ≥1 mg/dL	25 (89.2)	19 (73.1)	19 (90.4)
Erythrocyte sedimentation rate ≥20 mm/h	27 (96.4)	23 (88.4)	19 (90.5)
Nutritional indicators			
Weight-for-age *z* score	−0.84 (1.14)	−1.36 (1.08)	−1.45 (1.26)
Height-for-age *z* score	−0.87 (1.05)	−1.07 (1.03)	−1.11 (1.13)
BMI *z* score	−0.48 (1.12)	−0.95 (1.06)	−1.11 (1.25)
Children with WAZ <−1 SD	14 (50.0)	19 (73.0)	16 (76.1)
Children with HAZ <−1 SD	16 (57.1)	12 (46.1)	11 (52.3)
Children with BMI *z* score <−1 SD	11 (39.2)	12 (46.1)	11 (52.3)
Physician Global Assessment score, mean (SD)[h]	5.0 (1.4)	5.1 (1.2)	5.3 (1.4)

Abbreviations: BMI, body mass index; HAZ, height-for-age *z* score; PCDAI, Pediatric Crohn Disease Activity Index; WAZ, weight-for-age *z* score.

[a] Statistical tests and approaches are detailed in the Methods section.

[b] All children with fistulas had them in the context of perianal diseases.

[c] Number of children with extraintestinal manifestations. Thalidomide group: arthritis (2), erythema nodosum (5), panniculitis (1), vulvar metastasis (1), vasculitis (1), pericholangitis (1), orofacial granulomatosis (1), multiple manifestations (2). Placebo group: arthritis (5), erythema nodosum (6), arthralgia (2), growth delay (2), dermatitis (1), episcleritis (1), psoriasis (1), epistaxis (1), gluteal abscess (1), amenorrhea (1), multiple manifestations (4). Began receiving thalidomide after placebo: arthritis (4), erythema nodosum (5), arthralgia (2), growth delay (2), dermatitis (1), episcleritis (1), psoriasis (1), gluteal abscess (1), amenorrhea (1), multiple manifestations (5).

[d] $P = .48$ for the comparison between patients randomized to thalidomide and those who later began receiving thalidomide.

[e] These were steroid-dependent children enrolled during a flare-up while tapering. In the group that began receiving thalidomide after placebo, steroid had been tapered in the placebo period, and therefore at the beginning of thalidomide treatment only 4 children were receiving steroids.

[f] PCDAI score ranges from 0 to 95. A score >10 indicates active disease; a score ≥30 indicates moderate or severe disease activity.[18,19]

[g] $P = .05$ for the comparison between thalidomide and placebo groups.

[h] The physician global assessment score ranges from 0 to 10, with 10 indicating excellent health status.

Table 2. Efficacy Data

	Mean (95% CI)			
	Thalidomide (n = 28)	Placebo (n = 26)	RR (95% CI)	*P* Value[a]
Outcomes at Week 4				
Response, No. (%)				
≥75%	5 (17.9)	3 (11.5)	1.54 (0.43 to 5.91)	
≥50%	9 (32.1)	9 (34.6)	0.92 (0.43 to −1.97)	
≥25%	13 (46.4)	14 (53.8)	0.86 (−1.47 to 0.50)	
PCDAI score	21.0 (16.1 to 25.9)	22.0 (16.6 to 27.4)		
Change in ESR, mm/h	−12.7 (−20.7 to −4.7)	−0.4 (−7.3 to 6.5)		.02
Change in CRP, mg/dL	−1.0 (−2.0 to 0)	0.2 (−0.7 to 1.1)		
Change in WAZ	0.12 (0 to 0.24)	−0.09 (−0.20 to 0.02)		
WAZ <−1 SD, No. (%)	12 (42.8)	20 (76.9)	0.55 (0.34 to 0.89)	.02
Change in BMI *z* score	0.14 (0 to 0.28)	−0.13 (−0.28 to 0.02)		
BMI <−1 SD, No. (%)	8 (28.5)	15 (57.6)	0.49 (0.25 to 0.96)	
Physician global assessment score	6.0 (5.5 to 6.5)	5.6 (4.8 to 6.4)		
Change in physician global assessment score	1.0 (0.4 to 1.6)	0.5 (0 to 1.0)		
Outcomes at Week 8				
Clinical remission, No. (%)	13 (46.4)	3 (11.5)	4.0 (1.22 to 12.51)	.01
Response, No. (%)				
≥75%	13 (46.4)	3 (11.5)	4.0 (1.22 to 12.51)	.01
≥50%	18 (64.2)	7 (26.9)	2.3 (1.22 to 4.81)	.01
≥25%	18 (64.2)	8 (30.8)	2.11 (−1.11 to 3.90)	.01
PCDAI score[b]	16.8 (11.5 to 22.1)	26.0 (20.8 to 31.2)		.01
Change in ESR, mm/h	−20.9 (−28.8 to −13)	−1.1 (−4.3 to −2.1)		<.001
Change in CRP, mg/dL	−0.7 (−1.9 to 0.5)	0 (−0.5 to 0.5)		
Change in WAZ	0.18 (0.05 to 0.31)	−0.12 (−0.28 to 0.04)		.006
WAZ <−1 SD, No. (%)	12 (43)	19 (73.0)	0.58 (0.36 to 0.95)	.004
Change in BMI *z* score	0.23 (0.06 to 0.40)	−0.16 (−0.38 to 0.06)		.007
BMI <−1 SD, No. (%)	7 (25)	14 (56)	0.46 (0.22 to −0.96)	.03
Physician global assessment score[c]	6.7 (6.0 to 7.4)	5.3 (4.7 to 5.9)		.01
Change in physician global assessment score	1.7 (0.9 to 2.5)	0.1 (−0.3 to 0.5)		.007

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCDAI, Pediatric Crohn Disease Activity Index; RR, risk ratio; WAZ, weight-for-age *z* score.

[a] Only *P* values <.05 are reported. Unpaired categorical variables were compared with the Fisher exact test or Yates corrected χ^2, as appropriate; paired data were compared with the McNemar exact test. Quantitative variables were not normally distributed, and therefore we used nonparametric methods: the Wilcoxon 2-sample test for unpaired data and the Wilcoxon matched-pairs signed rank test for paired data. All statistical tests were 2-sided.

[b] The PCDAI score ranges from 0 to 95. A score >10 indicates active disease; a score ≥30 indicates moderate or severe disease activity.[18,19]

[c] The physician global assessment score can range from 0 to 10, with 10 indicating excellent health status.

Mean duration of clinical remission in all children who received thalidomide was 181.1 weeks (95% CI, 144.53-217.76 weeks) compared with 6.3 weeks (95% CI, 3.51-9.15 weeks) in the placebo group (χ^2 log-rank test $P < .001$) (eFigure 2 in the Supplement). There were no differences in the duration of remission in children originally randomized to thalidomide and those who began receiving it after failure of placebo (χ^2 log-rank test $P = .90$).

All the children had ceased receiving steroids by week 16. The thalidomide daily dose was progressively decreased during follow-up without losing clinical efficacy (eFigure 3 in the Supplement).

Adverse Events

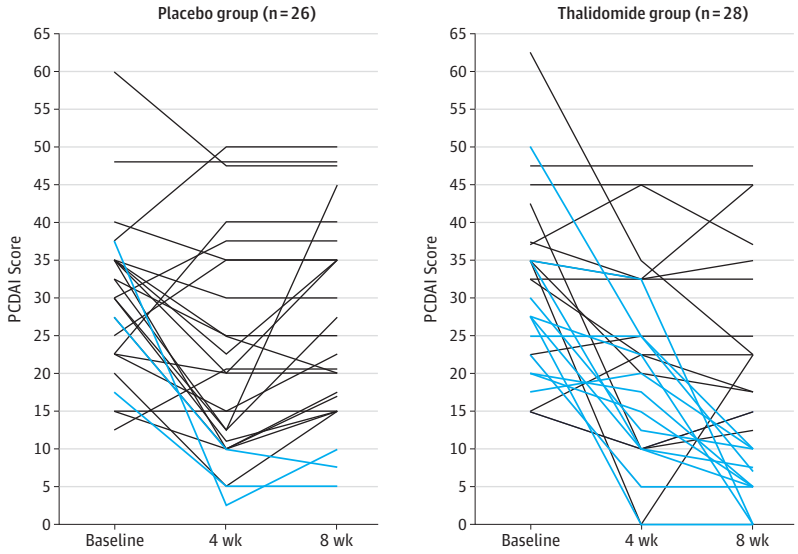
During the randomized controlled trial, 1 child had a seizure and later received a diagnosis of idiopathic epilepsy. Treatment was suspended in this patient as a precaution (**Table 3**). Cumulative duration of follow-up was 4025 patient-weeks (eTable 2 in the Supplement). Nine severe adverse events requiring treatment suspension occurred, for a cumulative incidence of 2.1 per 1000 patient-weeks (95% CI, 1.1-4.1). Peripheral neuropathy was the most frequent severe adverse event. Clinical neuropathy was observed with a minimum cumulative dose of 380 mg/kg (equivalent to 10 months of thalidomide therapy). Most patients reached very high cumulative doses of thalidomide without developing clinical neuropathy (eFigure 4 in the Supplement).

Cases not directly interpretable as neuropathy (ie, mild EMG alterations accompanied by mild clinical signs or symptoms) occurred with a cumulative incidence of 1.2 per 1000 patient-weeks (95% CI, 0.4-2.7). Isolated EMG altera-

tions (ie, without clinical manifestations of peripheral neuropathy) were relatively common (2.7/1000 patient-weeks; 95% CI, 1.4-4.7), whereas isolated clinical manifestations (without EMG alterations) had an incidence of 1.0 per 1000 patient-weeks (95% CI, 0.3-2.4). During thalidomide tapering, either improvement or stabilization of clinical disturbances or EMG alterations was observed in about half of the children presenting with them.

Other severe adverse events observed in the long-term follow-up included amenorrhea, bradycardia, and 1 case of an acute neurologic event, interpreted as possible migraine or transient ischemic attack (eTable 2).

Figure 2. PCDAI Scores by Group Over Time



PCDAI indicates Pediatric Crohn Disease Activity Index (range of scores, 0-105). Blue lines represent patients with remission; black lines, patients without remission.

Table 3. Adverse Effects

	Thalidomide (n = 49)	Placebo (n = 26)	*P* Value: Thalidomide vs Placebo
Patients with adverse events, No. (%)	14 (28.5)	1 (3.8)	.009
Patients with severe adverse events leading to discontinuation of treatment, No. (%)			
Seizure[a]	1 (2.0)	0	.99
Patients with severe adverse events not leading to discontinuation of treatment	0	0	
Patients with minor adverse events, No. (%)	13 (26)	1 (3.8)	.01
Minor adverse events, total	19	2	
Neurologic[b]			
Headache	2	0	
Somnolence	3	1	
Retrosternal pain	1	0	
Vertigo	1	0	
Scotomas	1	0	
Difficulties in concentrating	1	0	
Hemianopsia[c]	1	0	
Strength deficit	1	0	
Cutaneous			
Dermatitis	6	0	
Gastrointestinal			
Constipation	2	0	
Lack of appetite	0	0	
Cardiologic			
Asymptomatic bradycardia	1	0	

[a] An adolescent with active Crohn disease presented with a generalized tonic-clonic convulsion after 2 weeks of receiving thalidomide. Electroencephalography showed alterations in the frontal lobe after awaking and bilaterally in the parietal-frontal lobes during sleep. No lesions were found on brain computed tomography and magnetic resonance imaging. Laboratory tests excluded congenital prothrombotic factors. Thalidomide was immediately suspended as a precaution, although no direct relationship between thalidomide and seizures could be identified in existing literature. He was treated with carbamazepine. He presented further episodes of seizure and later received a diagnosis of idiopathic epilepsy.

[b] Neurologic adverse events: all these events were acute and brief.

[c] One child reported acute muscle weakness and hemianopsia lasting for a few hours; laboratory and neuroradiologic investigations found no evidence of cerebrovascular, neurologic, or muscular alterations and the episode was interpreted as a psychosomatic event.

Overall, nonserious adverse events had a total cumulative incidence of 12.2 cases per 1000 patient-weeks (95% CI, 9-15).

Discussion

To our knowledge, this is the first multicenter, double-blind, placebo-controlled, randomized clinical trial of thalidomide in refractory pediatric Crohn disease.

With this trial, we aimed to evaluate a new therapy for children with Crohn disease refractory to other immunosuppressive treatments. Children with refractory Crohn disease account for about 30% of pediatric Crohn disease cases[5-9] and represent a subgroup with a higher risk of permanent impairment and higher health care costs for the individual and society. New effective and safe drugs are needed for these children.[9]

This is a small trial; however, the size of the sample should be judged in the context of a lack of pediatric trials on Crohn disease. To our knowledge, only 4 other randomized controlled trials have focused on second- and third-line treatments for children and adolescents with Crohn disease.[10-13] Most important, the trial was a priori designed to be adequately powered to test a statistically significant difference between thalidomide and placebo on the primary outcome (clinical remission).

Overall, there was a general consistency of effect across different efficacy outcomes. The lack of statistical significance in few secondary outcomes (such as change in C-reactive protein values) is likely the result of the study not being powered to detect significant differences in all secondary outcomes (eg, possible type II error, false-negative results). Other studies have shown a benefit of thalidomide on indexes of inflammation (both erythrocyte sedimentation rate and C-reactive protein).[26,29] The fact that nonresponders to placebo responded to thalidomide further confirms that the effect of thalidomide is real.

Thalidomide was not used as add-on therapy but rather as the only immunosuppressive drug, and at low doses (approximately 2 mg/kg/d). This treatment scheme is based on previous uncontrolled studies in inflammatory bowel disease[22-29] and supports the idea that thalidomide is a powerful immunosuppressor.

The trial confirms reports from observational studies that effectiveness of thalidomide may not be evident at 4 weeks.[22-29] However, lack of a substantial effect at 4 weeks did not preclude a benefit at 8 weeks.

Thalidomide was effective even in children with previous failure or intolerance to infliximab. Other studies have reported a benefit of thalidomide after failure of infliximab[23-27] and adalimumab.[27] All these molecules have an anti-tumor necrosis factor α effect but work via different pathways.[19-22] However, thalidomide also has an independent antiangiogenetic effect on vascular endothelial growth factor and basic fibroblastic growth factor,[14,15,20] both of which are highly expressed in Crohn disease. This second mechanism may explain why thalidomide is particularly effective in inflammatory diseases with skin and mucosal involvement.[19,20]

The study protocol allowed the enrollment of children with mild to severe active disease, provided they were resistant or intolerant to steroids and other immunosuppressants. We believe that this reflects an actual situation because no child with active Crohn disease can be left untreated.[4-9] Although some children had mild Crohn disease at enrollment according to disease severity measured with the PCDAI, their characteristics included features regarded as strong predictors of negative outcomes, such as previous failure to other immunosuppressants, disease extension, perianal disease, poor nutritional status, or extraintestinal manifestations.[4-9] The poor response to placebo (11.5%) confirms that our sample represents cases of aggressive Crohn disease.

This study confirmed that peripheral neuropathy is the most frequent adverse event associated with use of thalidomide. However, the incidence of neuropathy was lower in our study than that observed by others.[32,33] This may be explained both by the low doses used (50-100 mg/d), the type of patients (children, not adults with multiple myeloma, which is the main indication for thalidomide), and the absence of concomitant drugs.

Bradycardia and amenorrhea are recognized possible adverse events related to thalidomide.[32-34] Patients treated with thalidomide should be monitored for bradycardia, and dose reduction or discontinuation may be required. The incidence of amenorrhea in the overall population of women treated with thalidomide is reported to be 0. 02%,[33,34] although the real incidence in women with inflammatory diseases in unknown.[34] Amenorrhea during thalidomide treatment is characterized by hypergonadotropic hypogonadism and is usually reversible within a few months after thalidomide suspension.[33,34]

An association between thalidomide and convulsions has not been reported. Seizures have been reported to the manufacturer as a rare event (incidence <1/10 000).[33] Such incidence is lower than that reported in the general population.

Although not observed in this study, thalidomide has been associated with an increased risk of thromboembolism when used in association with other chemotherapies in adults with multiple myeloma,[32,33,35] whereas in other diseases this adverse event has been reported only anecdotally.[35] Inflammatory bowel diseases are intrinsically associated with an augmented risk of thromboembolism.[36] The role of thalidomide, as well as of steroids and biological tumor necrosis factor α blockers (all associated with a possible prothrombotic effect),[37] in the genesis of thromboembolism in Crohn disease should be considered individually as a balance between benefits and risks.

The other adverse events observed in this study are consistent with those reported elsewhere.[32,33] Teratogenicity is a well-known adverse effect of thalidomide. However, it is also the most preventable. With adequate precaution, education, and the compulsory prevention program, which includes the use of contraceptives, the possibility of teratogenicity can be avoided. A review of 124 000 patients registered with the thalidomide distribution risk management program during a 6-year period found no case of teratogenicity.[38]

All immunosuppressants used for treating Crohn disease present a risk of severe adverse events. Concerns apply both to old drugs such as steroids (eg, growth failure, osteoporosis) and to new biological agents (increased risk of infections, autoimmunity, development of lymphoma, demyelinating disease, and worsening heart failure).[39] Overall, this study suggests that safety of thalidomide in children with Crohn disease may be acceptable compared with that of other drugs. However, the study was clearly underpowered to detect rare adverse events.

Conclusions

Among children and adolescents with refractory Crohn disease, the use of thalidomide compared with placebo resulted in improved clinical remission at 8 weeks of treatment and longer-term maintenance of remission in an open-label follow-up. These findings require replication to definitively determine the utility of this treatment.

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