

# Thalidomide induces clinical remission and mucosal healing in adults with active Crohn's disease: a prospective open-label study

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## Abstract

**Background:** Thalidomide is effective in inducing and maintaining clinical remission in children and adolescents with refractory Crohn's disease (CD). However, little is known about the efficacy and safety of thalidomide for adult patients with CD.

**Methods:** We conducted a prospective open-label cohort study between January 2013 and April 2015. A total of 47 adult patients with active CD who were dependent/resistant or intolerant to corticosteroids and/or immunomodulators or biologics received 50–100 mg of thalidomide daily. Primary outcome was clinical remission evaluated at week 8. Endoscopic assessment was performed at week 24 and defined as endoscopic response (decrease in Crohn's Disease Endoscopic Index of Severity [CDEIS] score > 5 points from baseline CDEIS of 6 or more), complete endoscopic remission (CDEIS score < 3), and mucosal healing (MH) (no ulceration).

**Results:** A total of 47 adults with active CD were enrolled. The clinical remission rate was 14.9% and 23.4% at week 4 and week 8, but increased to 46.8% at week 12 and 53.2% at week 24 out of all the 47 patients included (intention-to-treat analysis). Altogether 32 patients consented and underwent ileocolonoscopy at week 24. The rate of endoscopic response and complete endoscopic remission were 68.4% and 43.8%. MH (no ulceration) was achieved in 28.1% of patients. Adverse events occurred in 27/47 (57.4%) patients but necessitated therapy discontinuation in only 5/47 (10.6%) of patients.

**Conclusions:** Low-dose thalidomide was effective and tolerated for inducing and maintaining clinical remission in adult patients with active CD, but the optimal time frame for thalidomide to induce clinical remission may be longer than previously appreciated and is probably optimal at 12 weeks. MH could reasonably be achievable with thalidomide.

**Keywords:** mucosal healing, refractory Crohn's disease, thalidomide

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## Introduction

Crohn's disease (CD) is a chronic gastrointestinal inflammatory disease characterized by relapse and progression. The incidence and prevalence of CD are increasing in different regions around the world, indicating its emergence as a global disease.<sup>1–3</sup> Medical therapies, including immunomodulators and biologic agents, have revolutionized

the treatment of CD. However, the occurrence of steroid dependence and resistance or intolerance to medical therapy is still quite common.<sup>4–6</sup> The management of such refractory CD remains a great therapeutic challenge for clinicians.

Thalidomide is an oral agent that has immunomodulatory, anti-angiogenic, and tumor necrosis

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factor- $\alpha$  (TNF- $\alpha$ )-suppressing effects. The potential role for thalidomide in the treatment of refractory pediatric and adult CD has been investigated in small open-label studies and retrospective case series.<sup>7–14</sup> Recently a landmark randomized controlled trial showed thalidomide superiority over placebo for achieving clinical remission at 8 weeks of treatment and for longer-term maintenance of remission in children and adolescents with refractory CD.<sup>15</sup> Nonetheless, in this trial, as well as in clinical practice, thalidomide was used in patients resistant or intolerant to immunomodulators/biologics.<sup>16</sup> To date, only two studies with relatively small sample sizes investigated the efficacy of thalidomide in inducing mucosal healing (MH),<sup>17,18</sup> despite the fact that MH may be a more robust measure of biological response to treatment and a potential surrogate marker for the prospects of altering the natural history of the disease.<sup>19</sup> Therefore, the aim of this study was to evaluate prospectively the efficacy of thalidomide in inducing clinical and endoscopic remission in adults with active CD who were dependent/resistant or intolerant to corticosteroids and/or immunomodulators/biologics.

## Patients and methods

### Study design and patients

This was a prospective open-label study. Patients between the ages of 18 years and 75 years with a definite diagnosis of CD were recruited at The First Affiliated Hospital of Sun Yat-sen University, a tertiary inflammatory bowel disease referral center, between January 2013 and April 2015. Diagnoses of CD were made using standard clinical, radiographic, endoscopic, and histologic criteria.<sup>16</sup> Disease location and behavior were categorized according to the Montreal classification. The study protocol was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University and all patients signed an informed consent.

As biologics are not reimbursed in China, patients failing immunomodulators, who are unable to afford biologic self-pay, are conventionally offered treatment with thalidomide. The inclusion criteria for patients enrolled were: (a) being steroid-dependent<sup>11</sup>, unable to reduce steroids below the equivalent of prednisone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting steroids, or who have a relapse within 3 months of stopping steroids; (b) thiopurine-nonresponsive,

active disease or clinical relapse despite administration of azathioprine (1.5–2 mg/kg/day) or 6-mercaptopurine (0.75–1.5 mg/kg/day) for 4 months;<sup>15</sup> (c) thiopurine-intolerant, intolerance to or adverse events with thiopurines; (d) anti-TNF resistant or intolerant. A Crohn's disease activity index (CDAI) score greater than 150 at baseline was required for inclusion. The exclusion criteria were: (a) isolated upper gastrointestinal CD; (b) symptomatic stenosis of the intestine or an abdominal abscess requiring immediate surgery; (c) current or past history of malignancy or organ transplantation; (d) serious infections within 3 months including cytomegalovirus, *Clostridium difficile*, and tuberculosis, etc.; (e) previous history of peripheral neuropathy or symptoms of peripheral neuropathy or known abnormal electromyography (EMG) prior to thalidomide; (f) infliximab treatment in the previous 8 weeks; (g) progressive or uncontrolled renal, hepatic, hematologic, pulmonary, or cardiac disease; (h) ongoing or planned pregnancy.

### Thalidomide treatment

All patients signed informed consent before the initiation of thalidomide. All patients received counselling regarding teratogenicity risk and the mandatory requirement for contraception for male patients and for female patients of child-bearing potential.

Thalidomide was orally started at a daily dosage of 50 mg and increased to 75 mg or 100 mg according to patients' tolerance and clinical symptoms. To minimize the sedative effect of thalidomide, we recommended patients to take a single dose of the drug in the evening before bedtime.<sup>15</sup> Other ongoing immunosuppressives were maintained at stable dose during the trial except in the case of intolerable adverse events or in patients in whom a tapering steroid dose was possible after the initiation of thalidomide. The fact that the immunomodulators were maintained at stable dose was also methodologically helpful to ensure that clinical remission and endoscopic improvement were induced by thalidomide instead of by a confounding effect from change of other medications.

### Efficacy and adverse events

*Clinical evaluation.* The patients were examined at weeks 0, 4, 8, 12, and 24. Diary data including

body weight, general condition, frequency and type of abdominal pain, stool characteristics, and other complaints were recorded. Laboratory parameters including blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, hepatic, and renal function, and other laboratory values were tested. Disease severity was evaluated with the CDAI.

*Ileocolonoscopy evaluation.* At week 24, colonoscopy was performed in consenting patients to evaluate endoscopic activity using the Crohn's Disease Endoscopic Index of Severity (CDEIS).<sup>20</sup> Briefly, the extent of mucosal lesions in five sections of the bowel including the terminal ileum, right colon, transverse colon, combined sigmoid and left colon, and rectum were qualified. The total score ranged from 0 to 44, with greater scores indicating more severe disease activity. Baseline colonoscopy was performed before initiation of therapy, unless a patient had had a prior colonoscopy documenting active disease within the previous 12 months, and had noninvasive markers of active inflammation at the commencement of therapy, in which case a repeat baseline colonoscopy was deemed unethical.

*Primary and secondary outcomes.* The primary outcome was clinical remission at week 8, similar to that in the trial of Lazzarini and colleagues<sup>15</sup> However, as the inclusion criterion was a CDAI score greater than 150 in our study, we used a rigorous primary outcome of clinical remission defined by a CDAI score of 150 or less and a reduction in CDAI score of 100 points or greater from baseline. Secondary outcomes included clinical response and endoscopic efficacy. Clinical response was defined as a decrease in CDAI score of 100 or more points from baseline.<sup>16</sup> Endoscopic outcome measures included week 24 endoscopic response (decrease in CDEIS score of more than 5 points from the baseline of CDEIS of 6 or more), complete endoscopic remission (CDEIS score less than 3) and MH (no ulceration).<sup>21</sup>

All clinical outcomes were analyzed by intention-to-treat analysis, so that patients withdrawn from the study before a prespecified outcome time point (due to further clinical exacerbation, adverse events or other reasons) were considered as failure of therapy.

*Adverse events.* Adverse events were recorded including a detailed history, vital signs, physical

examination, and laboratory analysis (hematology, biochemistry, and urinalysis). Neurological evaluation was performed at each visit. EMG was not regularly performed except for patients developing severe peripheral neurologic symptoms. Adverse events were summarized as numbers and percentages of patients.

### *Statistical analysis*

Patients who were withdrawn from the study because of treatment failure or adverse events were considered to have failed treatment. The rate of primary outcome was analyzed by intention to treat for all 47 patients at weeks 4, 8, 12, and 24.

Demographic and clinical parameters were compiled and summary statistics were calculated. Data were described using medians with interquartile range (IQR) for continuous data and percentages for discrete data. Fisher's exact test or chi-square tests were used to compare the nonparametric categorical data between groups. The SPSS 15.0 software (SPSS, Chicago, IL, USA) was used to perform all appropriate statistical analyses. Statistical significance was set at  $p < 0.05$ .

## **Results**

### *Patients*

A total of 47 adults with active CD were enrolled. Table 1 shows the characteristics of the patients at thalidomide initiation. Of these 47 patients 14 (29.8%) had received prior surgery. All patients had received previous immunosuppressive or immunomodulating agents: corticosteroids in 23 patients (48.9%), infliximab in 12 patients (25.5%), azathioprine in 33 patients (70.2%), 6-mercaptopurine in 5 patients (10.6%), and methotrexate in 1 patient (2.1%).

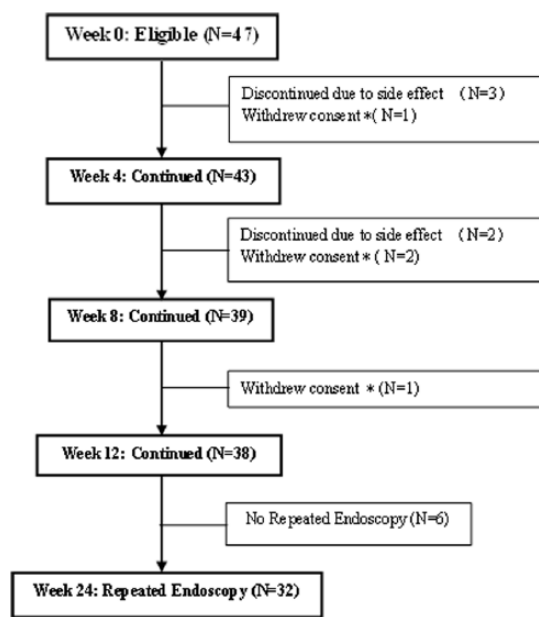
The dose of thalidomide was adjusted in 13 of the 47 (27.7%) patients according to patients' tolerance and clinical symptoms, whereas the majority of patients (34/47, 72.3%) kept the stable daily dose of 50 mg. Five patients withdrew thalidomide treatment because of side effects and four withdrew consent within the first 12 weeks. At week 24, 32 patients underwent repeated ileocolonoscopy (Figure 1).

Six patients (6/47, 12.7%) were on steroids and 26 patients were on thiopurine when starting

**Table 1.** Baseline demographic and clinical characteristics of patients.

	<i>n</i> = 47
Male	27 (57.4%)
Median (IQR) age at thalidomide initiation (years)	22 (18–34)
Median (IQR) duration of disease (years)	3.4 (2.1–5.3)
Disease location	
Ileal	3 (6.4%)
Colonic	4 (8.5%)
Ileocolonic	40 (85.1%)
Upper gastrointestinal tract	6 (12.8%)
Disease behavior	
Nonstricturing, nonpenetrating	25 (53.2%)
Stricturing	9 (19.1%)
Penetrating	13 (27.7%)
Perianal lesion	14 (29.8%)
Prior surgery	14 (29.8%)
Previous therapy for inflammatory bowel disease	
Steroids	23 (48.9%)
Azathioprine	33 (70.2%)
6-mercaptopurine	5 (10.6%)
Methotrexate	1 (2.1%)
Infliximab	12 (25.5%)
Antibiotics	10 (21.3%)
5-aminosalicylates	24 (64.9%)
Actively smoking	3 (6.4%)
Crohn's disease activity index score, mean (SD)	213.4 (48.4)
Body weight, mean (SD), kg	52.24 (9.32)
Baseline Crohn's Disease Endoscopic Index of Severity score, mean (SD)	7.78 (4.09)
Laboratory indexes	
CRP, median (IQR), mg/L	13.6 (4.7,15.0)
ESR, mean (SD), mm/h	50.8 (30.3)
Elevated CRP	40 (85.1%)
Elevated ESR	39 (83.0%)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SD, standard deviation.



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

thalidomide. All the six patients were able to taper the dose and discontinue steroids during treatment with thalidomide.

*Primary and secondary outcomes*

The changes in clinical and laboratory indices at weeks 4, 8, 12, and 24 compared with the baseline are shown in Table 2. Clinical remission at week 8 (primary outcome) was attained by 23% of the patients. The rate of clinical remission increased to 47% at week 12 and remained stable until week 24, when computed out of all 47 patients who started the study as per intention-to-treat analysis (Figure 2). At week 12, there was a significant decrease in CDAI, ESR, and high sensitivity-CRP compared with the baseline ( $p = 0.000$ ,  $p = 0.007$ ,  $p = 0.003$ , respectively). The clinical response rate was 23.4% and 27.7% at weeks 4 and 8, and increased to 51.1% and 55.3% at weeks 12 and 24, respectively. This was reflected by a decrease over time in the number of patients with a CDAI score greater than 150, elevated ESR, and elevated CRP (Figure 3).

*Endoscopic efficacy*

The secondary outcome of MH was assessed in 32 patients who consented to undergo repeated ileocolonoscopy at week 24. Results of ileocolonoscopy were compared with results of prior

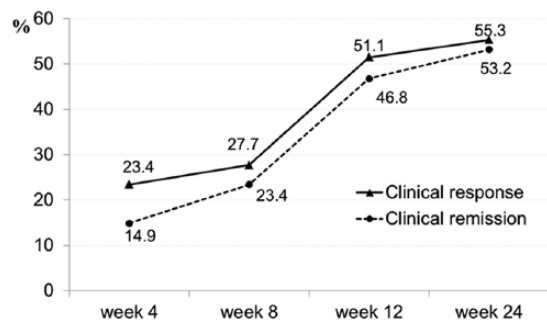
**Table 2.** Outcomes of thalidomide treatment over time.

	Week 4	Week 8	Week 12	Week 24
Clinical response <sup>1</sup> , No. (%)	11 (23.4%)	13 (27.7%)	24 (51.1%)	26 (55.3%)
Clinical remission <sup>2</sup> , No. (%)	7 (14.9%)	11 (23.4%)	22 (46.8%)	25 (53.2%)
CDAI score, mean (SD)	136.6 (51.9)*	115.3 (45.5)*	92.9 (36.8)*	81.7 (42.5)*
CRP, median (IQR), mg/L	9.7 (4.0,13.3)	8.9 (3.5,14.3)	2.7 (1.0,6.5)*	2.6 (1.3,9.5)*
ESR, mean (SD), mm/h	36.63 (23.09) <sup>§</sup>	34.17 (21.16) <sup>§</sup>	30.33 (22.36)*	25.93 (18.72)*
HB, mean (SD), g/L	115.90 (19.62)	122.23 (19.08)	125.39 (16.75) <sup>§</sup>	129.00 (15.29)*
BMI, mean (SD), kg/m <sup>2</sup>	19.43 (2.19)	18.49 (5.29)	20.17 (2.17) <sup>§</sup>	20.35 (2.11) <sup>§</sup>
Change in CRP, mg/L	-0.9 (-39.65,11.04)	-3.45 (-40.22,6.66)	-6.19 (-60.8,9.82)	-6.72 (-64.26,11.64)
Change in ESR, mm/h	-11 (-32,11)	-11 (-74,18)	-17.5 (-77,20)	-19 (-85,25)
Change in HB, g/L	-0.5 (-15,43)	3 (-13,48)	10 (-10,43)	12 (-10,53)
Change in BMI, kg/m <sup>2</sup>	0 (-0.93,4.33)	0.37 (-0.74,5.71)	0.74 (-1.04,4.96)	1.06 (-0.71,7.09)

<sup>1</sup>CDAI score decline  $\geq 100$  from baseline. <sup>2</sup>CDAI score  $< 150$  and CDAI score decline  $\geq 100$  from baseline.

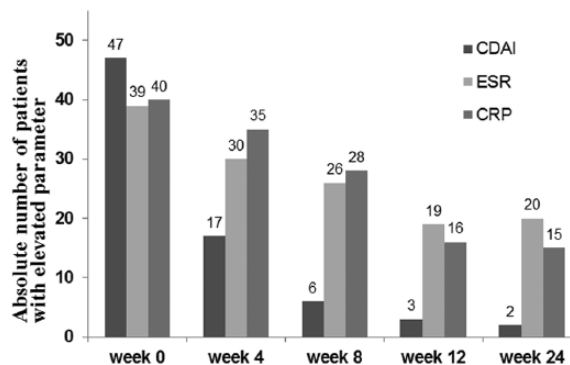
\* $p < 0.01$  (compared with baseline), <sup>§</sup> $p < 0.05$  (compared with baseline).

BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HB, hemoglobin; IQR, interquartile range; SD, standard deviation.

**Figure 2.** Rate of clinical remission and response over time.

pretreatment colonoscopy, which was performed at a median interval of 3 months (IQR: 0–7.8 months) before thalidomide treatment. Of these 32 patients, 23 had had two prior ileocolonoscopies before thalidomide initiation.

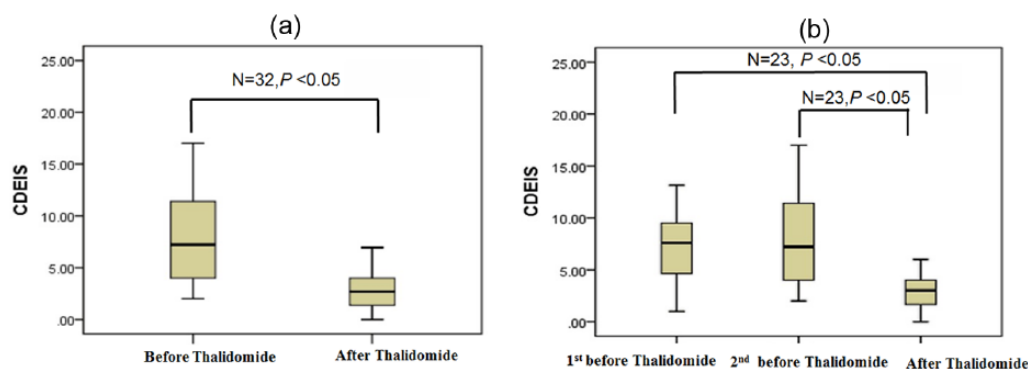
As shown in Figure 4(a), CDEIS was significantly decreased after thalidomide treatment compared with pretreatment colonoscopy. For those 23 patients who had had two prior ileocolonoscopies available for comparison before thalidomide initiation, there was no significant change in CDEIS between those two prior pretreatment examinations, but CDEIS was thereafter significantly decreased following thalidomide treatment (Figure 4(b)). Overall, the rate of endoscopic

**Figure 3.** Clinical efficacy measures over time, including absolute number of patients with CDAI  $> 150$  over time (dark bars), number of patients with elevated ESR (light gray bars), and number of patients with elevated CRP over time (dark gray bars). CDAI, Crohn's disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

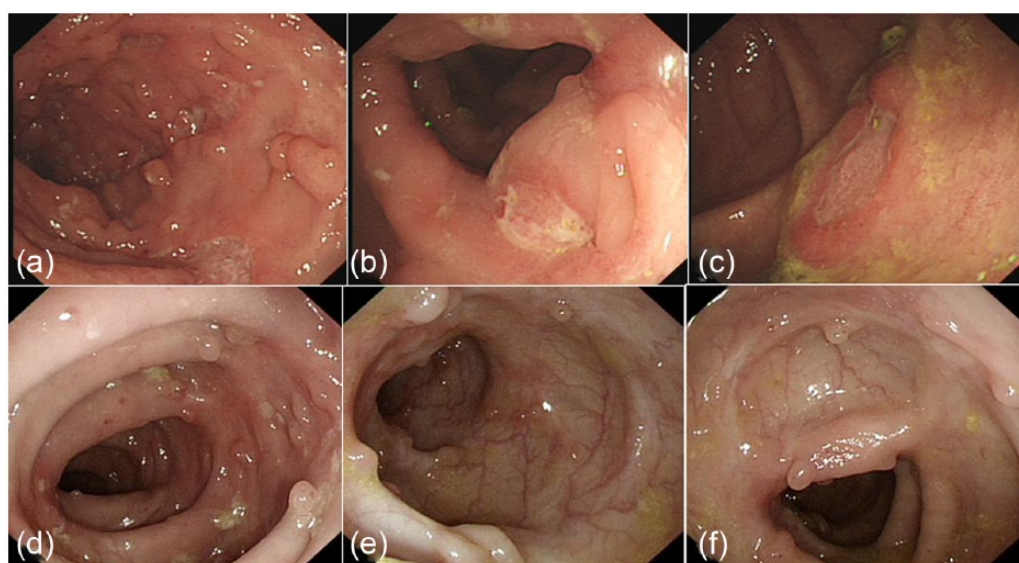
response and complete remission was 68.4% and 43.8%, respectively. The rate of MH (no ulceration) was 28.1% at week 24 (Figure 5).

#### Adverse events

A total of 43 adverse events occurred in 27 (27/47, 57.4%) patients during the thalidomide treatment. Constipation and somnolence were the most frequent adverse events (both occurred in



**Figure 4.** Crohn’s Disease Endoscopic Index of Severity (CDEIS) score before and after thalidomide treatment. (a) CDEIS at week 24 after thalidomide treatment was significantly lower than pretreatment CDEIS in 32 patients with repeated ileocolonoscopy; (b) CDEIS in the 23 patients who had had two prior ileocolonoscopies before thalidomide initiation. CDEIS was elevated and not significantly changed before thalidomide initiation, but was significantly decreased after thalidomide treatment.



**Figure 5.** A representative photograph of mucosal healing (MH) induced by thalidomide in a 25-year-old woman patient with active Crohn’s disease. (a,b,c) Multiple colonic ulcers before thalidomide treatment; (d,e,f) MH after 6-month treatment with thalidomide.

25.6% of patients), followed by peripheral neuropathy (20.9%) (Table 3). Five patients reported severe adverse events (two patients with severe somnolence, one with severe somnolence and dermatitis, and two with severe peripheral neuropathy) requiring treatment suspension within 3 months (5/47, 10.6%). The symptoms in all the five patients with severe adverse events were relieved after treatment suspension. In the two patients (one with constipation, and the other one with somnolence) experiencing adverse events leading to thalidomide dose reduction, the

symptoms were relieved by reducing the daily dose from 50 mg to 25 mg, and 100 mg to 75 mg, respectively.

### Discussion

Refractory CD remains a clinical challenge despite recent advances in medical treatment including the advent of biologics. The landmark randomized, placebo-controlled trial of thalidomide in children and adolescents with refractory CD showed a significant clinical remission rate,<sup>15</sup>

**Table 3.** Adverse effects.

	<i>n</i> = 47
Patients with adverse events	27 (57.4%)
Event led to thalidomide dose reduction	2 (4.3%)
Event led to thalidomide discontinuation	5 (10.6%)
Overall adverse events	43
Constipation	11 (25.6%)
Neuropathy	9 (20.9%)
Somnolence	11 (25.6%)
Blurred vision	3 (7.0%)
Vertigo	2 (4.7%)
Elevated liver enzyme	2 (4.7%)
Dermatitis	2 (4.7%)
Strength deficit	1 (2.3%)
Tremors	1 (2.3%)
Menstrual disorder	1 (2.3%)

but did not report on MH. We report a prospective open-label trial evaluating the efficacy and tolerance of thalidomide in 47 adults with active CD who were dependent/resistant or intolerant to corticosteroids and/or immunomodulators/biologics. The results demonstrate this agent to possess efficacy in inducing clinical and endoscopic remission in this challenging group of patients. Moreover, all the six steroid-dependent patients were able to taper the dose and discontinue steroids during treatment with thalidomide, which may indicate the potential steroid-sparing effects of thalidomide.

Four open-label studies have previously investigated the efficacy of thalidomide in adults with CD with sample sizes varying from 9 patients to 22 patients and thalidomide doses ranging from 50 mg to 300 mg.<sup>13,22–24</sup> However, the follow-up period in these studies was only up to 12 weeks, by which time point the rate of clinical remission varied from 20% to 83%. In two longer-term retrospective studies with a median follow up of 12 months and 58 months, the clinical remission rate was 37.5% and 14%, respectively.<sup>12,25</sup> In a recent retrospective multicenter observational study of 72 adult patients with refractory CD who had received a low dose of thalidomide (50–100 mg)

with a median follow up of 17.4 months, the cumulative probability of clinical remission was 33% at 3 months, 47% at 6 months, and 51% at 9 months.<sup>26</sup> These later rates are generally in agreement, albeit somewhat lower than the rates observed in our study using a similar low dose of thalidomide (50–100 mg). Our somewhat higher clinical response rate may be due to active inflammation by CRP and/or colonoscopy documented in all patients prior to therapy initiation. Another possible reason for this slight difference may be related to our inclusion of patients with a CDAI score greater than 150 rather than 220. However, a rigorous criterion for clinical remission was imposed in our study requiring a CDAI score lower than 150 together with a CDAI score decline of 100 points or more from baseline, therefore supporting the validity of the described findings.

MH is increasingly being considered as the treatment goal and outcome measure in patients with CD. Evolving evidence indicates that an intensive care strategy aiming at suppressing intestinal inflammation and inducing endoscopic MH might improve the long-term outcome of CD with diminished rates of relapse, hospitalizations, and the need for surgery.<sup>19,21,27</sup> In the SONIC trial, MH occurred in 43.9% of the patients who had received combination therapy at 6 months.<sup>19</sup> However, little is known about the efficacy of thalidomide in inducing MH. Until now, only studies with limited sample size have explored the achievement of MH in refractory CD by thalidomide.<sup>7,14,17,18,28</sup> Thus, there is insufficient evidence to evaluate the rate of MH induced by thalidomide. Our results showed that the percentage of patients who had CDEIS complete endoscopic remission and MH at week 24 was 43.8% and 28.1%, respectively. These results provide novel support for a role for thalidomide in reducing intestinal inflammatory activity and restoring mucosal integrity in patients with refractory CD. Moreover, our study also demonstrated that inflammatory markers including CRP and ESR decreased significantly after the initiation of thalidomide. By week 4, thalidomide had induced a significant decrease in ESR, which was consistent with the landmark study of Lazzarini and colleagues.<sup>15</sup> CRP, a more accurate marker of inflammation, decreased significantly by week 12. The value of CRP as a noninvasive inflammatory marker for predicting the long-term outcome has been previously investigated with other therapeutic agents. For instance, early normalization of CRP

levels predicted sustained long-term response in patients receiving biologics treatment.<sup>29</sup> Whether CRP could predict the long-term outcome in refractory CD patients using thalidomide warrants further future studies.

Another novelty of the present study was a design allowing delineation of the optimal time frame for thalidomide to induce clinical remission. Indeed, the clinical remission rate was 14.9% and 23.4% at weeks 4 and 8, and increased to 46.8% and 53.2% at weeks 12 and 24, and CRP decline was similarly evident at week 12 and beyond. These observations may suggest that the onset of action of thalidomide is delayed, and may require 12 weeks to be optimally appreciated. In the absence of such temporal data, the previous seminal trial employed a primary outcome set at 8 weeks.<sup>15</sup> Future trials are needed to elucidate if adopting the presently defined time point of thalidomide induction effect will result in even better results compared with placebo. In the meantime, an important message for clinicians prescribing thalidomide is that induction success should probably best be assessed at week 12, before further management decisions are undertaken.

Adverse events have traditionally been a concern when using thalidomide in refractory CD. Our trial was congruent with previous studies in finding a relatively high incidence of adverse events occurring during thalidomide use. In the present study, the most common adverse events were constipation, somnolence, and peripheral neuropathy. However, the cumulative probability of thalidomide withdrawal due to severe adverse events was 10.6% at 3 months, which was lower than previous studies.<sup>15,25,26</sup> This might be attributed to the fact that a lower dose (50–100 mg/day) of thalidomide was used in our study compared with most<sup>15,25</sup> albeit not all studies.<sup>26</sup>

Our study had certain limitations. Firstly, it was a noncontrolled study so the exact benefit of thalidomide over placebo is impossible to determine. However, the availability of more rigorous end points for assessment, including endoscopy and CRP serial measurements, partly offset this caveat. Secondly, baseline colonoscopy was not uniformly performed immediately before thalidomide initiation, due to ethical considerations.

Arguably, some patients may not have had active mucosal inflammation at the time of thalidomide initiation. However, all patients had active disease at their prior pretreatment colonoscopies and the subgroup of patients who had the two prior colonoscopies available had active disease on both examinations, which decreased after thalidomide treatment. Coupled with the fact that virtually all patients had elevated CRP at baseline testifying to active inflammation at inclusion, we believe this limitation is unlikely to impact significantly the aforementioned observations supporting thalidomide-mediated MH in active CD. Nonetheless, further long-term prospective studies are pertinent to corroborate the role of thalidomide in inducing MH. Of note, low azathioprine dose (no more than 2 mg/kg) and short delay (4 months) to conclude thiopurine nonresponsiveness was defined in the inclusion criteria. The use of low dose (1.0–2.0 mg/kg) azathioprine has been reported to be as effective in Asian populations as the standard dose in Caucasians, and Asian patients are more susceptible to dose-dependent adverse events.<sup>30–32</sup> Thus, it is unlikely that this selection criterion limits the conclusions of this study in any significant manner.

In conclusion, in a prospective open-label study, low-dose thalidomide was effective and tolerated for inducing and maintaining clinical remission in adult patients with active CD. Moreover, MH could reasonably be achieved with thalidomide. This study also suggests the optimal time frame for thalidomide to induce clinical remission in active CD is probably 12 weeks.

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### Conflict of interest statement

The authors declare that there are no conflicts of interest.



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