Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease

C. Yang*, P. Singh*, H. Singh†, M.-L. Le* & W. El-Matary*

*Department of Pediatrics, Faculty of Health Sciences, College of Medicine, University of Manitoba, Winnipeg, MB, Canada.
†Department of Internal Medicine, Faculty of Health Sciences, College of Medicine, University of Manitoba, Winnipeg, MB, Canada.

Correspondence to:
Dr W. El-Matary, Section of Pediatric Gastroenterology, Department of Pediatrics, College of Medicine, University of Manitoba, Winnipeg, MB, Canada
E-mail welmatary@hsc.mb.ca

SUMMARY

Background
It has been reported that thalidomide may be effective in treating inflammatory bowel disease (IBD).

Aim
To review the evidence examining the efficacy and safety of thalidomide for inducing and maintaining remission in Crohn’s disease (CD) and ulcerative colitis (UC).

Methods
The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed (1950–August 2014), EMBASE (1984–August 2014), Scopus, and Web of knowledge were searched for randomised controlled trials (RCTs), observational studies and case series. The primary outcomes were induction of remission or response for active IBD or relapse rate for patients in remission and subsequently on thalidomide/analogues for at least 3 months.

Results
Twelve studies (2 RCTs and 10 case series) met the inclusion criteria for inducing remission and included 248 patients (10 with UC, 238 with CD). Only one RCT of paediatric CD achieved high quality scores (remission rate thalidomide: 46%, placebo: 12%; p=0.01). The crude pooled remission rate for thalidomide was 49% and 25% in luminal and perianal CD respectively. For UC, 50% achieved remission and 10% had partial response. One case series reported 21 patients (17 CD, four UC) who maintained remission for 6 months. Many adverse events were reported including sedation (32%) and peripheral neuropathy (20%).

Conclusions
One high quality RCT showed that thalidomide is effective for inducing remission in paediatric CD. The current evidence is insufficient to support using thalidomide to induce remission in UC or adult CD, or to maintain remission in IBD. Significant adverse events may occur, necessitating dis-continuation of thalidomide.
INTRODUCTION

Inflammatory bowel disease (IBD) is a group of disorders characterised by chronic inflammation of the gastrointestinal tract with intermittent clinical remissions and relapses.\(^1\) The two most common subtypes are Crohn’s disease (CD) and ulcerative colitis (UC).\(^1\) The aetiology of IBD is unknown; however, it is currently believed that environmental and/or microbial triggers may induce IBD among the genetically predisposed.\(^2–6\) The prevalence of IBD is increasing worldwide both in children and adults,\(^7\) with 2.6 million people in Europe and 1.2 million in North America estimated to be affected.\(^8–12\)

As there is no cure for IBD, the main goals of therapy are induction and maintenance of remission.\(^1,2\) Commonly used medications include corticosteroids that have shown to be effective in inducing remission, but not maintenance of remission in IBD.\(^13,14\) Corticosteroids induce remission in up to 80% of patients with CD.\(^15,16\) Other commonly used agents include immunomodulators such as azathioprine (AZA), mercaptopurine, and methotrexate and biological agents such as anti-tumour necrosis factor (anti-TNF) therapies including infliximab and adalimumab.\(^17\) Maintenance of remission is achieved in 51–71% of CD patients receiving AZA/mercaptopurine.\(^18\) Remission rates with anti-TNF therapies may reach up to 60%,\(^16,19,20\) Corticosteroids induce remission in up to 46% of UC patients.\(^13\) A total of 56% of UC patients have been reported to be disease free after 1-year treatment with AZA.\(^21\) Infliximab induces remission in up to 57% of patients with UC.\(^22\)

Despite the array of drugs that are currently available, achieving and maintaining remission remains a challenge for many IBD patients. Hence, there remains a great need for new therapies that are both effective and safe.

Cytokines play a crucial role in controlling intestinal inflammation and pathogenesis of IBD.\(^23,24\) Uncontrolled activation of the mucosal immune system and subsequent production of cytokines promote chronic inflammation of the gastrointestinal tract.\(^23\) With the success of infliximab, an antibody specific for TNF, it became clear that TNF is a key target of therapy for IBD.\(^25–28\) Production of TNF by macrophages, adipocytes, fibroblasts and T cells is significantly elevated in patients with IBD.\(^23\) TNF exerts many pro-inflammatory effects that are involved in mucosal inflammation in IBD.\(^23,29\) TNF promotes angiogenesis, increases T-helper cell 1 (Th1) cytokine production, induces death of intestinal epithelial cells (IECs), and drives T-cell resistance to apoptosis.\(^30–33\) Therefore, therapies that target TNF can simultaneously suppress many pro-inflammatory pathways implicated in IBD.\(^23\) Studies in animal models and CD patients have shown that elevated mucosal TNF, excessive Th1 response and upregulation of angiogenesis may all be involved in the pathogenesis of CD.\(^31,34–38\) Increased production of interleukin-12 (IL-12) and interferon-\(\gamma\) (IFN-\(\gamma\)) were also seen in intestinal mucosa of CD patients, consistent with a Th1 type response.\(^39–43\) Both TNF and IFN-\(\gamma\) have been shown to cause tight junction disruption and apoptosis of IECs, contributing to the epithelial barrier dysfunction associated with IBD.\(^44–46\)

Originally used as an antiemetic agent in pregnancy, thalidomide was withdrawn from the market due to its teratogenic effects.\(^47\) It has been re-introduced to treat a number of conditions, including erythema nodosum leprosum, discoid lupus erythematosus, aphthous stomatitis, Behçet’s syndrome, graft-versus-host disease and IBD.\(^48\) However, it is limited by many side effects including peripheral neuropathy, sedation, constipation, mood disturbances, skin rash, pedal oedema, neutropenia and deep vein thrombosis.\(^2,49\)

Thalidomide has many immunomodulatory properties (Figure 1). It is an inhibitor of TNF, IFN-\(\gamma\) and IL-12.\(^50–53\) It also stimulates production of IL-4 and IL-5.\(^52\) This shifts the pattern of lymphocyte cytokine from a Th1 (IFN-\(\gamma\), IL-12) to Th2 (IL-4, IL-5) type.\(^52–54\) Thalidomide also interferes with integrin expression, decreases circulating helper T cells and inhibits angiogenesis.\(^49,55–57\)

In their attempt to understand the mechanism of action of thalidomide as a treatment of multiple myeloma, Segarra et al.\(^58\) demonstrated that thalidomide, on therapeutic doses, disrupted integrin mediated signalling pathway, resulting in less production of several mediators that promote invasiveness of malignant B lymphoid cell lines.

Thalidomide may block NF-\(\kappa\)B activation through a mechanism that involves the inhibition of activity of the IkB kinase. Thalidomide may also be able to block the cytokine-induced expression of NF-\(\kappa\)B-regulated genes such as those encoding interleukin-8, TRAF1 and c-IAP2. Consequently, the therapeutic potential for thalidomide may be based on its ability to block NF-\(\kappa\)B activation through suppression of IkB kinase activity.\(^59\) Moreover, thalidomide may block cell adhesion molecule expression in human intestinal microvascular endothelial cells (HI-MEC), the relevant endothelial cell population in inflammatory bowel disease.\(^60\) Rafii et al.,\(^60\) investigated the effect of thalidomide on primary cultures of human HI-MEC. Expression of cell adhesion molecules (E-selectin, intercellular adhesion molecule-1 (ICAM1), vascular cell neovascularisation and Th1 type cytokine production (IFN-\(\gamma\), IL-12) was significantly reduced by thalidomide at therapeutic doses.

C. Yang et al.
adhesion molecule-1 (VCAM1)) was examined using radioimmunoassay. Although thalidomide did not alter the expression of E-selectin, ICAM-1 or VCAM-1 on resting HIMEC, it was associated with inhibition of the upregulation of all three molecules. Thalidomide blocked vascular endothelial growth factor (VEGF) with subsequent decrease in HIMEC growth and activation. Enhanced expression of VEGF may play an important pathological mechanism in chronic inflammation in IBD.

The effect of thalidomide on leucocyte-endothelial interaction in rats with experimental colitis was investigated by Lienenlüke and colleagues. The investigators demonstrated a reduction in VCAM-1 expression with subsequent decrease in leucocyte adhesion to endothelial cells.

The aim of this study was to systematically review the evidence examining the efficacy and safety of thalidomide/thalidomide analogue in either induction of remission/response or maintaining remission in patients with IBD.

METHODS
The current systematic review was registered in PROSPERO. Registration number: CRD42014010361.

Search strategy and study selection
A literature search was performed in the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane IBD/FBD Specialised Trial Register, MEDLINE (1966–August 2014), PubMed (1950–August 2014), EMBASE (1984–August 2014), SCOPUS, Web of Knowledge. An example of search terms used is provided in Table S1.

Inclusion criteria
(i) Randomised controlled trials (RCT), cohort studies, case series (involving five or more patients) examining the efficacy of thalidomide/thalidomide analogue in either induction of remission/response or maintaining remission in
• Luminal CD
• Perianal CD
• UC
• IBD
(ii) Participants: Patients with IBD of all age groups

Figure 1 | Thalidomide proposed mechanism of action in inflammatory bowel disease. TNF- tumour necrosis factor; TH - T helper; IL - interleukin; IFN-γ - interferon-γ; NF - nuclear factor; HIMEC - human intestinal microvascular endothelial cells.
C. Yang et al.

(iii) Intervention: Thalidomide and thalidomide analogues (any route, dose, duration)
(iv) Human trials
(v) Full papers
(vi) Published in English

Exclusion criteria
(i) Individual case reports (<5 CD patients)
(ii) Review articles
(iii) Abstracts
(iv) Studies not published in English

PICOS criteria
P (Participants: Patients of all ages with IBD including Crohn’s [both luminal and perianal] and Ulcerative colitis). I (Interventions: Thalidomide and thalidomide analogues [any route]). C (Comparisons: Any comparator including placebo or no placebo). O (Outcome: Induction or maintenance of remission). S (Study design: Case series [five or more patients], cohort studies and RCTs).

Data extraction and quality assessment
Articles retrieved from the literature search were independently screened based on the title and abstract by two authors (PS and CY) and categorised as either ‘include’, ‘exclude’ or ‘unsure’. The full-text articles of all ‘include’ and ‘unsure’ categories were reviewed independently by two authors (PS and CY) and eventually categorised as ‘included’ or ‘excluded’. Any disagreements were resolved by mutual discussion or by consulting with the senior author (WE). Data extraction was then carried out independently by two authors (PS and CY). Data extracted from each article included: study methods (study design, method of randomization if RCT, withdrawals and loss to follow-up), study participants (sample size, age and gender), method used for assessing disease activity, intervention type, dose, route, compliance, comparator if available, co-medications, route, duration of treatment, adverse events and outcomes (types of outcome measures, timing of measurements, reported outcomes). For quality assessment, the Cochrane Risk of Bias tool, the RCT by Lazzerini et al., was assessed to have a low risk of bias, whereas the RCT by Mansfield et al., had an unclear risk of bias.

RCT: Induction of remission in unspecified Crohn’s disease by thalidomide
There was only one RCT by Lazzerini et al., that studied the effect of thalidomide in IBD (Table 1). Specifically, it examined the use of thalidomide for induction of remission in paediatric CD. However, they did not differentiate between luminal and perianal CD. Remission was defined as PCDAI <10. Results showed significant differences in remission rate between thalidomide group and placebo (46% vs. 12%; P = 0.01). In the open-label extension of their study, 21 non responders
to placebo began receiving thalidomide and 11 of these patients (52% vs. 12%; \( P = 0.01 \)) subsequently achieved remission.\textsuperscript{71}

RCT: Induction of remission in Crohn’s disease by lenalidomide

One RCT by Mansfield et al.,\textsuperscript{72} examined lenalidomide for the induction of remission in adult CD (Table 2). Remission and response were defined using CDAI. Twenty-three patients received lenalidomide at 25 mg per day; 33 patients received 5 mg per day and 28 patients were given placebo. Rates of remission were 9% \( (P = 0.15) \), 30% \( (P = 1.00) \) and 25% for the three groups respectively. Therefore, lenalidomide was not effective for induction of remission in adult CD when compared to placebo. A total of 27 patients (48%) on Lenalidomide and 13 patients (46%) on placebo withdrew from the study due to adverse events.
There were no RCTs or comparative cohort studies specifically examining the use of thalidomide in luminal CD, but six case series were found to fulfil inclusion criteria (Table 3).67–69, 74–76 Two of these studies used CD activity index (CDAI) alone as the primary measure for determining remission.67, 75 The remaining studies used either: CDAI and clinical improvement, CDAI and steroid withdrawal, Harvey-Bradshaw Index (HBI) or endoscopic evaluation for this purpose.

### Table 1 | RCTs assessing efficacy of thalidomide for induction of remission in CD

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals*, n (%)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzerini et al. 201371 – RCT</td>
<td>28</td>
<td>50–150 mg/day</td>
<td>PO</td>
<td>8 weeks</td>
<td>Remission: PCDAI ≤10.</td>
<td>13 (46)</td>
<td>5 (18)</td>
<td>10 (36)</td>
<td>0</td>
<td>In children and adolescents with refractory Crohn disease, thalidomide compared with placebo resulted in improved clinical remission at 8 weeks of treatment and long-term maintenance of remission in an open-label follow-up. These findings require replication to definitively determine clinical utility of this treatment.</td>
</tr>
<tr>
<td>Lazzerini et al. 201371 – open-label extension</td>
<td>21</td>
<td>50–150 mg/day</td>
<td>PO</td>
<td>8 weeks</td>
<td>Remission: PCDAI ≤10.</td>
<td>11 (52%)</td>
<td>4 (19)</td>
<td>6 (29%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; PO, per oral; PCDAI, paediatric Crohn’s disease activity index.

* Withdrawals here refer to number of patients who did not have their responses evaluated due to early suspension of therapy, and does not include patients who discontinued thalidomide after achieving remission or response. Same applies for subsequent tables. Refer to Safety Profile of Thalidomide and Lenalidomide for information regarding total number of discontinuations.

### Table 2 | RCTs assessing efficacy of lenalidomide for induction of remission in CD

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals, n (%)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mansfield et al. 200772</td>
<td>23</td>
<td>25 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: CDAI ≤150 and reduction in CDAI by ≥100 point.</td>
<td>2 (9)</td>
<td>4 (17)</td>
<td>2 (9)</td>
<td>15 (65)</td>
<td>Lenalidomide, an oral agent with anti-tumour necrosis factor-α properties, was not effective in active Crohn’s disease in contrast to reports of benefit from thalidomide. The reasons for this lack of efficacy are speculative, other physiological activities may offset its action on inflammatory cytokines, or its anti-tumour necrosis factor-α action without apoptosis may be insufficient for activity in Crohn’s disease.</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>5 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: Reduction in CDAI by ≥70 point.</td>
<td>10 (30)</td>
<td>6 (18)</td>
<td>5 (15)</td>
<td>12 (36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Placebo PO</td>
<td>12 weeks</td>
<td>7 (25)</td>
<td>4 (14)</td>
<td>4 (14)</td>
<td>13 (46)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total no. of patients receiving lenalidomide = 56 12 10 7 27

Total % 21.4 17.9 12.5 48.2

CD, Crohn’s disease; CDAI, Crohn’s disease activity index; PO, per oral.
A total of 56 patients with luminal CD received thalidomide for inducing remission. Twenty-seven patients (48.2%) achieved remission as defined in the respective studies. Twelve patients (21.4%) had a partial response to thalidomide. Nine patients (16.1%) had no response. Eight patients (14.3%) withdrew from the studies due to adverse events from thalidomide.

### Case series: Induction of remission in perianal Crohn’s disease

Similar to luminal CD, there were no RCTs or comparative cohort studies that specifically examined induction of remission in perianal CD by thalidomide. There were a total of four case series that examined the use of thalidomide for perianal disease (Table 4). Remission was defined as complete closure of fistulas in three of these studies. One study defined remission as a score of greater than 2+ in all clinical parameters of treatment goal interval score (GIS).

Based on these studies, 40 perianal CD patients received thalidomide for induction of remission. Ten of these patients (25%) achieved remission as defined by each study. Eleven patients (27.5%) had a partial response to thalidomide and 8 (20%) withdrew from the studies due to adverse events. The criteria for remission and response varied among studies, with one study using a GIS score of greater than 2+ in all treatment parameters to define remission.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrenpreis et al. 1999</td>
<td>9</td>
<td>50–300 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: CDAI &lt;150. Response: Reduction in CDAI by &gt;150.</td>
<td>3 (33)</td>
<td>2 (22)</td>
<td>0</td>
<td>4 (44)</td>
</tr>
<tr>
<td>Facchini et al. 2001</td>
<td>5</td>
<td>1.5–2 mg/kg/day</td>
<td>PO</td>
<td>Variable (19–24 months)</td>
<td>Remission: Confirmed with endoscopy. Response: Assessed by using PCDAI, modified Harvey-Bradshaw scores and reduction in steroid therapy; exact criteria not defined.</td>
<td>4 (80)</td>
<td>0</td>
<td>0</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Felipez et al. 2012</td>
<td>12</td>
<td>0.7–3.0 mg/kg/day</td>
<td>PO</td>
<td>Mean 39.5 months (range 1–96 months)</td>
<td>Remission: Resolution of symptoms and a HBI &lt;5. Response: Reduction in symptoms at 2–6 months on thalidomide and a HBI of 5–7.</td>
<td>10 (83)</td>
<td>0</td>
<td>2 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Plamondon et al. 2007</td>
<td>12</td>
<td>50–200 mg/day</td>
<td>PO</td>
<td>Mean 14 weeks (range 2–236 weeks)</td>
<td>Remission: Symptom resolution and an ‘estimated’ CDAI &lt;150. Response: Symptom improvement and a reduction in ‘estimated’ CDAI by &gt;100.</td>
<td>5 (42)</td>
<td>4 (33)</td>
<td>2 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Sabate et al. 2002</td>
<td>6</td>
<td>100 mg/day</td>
<td>PO</td>
<td>Variable</td>
<td>Remission: CDAI &lt;150. Response: Reduction in CDAI by &gt;70.</td>
<td>3 (50)</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Vasilisioskas et al. 1999</td>
<td>12</td>
<td>50–100 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: Reduction in CDAI by ≥100, CDAI &lt;150 and complete withdrawal of steroids. Response: Reduction in CDAI by ≥100 and reduction in steroid dosage by ≥50%.</td>
<td>2 (17)</td>
<td>5 (42)</td>
<td>3 (25)</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Total no. of patients = 56

<table>
<thead>
<tr>
<th>Total</th>
<th>27</th>
<th>12</th>
<th>9</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total %</td>
<td>48.2</td>
<td>21.4</td>
<td>16.1</td>
<td>14.3</td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; CDAI, Crohn’s disease activity index; PCDAI, paediatric Crohn’s disease activity index; HBI, Harvey-Bradshaw Index; PO, per oral.
response to thalidomide and five patients (12.5%) had no response. The remaining 14 patients (35%) withdrew from the study due to adverse events. This included one study where all eight patients involved withdrew before the completion of the study due to adverse effects from prolonged exposure to thalidomide.  

**Case series: Induction of remission in unspecified Crohn’s disease**

Three case series examining thalidomide use in CD did not specify whether patients had perianal or luminal CD, or did not stratify the results by disease location (Table 5). One of these studies defined remission as paediatric CD activity index (PCDAI) <7.5. Another study defined remission using CDAI. Finally, one of the three studies used a combination of CDAI and PCDAI depending on the age of the patient. The criteria used to define partial response were not clear in the three case series.

Based on the three studies that met the inclusion criteria, a total of 34 patients received thalidomide. Twenty-eight patients (82.3%) achieved remission. Two

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrenpreis et al. 1999</td>
<td>12</td>
<td>50–300 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: Scores of ≥2+ in all clinical parameters of treatment goal interval score (GIS); if not receiving steroids at start, need 2 scores of ≥2+ in all clinical parameters. Response: 2 scores of ≥1+ in two of the three clinical parameters of the GIS.</td>
<td>6 (50)</td>
<td>2 (17)</td>
<td>0</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Ng et al. 2009</td>
<td>8</td>
<td>50–300 mg/day</td>
<td>PO</td>
<td>Variable (2–52 weeks)</td>
<td>Remission: Cessation of fistula drainage on history, absence of perianal drainage to gentle finger compression of external opening, and absence of spontaneous drainage between two consecutive visits. Response: Closure of ≥50% of externally draining fistulas or marked reduction in drainage of all fistula together with less pain and induration as reported by the patient for at least two consecutive visits.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Plamondon et al. 2007</td>
<td>14</td>
<td>50–200 mg/day</td>
<td>PO</td>
<td>Median 14 weeks (range 2–236 weeks)</td>
<td>Remission: Fistulizing Disease: Complete fistula closure (absence of active drainage from all fistula based on history and clinical exam). Perianal ulcerating disease: Complete ulcer healing. Response: Fistulizing Disease: Improvement by ≥50% in the number of draining fistulas. Perianal ulcerating disease: Global improvement as assessed by attending doctor and reduction in discomfort.</td>
<td>3 (21)</td>
<td>8 (57)</td>
<td>3 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Vasiliauskas et al. 1999</td>
<td>6</td>
<td>50–100 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: Complete fistula closure. Response: Decreased drainage, induration, pain and/or reduction in pain medication requirement.</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

| Total no. of patients = 40 | | | | | | 10 | 11 | 5 | 14 |
| Total % | | | | | | 25.0 | 27.5 | 12.5 | 35.0 |

CD, Crohn’s disease; PO, per oral.
patients (5.9%) experienced partial response and zero patients (0%) had no response. Four patients (11.8%) withdrew prior to the completion of the study.

### Case series: Induction of remission in ulcerative colitis

There were only two case series that examined the use of thalidomide for induction of remission in UC (Table 6).  

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauditz et al. 2002</td>
<td>1</td>
<td>300 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: CDAI &lt;150. Response: Not defined.</td>
<td>4 (44)</td>
<td>2 (22)</td>
<td>0</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Lazzerini et al. 2007</td>
<td>9</td>
<td>1.5–2.5 mg/kg/day</td>
<td>PO</td>
<td>Variable</td>
<td>Remission: Complete resolution of clinical symptoms (all clinical UCSS subscores equal to 0) with a proctosigmoidoscopy score of 0 or 1. Response: Not defined.</td>
<td>18 (95)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Zheng et al. 2011</td>
<td>6</td>
<td>0.5–3.0 mg/kg/day</td>
<td>PO</td>
<td>Mean 10 months (range 7–14 months)</td>
<td>Remission: PCDAI &lt;7.5. Response: Not defined.</td>
<td>6 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total no. of patients = 10
Total % 50.0 10.0 10.0 30.0

UC, ulcerative colitis; CDAI, Crohn’s disease activity index; PCDAI, paediatric Crohn’s disease activity index; PO, per oral.

---

### Case series: Maintenance of remission in IBD

Only one case series examined the efficacy of thalidomide for maintenance of remission in IBD (both CD and UC) (Table 7). Remission and relapse were defined by PCDAI and CDAI depending on the age of the patient. A total of 21 patients (17 CD, 4 UC) achieved remission with thalidomide and continued the drug for maintenance of remission. All 21 patients were in remission at 6 month follow-up. Twenty patients (95%) achieved remission. One patient achieved partial response and one patient did not achieve any response. Three patients (30%) withdrew from the studies due to adverse events.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of Therapy</th>
<th>Evaluation of response</th>
<th>Remission, n (%)</th>
<th>Partial response, n (%)</th>
<th>No response, n (%)</th>
<th>Withdrawals, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauditz et al. 2002</td>
<td>9</td>
<td>300 mg/day</td>
<td>PO</td>
<td>12 weeks</td>
<td>Remission: CDAI &lt;150. Response: Not defined.</td>
<td>4 (44)</td>
<td>2 (22)</td>
<td>0</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Lazzerini et al. 2007</td>
<td>19</td>
<td>1.5–2.5 mg/kg/day</td>
<td>PO</td>
<td>Variable</td>
<td>Remission: If &lt;18 years old: PCDAI &lt;7.5; if &gt;18 years old: CDAI &lt;150, with decrease of at least 70 points from baseline. Response: Not defined.</td>
<td>18 (95)</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Zheng et al. 2011</td>
<td>6</td>
<td>0.5–3.0 mg/kg/day</td>
<td>PO</td>
<td>Mean 10 months (range 7–14 months)</td>
<td>Remission: PCDAI &lt;7.5. Response: Not defined.</td>
<td>6 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total no. of patients on thalidomide = 34
Total % 82.4 5.9 0 11.8

CD, Crohn’s disease; CDAI, Crohn’s disease activity index; PCDAI, paediatric Crohn’s disease activity index; PO, per oral.
completed twelve-month follow-up and all were in remission. By 24 months, 15 patients (71%) were still taking thalidomide and were in remission. The others had to discontinue because of neuropathy.

Safety profile of thalidomide and lenalidomide

Many adverse events with thalidomide use have been reported in the 12 included studies (Table 8). A total of 192 patients on thalidomide and 56 patients on lenalidomide were included in the analysis of safety profile. The most commonly reported adverse events were sedation (32.3%), peripheral neuropathy (19.8%) and dermatitis (12%). Peripheral neuropathy was the most common reason for discontinuation with thalidomide therapy, with 14.6% of all patients having to discontinue the drug due to neuropathy. In total, 29% of all patients had to discontinue thalidomide therapy at some point due to adverse events. Seven of the case series reported that peripheral neuropathy was reversible by discontinuation of thalidomide in the majority of patients. The other case series did not comment on reversibility of adverse effects. However, Lazzerini et al.,71 reported only half of patients recovered from peripheral neuropathy following dose tapering.

In the only study that examined lenalidomide, leukopenia, rash, worsening IBD and abdominal pain were the main adverse events associated with its use (Table 9).72 Worsening IBD and abdominal pain were the most common reason for discontinuation of lenalidomide. In total, 32% of all patients discontinued lenalidomide therapy due to adverse events.

**DISCUSSION**

Inflammatory bowel disease is a major cause of morbidity. Many agents have been examined and have shown success in inducing or maintaining remission, including corticosteroids, immunomodulators (AZA, mercaptopurine, methotrexate) and biological agents such as anti-TNF therapies.

Based on one high quality RCT, thalidomide may be an effective therapeutic agent for the induction of remission in paediatric CD. However, there is no good evidence to support its efficacy in the induction of remission in adult CD, induction of remission in UC or maintenance of remission in IBD. There is no evidence of lenalidomide’s efficacy in IBD.

There were many adverse effects associated with thalidomide. The most common adverse effect was sedation, which was reported in 32.3% of all patients, followed by peripheral neuropathy, which was reported in 19.8% of patients. Peripheral neuropathy was the most common cause of discontinuation. A total of 14.6% of patients discontinued thalidomide due to peripheral neuropathy, and 5.7% of patients discontinued due to sedation. Thalidomide-induced peripheral neuropathy (TiPN) is generally reversible with dose reduction or cessation of therapy, though there have been cases of irreversible injury after therapy is discontinued.78, 79 Several mechanisms of TiPN has been proposed, including capillary damage, secondary anoxemia in nerve fibres and acceleration of neuronal cell death secondary to downregulation of TNF-α.78, 80 Patients on thalidomide should be closely monitored for symptoms and signs of peripheral neuropathy.

The strength of the available evidence is limited by the poor quality of many of the studies. Results from the two RCTs were not combined in meta-analyses because they examined different medications (thalidomide vs. lenalidomide) and included patients in different age groups (paediatric vs. adult).

Historically, remission rates achieved by placebo for patients with CD have been reported to be about 18%.81

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Rx route</th>
<th>Duration of therapy</th>
<th>Duration of Follow-up</th>
<th>Evaluation of response</th>
<th>Relapse rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lazzerini et al. 2007</td>
<td>21 (17 CD, 4 UC)</td>
<td>0.5–1.5 mg/kg/day</td>
<td>PO</td>
<td>Variable</td>
<td>Median 32 months</td>
<td>Remission: If &lt;18 years old: PCDAI &lt;7.5; if &gt;18 years old: CDAI &lt;150, with decrease of at least 70 points from baseline. Relapse: PCDAI &gt;15 or CDAI &gt;200.</td>
<td>6 months: 0/21 pts 12 months: 0/20 pts 18 months: 0/18 pts 24 months: 0/15 pts</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; CD, Crohn’s disease; UC, ulcerative colitis; CDAI, Crohn’s disease activity index; PCDAI, paediatric Crohn’s disease activity index; PO, per oral.
One should take into account the placebo effect of therapy for CD patients when interpreting remission rates reported by case series that lack controls. Overall, the majority of studies conducted thus far on the use thalidomide and thalidomide analogues in IBD has been case series with small sample size and were found to be of poor quality. There were no case–control or comparative cohort studies and there are only two RCTs in this area. Only one RCT examined the use of thalidomide in paediatric CD, and another RCT on the use of lenalidomide in adult CD. Lazzerini et al. demonstrated efficacy of thalidomide over placebo for the induction of remission in paediatric CD (46% vs. 12%; \( P = 0.01 \)). The majority of children in the study had luminal disease and few had perianal disease. However, based on the information given, we could not extrapolate the rate of remission specific to the type of CD. There have been very limited studies examining the efficacy of thalidomide in UC and maintenance of remission in IBD.

To our knowledge, this is the most complete systematic review looking at the role of thalidomide and thalidomide analogues in IBD. This is also the first review that included studies on the efficacy of thalidomide in UC and stratified the efficacy for luminal and perianal CD.

### Table 8 | Adverse events with use of thalidomide

<table>
<thead>
<tr>
<th>Adverse events of thalidomide</th>
<th>No. of cases reported</th>
<th>% of total patients</th>
<th>% of total patients discontinued as a result of the adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>62</td>
<td>32.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>38</td>
<td>19.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>23</td>
<td>12.0</td>
<td>0</td>
</tr>
<tr>
<td>EMG alterations with no neuropathy</td>
<td>16</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>5.2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>3.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Worsening IBD</td>
<td>5</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>5</td>
<td>2.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>4</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Vision changes</td>
<td>3</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Oedema</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Strength deficit</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Scotoma</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Hemeralopia</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Table 9 | Adverse events with use of lenalidomide

<table>
<thead>
<tr>
<th>Adverse events of lenalidomide</th>
<th>No. of cases reported</th>
<th>% of total patients</th>
<th>% of total patients discontinued as a result of the adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>11</td>
<td>19.6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
<td>12.5</td>
<td>0</td>
</tr>
<tr>
<td>Worsening IBD</td>
<td>6</td>
<td>10.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6</td>
<td>10.7</td>
<td>10.7</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>5.4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>5.4</td>
<td>5.4</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>1.8</td>
<td>0</td>
</tr>
</tbody>
</table>
Although there have been systematic reviews in the past for CD, their primary focus was on RCTs and did not include other available evidence such as cohort studies or case series.²₂, ²₃

There were some limitations to our study. First, abstracts were excluded in our literature search, because they are not available in full text and often represent preliminary data. Several attempts were made to contact the authors, but we were unsuccessful in retrieving the full data of these studies. Second, several studies did not stratify between luminal and perianal CD. For example, Bauditz et al.,⁶⁶ Lazzerini et al.,⁷₀ and Lazzerini et al.,⁷₁ did not stratify patients into luminal and perianal CD. Consequently, we could not include their data in our stratified analysis for the induction of remission in luminal and perianal CD. These results were reported separately as unspecified CD. Another limitation was the wide variation in the definition of the outcome measures used in the studies. For instance, Ehrenpreis et al.,⁵⁷ defined remission as CDAI <150, Facchini et al.,⁶₈ based remission on endoscopy findings and Felipez et al.,⁶⁹ defined remission as symptom resolution and a Harvey-Bradshaw Index (HBI) <5. Furthermore, some studies reported results on disease outcomes that were not the main focus of the respective study. For example, the main focus of Vasiliauskas et al.,⁷₆ was to assess induction of remission in luminal CD, but they also reported results for perianal CD as well. Therefore, the results for perianal CD from this study should be considered of lower quality as the study was not initially designed for that purpose. Last, variable treatment regimens with regard to duration and dose were used in the different studies. This resulted in not only heterogeneity among different studies but also variability within the same study as well. For example, Facchini et al.,⁶₈ used thalidomide at a dose of 1.5–2.0 mg/kg/day for 19–24 months, compared to Felipez et al.,⁶⁹ who used a dose of 0.7–3.0 mg/kg/day for 1–96 months. Some studies reported dose as mg/kg/day while others only reported it as mg/day, making it difficult for comparison. Some studies, such as the one by Sabate et al.,⁷₅ did not report the duration of the treatment.

There was a limited number of studies for maintenance of remission. The maintenance of remission data from the study by Sabate et al.,⁷₅ had to be excluded because it was not clear how many patients with luminal or perianal disease were in remission prior to thalidomide treatment, and how many of those relapsed.

**CONCLUSIONS**

Despite the poor quality of the available evidence, this systematic review demonstrated that thalidomide may be an effective therapeutic agent for the induction of remission in paediatric CD, based on one RCT that compared thalidomide to placebo for induction of remission in children with active CD. Using a placebo as a sole treatment for active CD in children was unusual and initiated some discussions.⁸₄ The results of this study need to be reproduced in future studies before a solid conclusion can be established. Currently, there is not enough high quality evidence to support use of thalidomide or its analogue for the induction of remission in adult CD or patients of any age with UC. There is also a lack of evidence for the use of thalidomide or thalidomide analogue in maintenance of remission in CD and UC. Many adverse events may occur with the use of thalidomide or lenalidomide, some of which cause discontinuation of therapy. This highlights major safety concern on the use of these medications. For lenalidomide, there is probably sufficient evidence of no benefit in adult patients with CD and further trials in CD would be difficult to support. Further controlled trials with larger sample size are needed to verify the role of thalidomide in IBD.

**AUTHORSHIP**

**Guarantor of the article:** W El-Matary.

**Author contributions:** CY and PS performed screening of papers, data extraction, quality assessment, collected and analysed the data and wrote the manuscript. HS critical appraisal and edited the manuscript. ML performed the literature search. WE developed the study concept and protocol, leading role of coordinating the project, senior authorship to resolve disagreements on inclusion, exclusion and quality assessment of papers and critiquing and editing the manuscript.

All authors approved the final version of the article, including the authorship list.

**ACKNOWLEDGEMENTS**

**Declaration of personal interests:** Dr El-Matary’s has served as a member in the Pediatric Advisory Boards of both Janssen, Canada and Abbvie, Canada. Dr Singh has consulted to Medial Cancer Screening Ltd., Israel.

**Declaration of funding interests:** Dr El-Matary’s research programme is supported by a grant from the Manitoba Institute of Child Health and Winnipeg Children’s Hospital Foundation.
**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Example of search strategy: MEDLINE (OVID).

---

**REFERENCES**

29. Günther C, Martini E, Wittkopf N, et al. Caspase-8 regulates TNF-α-induced epithelial necroptosis and...
Systematic review: thalidomide in IBD


