Systematic Review and Meta-Analysis

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Thalidomide for inflammatory bowel disease

Systematic review

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Abstract

Background: Thalidomide is an immunomodulatory drug used in the experimental treatment of refractory Crohn disease and ulcerative colitis. We aimed to review the existing evidence on the efficacy and safety of thalidomide in the treatment of inflammatory bowel diseases.

Methods: CENTRAL, MEDLINE, LILACS, POPLINE, CINHAL, and Web of Science were searched in March 2016. Manual search included conference and reference lists. All types of studies, except single case reports, were included. Outcomes evaluated were: induction of remission; maintenance of remission; steroid reduction; effect on penetrating Crohn disease; endoscopic remission; adverse events.

Results: The research strategies retrieved 722 papers. Two randomized controlled trials and 29 uncontrolled studies for a total of 489 patients matched the inclusion criteria. Thalidomide induced a clinical response in 296/427 (69.3%) patients. Clinical remission was achieved in 220/427 (51.5%) cases. Maintenance of remission was reported in 128/160 (80.0%) patients at 6 months and in 96/133 (72.2%) at 12 months. Reduction in steroid dosage was reported in 109/152 (71.7%) patients. Fistulas improved in 49/81 (60.5%) cases and closed in 28/81 (34.6%). Endoscopic improvement was observed in 46/66 (69.7%) and complete mucosal healing in 35/66 (53.0%) patients. Cumulative incidence of total adverse events and of those leading to drug suspension was 75.6 and 19.7/1000 patient-months, respectively. Neurological disturbances accounted for 341/530 (64.3%) adverse events and were the most frequent cause of drug withdrawal.

Conclusion: Existing evidence suggests that thalidomide may be a valid treatment option for patients with inflammatory bowel diseases refractory to other first- and second-line treatments.

Abbreviations: AE = adverse effect, CD = Crohn disease, IBD = inflammatory bowel disease, IC = indeterminate colitis, RCT = randomized controlled trial, RR = risk ratio, TNF = tumor necrosis factor, UC = ulcerative colitis.

Keywords: Crohn disease, inflammatory bowel disease, systematic review, thalidomide, ulcerative colitis

1. Introduction

Thalidomide is a small molecule with immunomodulatory properties. It is currently approved for the treatment of erythema nodosum leprosum, an immunological complication of leprosy[1,2] and multiple myeloma. It has also been used in several other inflammatory diseases of the skin and of the mucosal membranes, such as Behcet disease, oropharingeal ulcers in AIDS, cutaneous lupus, and graft versus host disease.[3]

Two Cochrane reviews explored the efficacy and safety of thalidomide for the induction and maintenance of remission in Crohn disease (CD).[4,5] These reviews, which were published and last updated in 2009, included only studies with a randomized controlled trial (RCT) design, and did not identify at time of publication any paper matching these criteria. More recently another systematic review was published on the subject, but the number of studies included and the type of outcomes reported was limited.[6] In order to evaluate the most recent literature, and in order to explore and report a wide range of outcomes that may be important in clinical practice in guiding decision for treatment of patients with CD or ulcerative colitis (UC), we conducted the present systematic review.

1.1. Objectives

The objective of this review is to synthesize the existing evidence on the efficacy and safety of thalidomide in patients, both adults and in children, with either CD or UC.

2. Methods

2.1. Criteria for considering studies for this review

This review follows the PRISMA standards on reporting on systematic review (see Table, Supplemental Digital Content 1,

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http://links.lww.com/MD/B139—PRISMA Checklist, which illustrates PRISMA Checklist).[7] Approval of ethics committee was not required because the study consisted in reviewing the existent literature. The following were the inclusion criteria that we used: as study design, all study types, excluding single case reports, were considered; as participants, patients with inflammatory bowel disease (IBD), defined as CD, UC, or indeterminate colitis (IC), of any age; as intervention, thalidomide, any dosage; in case of controlled trials, either placebo or active treatment were accepted as a control intervention; as efficacy outcomes, induction of clinical remission, maintenance of clinical remission, clinical response, steroid reduction, effect on fistulas and perianal disease in patients with Crohn disease, endoscopic remission. As a safety outcome, we included in the review any adverse effects (AE), as defined by the study authors.

When studies allowed and when a considerable number of patients were described (>10 patients), the effects of thalidomide when given in association with biological therapies or other major immunosuppressive treatments were reported separately.

2.2. Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, LILACS, POPLINE, CINHAL, and Web of Science were searched in March 2016 (last search date, March 31st). The following search strategy was used for MEDLINE: ("Thalidomide"[Mesh] OR thalidomide) AND ("Inflammatory Bowel Diseases"[Mesh] OR "Crohn Disease" [Mesh] OR "Colitis, Ulcerative" [Mesh] OR Crohn OR colitis OR "inflammatory bowel"). For LILACS, and CINHAL, we used the combination of the following Keywords: "thalidomide AND Crohn's disease"; "thalidomide AND ulcerative colitis"; "thalidomide AND inflammatory bowel disease." For POPLINE and Web of Science the search strategy was: "(thalidomide AND [Crohn's disease OR ulcerative colitis OR inflammatory bowel disease])."

Manual searching included presentations from European Crohn's and Colitis Organisation and from the most recent European Society for Paediatric Gastroenterology Hepatology and Nutrition Congresses, plus reference lists from studies identified.

The above-described searches were performed to retrieve all relevant trials regardless of language, publication status, or study type.

2.3. Data collection and analysis

Two authors (ML and MB) independently evaluated studies for inclusion. The full text of all potentially relevant studies was assessed, except for 1 single study in Chinese that we could not translate. For studies existing only as conference abstract, the authors were contacted.

In cases of duplicate case series, the most recent and complete series was considered as the "primary study"; duplicates presenting additional information available in the primary report were considered as "secondary studies" and they were used, if appropriate, only as a complementary source of data. Similarly, if 2 very similar abstracts were published by the same author within a short time period (<36 months), and if no further information was available from the author, the most recent report was included in the review whereas the one published earlier was considered as a duplicate.

Data were extracted from studies using a predefined data extraction form. To avoid mistakes due to data manipulation, we first collected the data as they were reported and only subsequently we performed data transformations.

Pooled results on the efficacy outcomes were reported for each outcome as the percentage of patients with the outcome, calculated as the rate between the total absolute number of patients with the event, on the total absolute number of patients treated (by intention to treat).

In order to compare safety outcomes, we used the cumulative incidence rate of AE, calculated based on the total number of AE on the total follow-up of patients expressed in months. When mean follow-up time was reported, it was multiplied by the number of patients included in the case series. When only median follow-up time was reported and no other information was available from study authors, this was approximated to the mean follow-up, as this was considered to be the best possible approximation.

Risk of bias was rated for each study by 2 authors independently, using the Cochrane criteria[8] for RCTs. Uncontrolled studies were always rated as moderate or high risk of bias (never at low risk of bias) and were categorized as follows: moderate risk of bias, when the description of both patients, intervention, and outcomes of interest was complete and clear throughout the observation period; high risk of bias, when the description of patients, intervention, and outcomes was incomplete or unclear, or when follow-up was incomplete.

As data could not be pooled in forest plots, findings were reported in tables and text.

3. Results

The process of study selection is reported in Fig. 1. The search strategy retrieved 722 papers. Among these, we identified for inclusion 31 primary studies.[9–39] Five reports were considered duplicate studies[40–44] and used to complement information given in the primary reports.

3.1. Characteristics of included studies

Characteristics of primary studies are detailed in Table 1 (see Table, Supplemental Digital Content 2—Table 1, http://links.lww.com/MD/B139, which illustrates the characteristics of the studies included). Except for 2 prospective placebo-controlled randomized trials, all studies were uncontrolled before and after studies (case series). Risk of bias was ranked as low for the primary analysis of the 2 RCTs (8 weeks)[10,15] and moderate to high in all the other studies.

Characteristics of patients are reported in Table 2. Overall, 435/489 (89.0%) patients had CD, whereas only 50 (10.2%) presented with UC (risk ratio, RR 9.7, 95% $P < 0.001$). The total population included 135 (28.4%) children < 18 years of age (RR 0.5, $P < 0.001$). With regard to sex, 247/475 (50.5%) patients were males whereas 178/475 (36.4%) were females (RR 1.4 $P < 0.001$). Patients treated with thalidomide were characterized by being in moderate to severe activity, and by being refractory to standard or biological treatments.

Thalidomide was used at doses ranging from 50 to 400 mg/d in adults and 1.5 to 2.5 mg/kg/d in children.

All patients of 1 study[28] and selected patients in a second study[14] were treated concomitantly with thalidomide and infliximab or adalimumab, whereas in another case series,[20] thalidomide was administered together with cyclophosphamide;

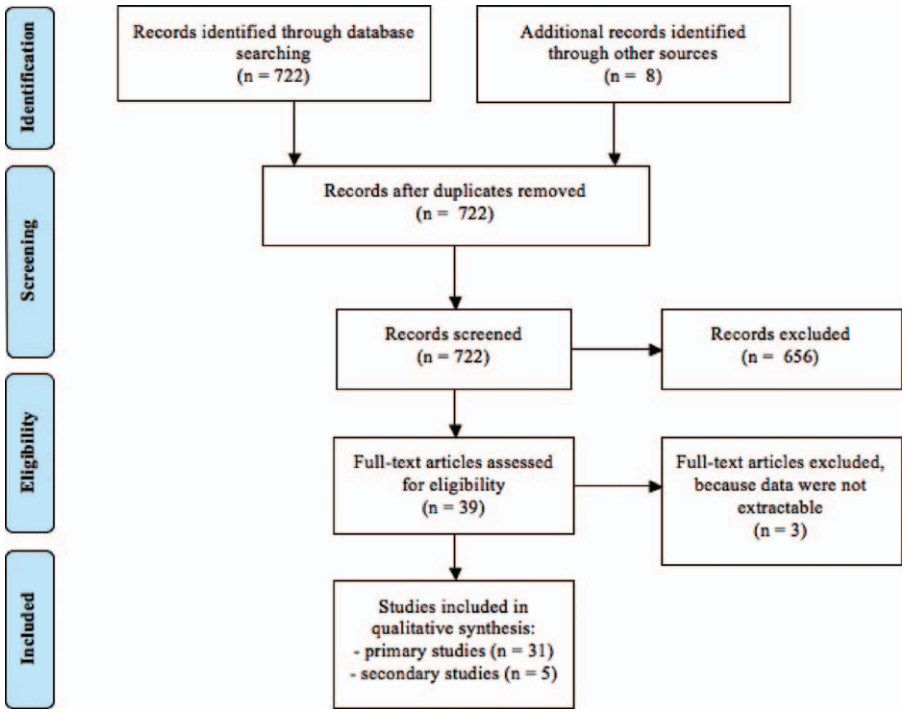

Figure 1. Flow diagram of study selection.

findings from these studies were reported separately from findings of studies where thalidomide was not associated with other immunosuppressive drugs.

Studies reported on outcomes of interest as follows: 25 studies (80.6%) reported on induction of clinical remission, generally in the short term (4–16 weeks); 27 (87.1%) reported on clinical response in the short term; 15 (48.4%) reported on the follow up after the induction period (6–24 months); 17 (54.8%) reported on steroid reduction; 8 (25.8%) evaluated endoscopic remission; 10 (32.2%) reported fistulas outcome; 7 (22.6) reported on thalidomide's efficacy after a biological drug failure; 29 (93.5%) reported on AE.

3.2. Effects of thalidomide

3.2.1. Efficacy in inducing clinical response or remission. Twenty-eight studies[9–11,13–19,21–25,27,29,31–39] overall reported on thalidomide's efficacy in inducing clinical response, and of these 25 reported on clinical remission (Table 3). Out of 427 patients included in the analysis, 296 (69.3%) had a clinical response (27 studies) and 220 (51.5%) achieved clinical remission (25 studies). When the effect of thalidomide was evaluated over time, generally this was done at 4, 8, or 12 weeks from the onset of the therapy, and the percentage of patients with a benefit increased at the 8th and 12th week compared to the 4th week.

Seven studies[12–15,19,23–25] enrolled patients with UC, but only 2 focused specifically on UC. In a pilot RCT on children with UC 18/23 (78.3%) children treated with thalidomide achieved clinical remission, compared to 2/11 (18.2%) in placebo.[15] In 4 other studies[13,23,24,29] outcomes of patients with UC were as follows: of the 16 patients identified, 9 (56.2%) responded to thalidomide, and 7 (43.7%) achieved remission.

Efficacy of thalidomide in inducing clinical remission or clinical response according to IBD type is reported in Fig. 2.

3.2.2. Efficacy in maintaining clinical remission in the long term. Overall, the effect of thalidomide in maintaining clinical remission in the long term was reported in 170 patients (15 studies).[10,13–15,17,22,27,33–36,38–41,43] The number of patients evaluated at each time-point is specified in Table 4. The remission rate over time was as follows: 128/1160 (80.0%) at 6 months (15 studies); 96/133 patients (72.2%) at 12 months (13 studies); and 61/112 patients (54.5%) at 24 months (11 studies).

Occurrence of relapses were described after thalidomide tapering or withdrawn in 4 studies, with subsequent recovery of clinical remission following the re-establishment of the full drug treatment.[9,13,34,38]

Twelve papers[10,11,13–15,17,19,24,27,31,36,39] stated the cause of drug discontinuation during the long-term period: 58/68 patients (85.3%) withdrawn thalidomide because of an AE, whereas 10/68 patients (14.7%) discontinued because of a loss of efficacy despite an initial clinical response.

3.2.3. Steroids reduction or suspension. Seventeen studies[10,11,13–17,21,22,24,29,31,33,34–36,42] reported reduction or complete suspension of steroids in 109/152 (71.7%) patients during treatment with thalidomide (Table 5). The time frame for steroid reduction/suspension was generally 12 to 16 weeks from thalidomide start.

3.3. Efficacy on fistulizing Crohn's disease

Ten studies (81 patients)[11,14,16,19,21,22,16,27,36,43] reported on the efficacy of thalidomide in patients with fistulizing disease (Table 6): 50 patients had perianal fistulas, 18 had enteric fistulas, 5 had both, whereas in 8 cases the localization of fistulas was not specified. Overall, a clinical improvement was noted in 49/81 (60.5%) patients, whereas a complete healing of the fistula was reported in 28/81 (34.6%) patients.

Table 1

Characteristics of included studies.

Primary studies					
Study	**Population**	**Intervention**	**Outcomes**	**Duration follow-up**	**Quality**
Simon et al[9]	Number: 72	Thal dose: 50–100 mg/d	Remission (HBI < 4 without STE or infliximab; perianal examination and anal score < 1)	Median 17.4 months	Multicentric, retrospective observational open label
	Site: France		Safety	(range 0.9–86.9 mo)	
	Age: median 31 y	Concomitant interventions:			
	Sex: 24 males, 48 females	STE, AZA, 6MP, MTX, infliximab			
	Characteristics: luminal or perianal CD (disease duration median 7.2 y) refractory to standard medical therapy				
Lazzerini et al[10]	Number: 49	Thal dose: 2 mg/kg/d (50–150 mg/d)	Remission (PCDAI < 10 and drop >75%)	Mean 122±71.2 weeks	Multicentric, randomized, prospective, double blind,
	Site: Italy		Safety	(range 10–260 wk)	
	Age: <18 y	Concomitant interventions:	Steroid reduction		
	Sex: 28 males, 21 females	Steroids			
	Characteristics: luminal or fistulizing CD (mean disease duration 3.5 y) refractory to standard or anti TNF medical therapy				
Gerich et al[11]	Number: 37	Thal dose : 50–200 mg/d	Response: improvement of 1 or more of the following after 7 days: bowel movement frequency, fistula output, rectal bleeding, abdominal pain, extraintestinal manifestations, overall well being.	NS—long-term follow up with telephone interview	Single center, retrospective, open label
	Site: USA		Remission: all of the following within 1 y: < 3 stools/d, no bleeding, no abdominal pain, no EIM, increased well being.		
	Age: 38–60 y	Concomitant intervention: steroids, thiopurines, MTX	Steroid reduction		
	Sex: 28 males, 9 females		Safety		
	Characteristics: luminal or fistulizing CD (median duration 17 y) refractory to standard or biological medical therapy				
Luo et al[12]	Number: 35	Thal dose: mean 109.29±30.37 mg/d	Safety	Mean 18.8±12.4 months	Single center, retrospective, open label (abstract)
	Site: China				
	Age: NS	Concomitant intervention: NS			
	Sex: NS				
	Characteristics: 31 CD, 2 UC, 2 Behcet's disease				
Lazzerini et al[13]	Number: 28	Thal dose: 1.5–2 mg/kg/d	Remission (PCDAI <7.5 or CDAI <150 and drop CDAI <70 for CD; UCSS=0 for UC)	Mean 36 months	Single center retrospective observational, open label
	Site: Italy		Safety	(median 32 months, IQR 10–78 months)	
	Age: 2–20 y	Concomitant interventions:	Steroid reduction		
	Sex: 18 males, 10 females	STE			

Primary studies

Study	Population	Intervention	Outcomes	Duration follow-up	Quality
	Characteristics: IBD (19 CD, 9 UC), (disease duration 4–12 y) refractory to standard medical therapy				
Plamondon et al[14]	Number: 25	Thal dose: 50–300 mg/d	Response (drop CDAI 100 or improving 50% of draining fistulas)	Mean 22 months	Single center, retrospective observational, open label
	Site: UK		Remission (CDAI < 150 or fistula closure)	(range 1–60 mo)	
	Age: 19–57 y	Concomitant interventions:	Safety		
	Sex: 11 males, 14 females	STE	Steroid reduction		
	Characteristics: luminal or fistulizing CD, disease duration 1–27 y, refractory to standard medical therapy				
Lazzerini et al[15]	Number: 23	Thal dose: 50–150 mg/d	Response (Rach drop 25% and 75%)	Mean 109.9±108.7 weeks	Multicentric, randomized, prospective, double blind
	Site: Italy		Remission (Rach < 4) (clinical)	(range 8–312 wk)	
	Age: < 18 y	Concomitant interventions:	Safety		
	Sex: 8 males, 15 females	STE	Steroid reduction		
	Characteristics: UC refractory to standard medical therapy (disease duration 1.8–5.8 y)				
Ehrenpreis et al[16]	Number: 22	Thal dose: 200–300 mg/d	Response (drop in CDAI or scores >1+ in 2 of 3 GIS parameters for fistulas)	12 wk	Single center, retrospective, open label
	Site: USA		Remission (CDAI <150 or scores >2+ in GIS)		
	Age: 23–61 y	Concomitant interventions:	Safety		
	Sex: 16 males, 6 females	STE, AZA, 6MP, MTX	Steroid reduction		
	Characteristics: luminal or fistulizing CD refractory to standard medical therapy (disease duration NS				
Leung et al[17]	Number: 17	Thal dose: 2 mg/kg/d	Response (clinical, PCDAI reduction)	12 months	Single center prospective open label
	Site: China		Steroid reduction		(abstract)
	Age: < 18 y	Concomitant interventions:	VEGF and CD31 reduction		
	Sex: 9 males, 8 females	STE			
	Characteristics: CD (disease duration NS), refractory to standard medical therapy				
Scribano et al[18]	Number: 16	Thal dose: 50–300 mg/d	Response (CDAI decline >100 from baseline)	Mean 112.7 weeks	Single center, retrospective, open label
	Site: Italy		Remission (CDAI<150)	(range 1–336 mo)	(abstract)
	Age: 19–72 y	Concomitant interventions:	Safety		
	Sex: 6 males, 10 females	Immunosuppressors in 4 patients			
	Characteristics: CD disease (duration 3–31 y) refractory to standard medical therapy or anti-TNF alpha drugs				
Sabate et al[19]	Number: 15	Thal dose: 50–300 mg/d	Maintenance of infliximab induced response (drop in CDAI >70 or >50% fistula closure) or remission (CDAI <150 or fistula closure)	Median 238 days	Single center, retrospective, open label
	Site: France		Safety	(range 10–458 d)	
	Age: 20–78 y	Concomitant interventions:			
	Sex: 5 males, 10 females	STE, AZA, MTX			

Primary studies

Study	Population	Intervention	Outcomes	Duration follow-up	Quality
	Characteristics: luminal or fistulizing CD (disease duration 3.1–35.5 years), manteinance of infliximab induced response in CD refractory to standard medical therapy				
Tang et al[20]	Number: 15 Site: China Age: NS Sex: NS Characteristics: CD (disease duration NS), steroid-dependent or steroid-resistant or refractory to infliximab	Thal dose: 25–75 mg/d Concomitant interventions: Cyclophosphamide 200 mg qod × 2 weeks followed by 400 mg/wk until reached a total dose of 6.0–8.0 g)	Remission (drop CDAI) Endoscopic Remission (drop SESCD) Safety	3–4 mo	Single center, prospective, open label, uncontrolled (abstract)
Vasiliauskas et al[21]	Number: 12 Site: USA Age: 19–61 y Sex: males Characteristics: CD, disease duration 1–30 y, refractory to standard medical therapy	Thal dose: 50–100 mg/d Concomitant interventions: STE, 5ASA, 6MP, antibiotics, CYA, MTX	Response (CDAI drop >100) Remission (CDAI <150 and CDAI drop >100) (clinical, serological) Quality of life Safety	12 wk	Single center, retrospective, open label
Felipez et al[22]	Number: 12 Site: USA Age: 8–19 y Sex: 9 males, 3 females Characteristics: CD (disease duration 24–240 mo), resistance to standard medical therapy and anti-TNF biologics	Thal dose: 0.7–3 mg/kg/d Concomitant interventions: STE	Response (drop HBI of 5–7 points or reduction of 50% of draining fistulas) Remission (HBI <5 of fistula closure) Safety Steroid reduction	Mean 39.5 months (range 1–96 mo)	Single center, retrospective, open label
Bariol et al[23]	Number: 11 Site: Australia Age: 20–77 y Sex: 9 males, 2 females Characteristics: IBD (4 UC, 6 CD, 1 IC) (disease duration > 6 months) refractory to standard medical therapy	Thal dose: 100–400 mg/d for 12 weeks, then 100 mg/day Concomitant intervention: STE, AZA, 5ASA	Response (clinical, CDAI drop endoscopic, histological) Safety TNFa levels	12 weeks of treatment 8–12 weeks after cessation of treatment	Single center, retrospective, open label
Bauditz et al[24]	Number: 10 Site: Germany Age: 22–61 y Sex: 8 males, 2 females	Thal dose: 300 mg/d Concomitant intervention: STE, AZA	Remission (CDAI <150 or CAI<5 Safety Steroid reduction Effects on cytokine production (drop in TNFa and IL12 levels)	12 wk	Single center, prospective, open label

Primary studies

Study	Population	Intervention	Outcomes	Duration follow-up	Quality
	Characteristics: IBD (1 UC, 9 CD), disease duration 2–13 y, refractory to standard medical therapy				
Macumber et al[25]	Number: 10 Site: Australia Age: 30–77 y Sex: 8 males, 2 females Characteristics: IBD (5 CD, 4 UC, 1 IC), (disease duration NS), refractory to standard medical therapy	Thal dose: 100–300 mg/d Concomitant intervention: NS	Response (clinical, serological, histological) Safety	3 mo	Single center, retrospective, open label (abstract)
Gupta et al[26]	Number: 9 Site: USA Age: 7–18 y Sex: 6 males, 3 females Characteristics: fistulizing and luminal CD, (disease duration NS), refractory to standard medical therapy	Thal dose: 25–100 mg/d Concomitant intervention: NS	Response/remission (clinical, laboratoristic) Safety Steroid reduction	Mean 14 months (range 1–24 mo)	Single center, retrospective, open label (abstract)
Ng et al[27]	Number: 8 Site: Australia Age: NS Sex: NS Characteristic: CD with perianal disease (disease duration NS), 4 refractory to anti-TNF alpha monotherapy	Thal dose: 50–150 mg/d Concomitant interventions: stable doses of 5-aminosalicylates, oral corticosteroids ($\leq$ 5 mg/ day), azathioprine, 6-Mercaptopurine, methotrexate, tacrolimus, antibiotics	Fistula response/remission (clinical, MRI, CDAI, PDAI, IBDQ)	Mean 3.1 $\pm$ 2.6 months (range 0.5–5.5 mo)	Single center prospective open label
Scribano et al[28]	Number: 8 Site: Italy Age: 19–72 y Sex: 5 males, 3 females Characteristics: CD disease (duration 5–31 y) refractory to standard medical therapy and anti-TNF alpha drugs	Thal dose: 50–200 mg/d Concomitant interventions: Adalimumab in 5, infliximab in 3, immunosuppressors in 2 patients	Response (HBI decline >3 point from baseline) Remission (HBI<5) Safety	Mean 32.5 weeks (range 1–100 mo)	Single center, retrospective, open label (abstract)
Kam et al[29]	Number: 7 Site: USA Age: > 18 y Sex: males Characteristics: moderately active UC resistant or intolerant to conventional medical therapy	Thal dose: 50–100 mg/d Concomitant intervention: NS	Response (drop mTLW $\geq$ 7 pts); response (mTLW $\leq$ 3) Steroid Safety	3–6 mo	Single center prospective open label
Srinivasan and Casson[30]	Number: 7	Thal dose: 1.2 mg/kg/d (mean)	Response (drop PCDAI)	3–6 mo	Single center prospective open label

Primary studies

Study	Population	Intervention	Outcomes	Duration follow-up	Quality
	Site: UK Age: 10.2 y (5.79–13.09) Sex: 6 males, 1 female Characteristics: refractory CD following infliximab	Concomitant intervention: NS	Safety		
Ahmed et al[31]	Number: 6 Site: UK Age: < 18 y Sex: NS Characteristics: OFG or CD, children, refractory to conventional medical therapy	Thal dose: 50–200 mg/d Concomitant intervention: NS	Response (NS) Steroid or other drug reduction Safety (neuropathy)	Median 1.39 years (0.24–2.38)	Single retrospective open label
Trebble et al[32]	Number: 6 Site: UK Age: 20–78 y Sex: 3 males, 3 females Characteristics: CD (disease duration NS) resistance to steroids,	Thal dose: 200 mg/d Concomitant intervention: NS	Response (drop CDAI, CRP, ESR, endoscopic improvement) Safety	8 wk	Single center prospective open label (abstract)
Zheng et al[33]	Number: 6 Site: China Age: 9–22 y Sex: 4 males, 2 females Characteristics: CD, (disease duration 2–10 y), refractory to standard medical therapy	Thal dose: 1.5–3 mg/kg/d Concomitant intervention: STE, 5ASA	Remission (PCDAI <7.5) (clinical, serological, endoscopic) Safety Steroid reduction	Mean 10.0±2.7 months (range 7–12 mo)	Single center case series
Hegarty et al[34]	Number: 5 Site: UK Age: 11–61 y Sex: 4 males, 1 female Characteristics: CD (disease duration 1–8 y), refractory to standard medical therapy	Thal dose: 50 mg/d or on alternate days Concomitant interventions: STE	Response (clinical) Safety Steroid reduction	Mean 6.0±1.6 months (range 5–8 mo)	Single center case series
Lazzerini et al[35]	Number: 5 Site: Italy Age: 7–15 y Sex: 3 males, 2 females Characteristic: CD with OGF (disease duration 0–2 y)	Thal dose: 100–150 mg/d Concomitant interventions: STE	Response (clinical)	Mean 1.7±1 years (range 0.5–3 y)	Multicenter case series
Kane et al[36]	Number: 4 Site: USA Age: 39–49 y Sex: 2 males, 2 females Characteristics: luminal or fistulous CD, (disease duration NS), delayed hypersensitivity response to infliximab	Thal dose: 50–200 mg/d Concomitant interventions: STE	Response (drop CDAI >100 or fistula improvement in 2 of 3 GIS parameters) Safety Steroid reduction	Mean 3.5±2.8 months (range 0–7 mo)	Single center case series
Cohen[37]	Number: 4	Thal dose: 100 mg/d	Response (clinical)	3–4 mo	Single center case series

Primary studies

Study	Population	Intervention	Outcomes	Duration follow-up	Quality
	Site: USA		Safety		
	Age: 29–51 y	Concomitant interventions:			
	Sex: 3 males and 1 female	NS			
	Characteristics: CD, (disease duration NS), refractory to standard medical therapy				
Bauditz et al[38]	Number: 3	Thal dose: 100–300 mg/d	Response (clinical)	Mean 31.6±6.8 months	Single center case series
	Site: Germany			(range 34–37 mo)	
	Age: 33–42 y	Concomitant interventions:			
	Sex: males	NS			
	Characteristics: CD, (disease duration 4–11 y), refractory to standard medical therapy				
Fleming et al[39]	Number: 2	Thal dose: 2.3–2.4 mg/kg/d	Response (clinical)	Mean 14±5.6 months	Multicenter case series
	Site: USA–Australia		Safety	(range 10–18 months)	
	Age: 9–12 y	Concomitant interventions:			
	Sex: 2 males	NS			
	Characteristics: CD disease (duration 4–5 y) refractory to standard medical therapy				

Secondary studies

Simon et al[40]	Number: 58	Thal dose: 50–100 mg/d	Safety	Mean 19.1 months	Multicentric, retrospective observational open label
	Site: France			(range 0.9–42.2 mo)	(abstract)
	Age: 20–78 y	Concomitant interventions:			
	Sex: 17 males, 41 females	Steroids, thiopurines, cyclosporine, infliximab			
	Characteristics: luminal or perianal CD (disease duration 3.1–35.5 years) in CD refractory to standard medical therapy				
Qian and Li[41]	Number: 27	Thal dose: 100–150 mg/kg/d	Remission (HBI <4, mucosal healing)	NS	Single center case series
	Site: China		Safety		
	Age: 33.6±15.1	Concomitant intervention:	Steroid reduction		Duplicated in Luo[11]
	Sex: NS	NS			
	Characteristics: CD refractory to standard medical therapy or biologic drugs				
Facchini et al[42]	Number: 5	Thal dose: 1.5–2 mg/kg/d	Response/remission (HBI reduction) (clinical, laboratoristic, endoscopic)	Mean 16.8±9.6 months	Single center case series
	Site: Italy		Safety	(range 0–24 mo)	
	Age: 13–22 y	Concomitant intervention:	Steroid reduction		Duplicated in Lazzerini[12]
	Sex: males	STE			
	Characteristics: luminal CD (disease duration 3–7 y), refractory to standard medical therapy				
Scribano et al[43]	Number: 3	Thal dose: 50–300 mg/d	Response (clinical, endoscopic)	Mean 6.3±2.1 years	Single center case series
	Site: Italy		Safety	(range 4–8 y)	
	Age: 28–39 y	Concomitant interventions:			Duplicated in Scribano[17]
	Sex: 1 male, 2 females	Steroids, antibiotics			

Secondary studies					
Lazzerini et al[44]	Characteristics: moderate to severe complicated CD (disease duration 6 y) refractory to anti-TNF alpha drugs Number: 2 Site: Italy Age: 9–12 y Sex: 2 females Characteristics: 1 CD, 1 UC (duration 4–5 y) refractory to standard medical therapy	Thal dose: 100–150 mg/d Concomitant interventions: None	Safety	Mean 12.5 ± 2.1 months (range 11–14 mo)	Multicenter case series Duplicated in Lazzerini[9,14]

Studies are ordered by the numerosity of the casuistry.
5ASA = aminosalicylates; 6MP = 6mercaptopurine; AZA = azathioprine; CAI = colitis activity index; CD = Crohn's disease; CDEIS = CD endoscopic index of severity; CyA = cyclosporine A; EIM = extraintestinal manifestation; GIS = goal interval score; HBI = Hervey–Bradshaw index; mTLW = modified Truelove Witts scale; MTX = methotrexate; NS = not specified; PUCAI = pediatric ulcerative colitis activity index; Rach = Rachmilewitz score; SESCD = simple endoscopic score for Crohn's disease; STE = steroid; Thal = thalidomide; UC = ulcerative colitis; UCSS = ulcerative colitis scoring system.

Table 2

Characteristics of patients.

	Patient number (%)	Statistical P^*
Total patients	489	
IBD type		
CD	435 (89.0)	< 0.001
UC	50 (10.2)	
IC	2 (0.4)	
Behcet's disease†	2 (0.4)	
Age		
< 18 y	135 (27.6)	< 0.001
> 18 y	268 (54.8)	
Mixed‡	36 (7.3)	
NS	50 (10.2)	
Sex		
Males	247 (50.5)	< 0.001
Females	178 (36.4)	
NS	64 (13.1)	

CD = Crohn's disease, IBD = inflammatory bowel disease, IC = indeterminate colitis, N = number; NS = not specified, UC = ulcerative colitis.
* Statistical *P* refers to the 2 main groups for each category.
† One study[12] included 2 patients with Behcet's disease and data could not be reported separately.
‡ Two studies included a mixed population of adults and children, and data could not be reported separately.[13,28]

3.4. Efficacy of thalidomide after or in association with biological therapy

Eight studies[10,15,16,18,22,26,35,36] reported on thalidomide efficacy after failure of either infliximab or adalimumab. Of the 73 patients identified, 47 (64.4%) had a clinical response and 37 (50.7%) achieved clinical remission (Table 7). Two additional studies[14,28] reported the association between thalidomide and infliximab or adalimumab in patients who lost response to the antitumor necrosis factor (TNF) alpha biologic drug: 7/10 (70.0%) had a clinical response, whereas 3/10 (30.0%) achieved clinical remission.

Moreover 1 further study[19] used thalidomide in patients with CD after infliximab as a maintenance therapy. Of the 15 patients enrolled, at the time of starting thalidomide treatment, 5 (33.3%) were still in clinical remission after infliximab, whereas 10 (66.6%) had experienced a relapse; the clinical remission rate during thalidomide treatment, as reported by the authors, was 73%, 73%, and 59% on an intention-to-treat analysis respectively at 3, 6, and 12 months after the last infliximab infusion.

3.5. Thalidomide in association with other immunosuppressive drugs

One study[20] reported the experimental association between cyclophosphamide and thalidomide (25–75 mg/d) for 3 to 4 months in 15 patients refractory to standard therapy or to infliximab. Clinical remission was achieved in 10/15 (66.6%) patients within 2 weeks and in 12/14 (85.7%) patients at week 10. Endoscopic improvement was noted in 12/14 (85.7%) patients; mucosal healing was observed in 4 (33.3%) patients. Five patients (33.3%) had adverse events (3 mild aminotrasferase level elevation, 1 leukemia), but they were supposed to be more closely correlated to cyclophosphamide therapy than to thalidomide.

3.6. Efficacy of thalidomide on endoscopic remission

Eight studies reported findings from the endoscopic evaluations[15,23,25,32,33,41,43] on an overall sample of 66 patients. Of

Table 3

Efficacy in inducing clinical response or remission.

Study	Population	Clinical response (%)*	Complete clinical remission (%)*
Simon et al[9]	72	38 (52.8)	38 (52.8)
Lazzerini et al[10]	49	32 (65.3)	31 (63.2)
Gerich et al[11]	37	20 (54.1)	7 (18.9)
Lazzerini et al[13]	28	21 (75.0)	21 (75.0)
Plamodon et al[14]	23	18 (78.3)	8 (34.8)
Lazzerini et al[15]	23	18 (78.2)	18 (78.2)
Ehrenpreis et al[16]	22	15 (68.1)	9 (40.9)
Leung et al[17]	17	15 (88.2)	15 (88.2)
Scribano et al[18]	16	10 (62.4)	5 (31.2)
Sabate et al[19]	15	13 (86.7)	10 (66.7)
Qian and Li[41]	14	13 (92.8)	12 (85.7)
Vasiliauskas et al[21]	12	7 (58.3)	2 (16.7)
Felipez et al[22]	12	12 (100)	10 (83.3)
Bariol et al[23]	11	8 (72.7)	NS
Bauditz et al[24]	10	7 (70.0)	4 (40.0)
Macumber et al[25]	10	9 (90.0)	4 (40.0)
Ng et al[27]	8	3 (37.5)	1 (12.5)
Kam et al[29]	7	3 (42.8)	2 (28.6)
Ahmed et al[31]	6	3 (50.0)	NS
Trebble et al[32]	6	5 (83.3)	2 (33.3)
Zheng et al[33]	6	6 (100)	5 (83.3)
Hegarty et al[34]	5	5 (100)	5 (100)
Lazzerini et al[35]	5	5 (100)	5 (100)
Kane et al[36]	4	3 (75.0)	3 (75.0)
Cohen et al[37]	4	2 (50.0)	0 (0)
Bauditz et al[38]	3	3 (100)	3 (100)
Fleming et al[39]	2	2 (100)	0 (0)
Total	427	296 (75.3%)	220 (53.9%)

Response and remission was reported as defined by the authors. Data were reported as on Intention-to-treat (ITT), and if available on Per-Protocol (PP). If more than 1 time-point reported, the longer follow-up was considered.

In the study by Simon and colleagues,[9] the number of responders was not reported and it was considered as the number of patients in remission.

In the study by Plamondon and colleagues,[14] 2 patients of the original series were excluded from the analysis because of the concomitant therapy with infliximab.

In 1 study,[32] outcomes were evaluated on endoscopy findings and in 1 study on intestinal bleeding resolution.[38] Two studies[26,30] reported drug efficacy through the mean PCDAI reduction and the exact number of patients going into remission was not specified: patients from these studies were not included in the calculation of thalidomide-induced remission rate.

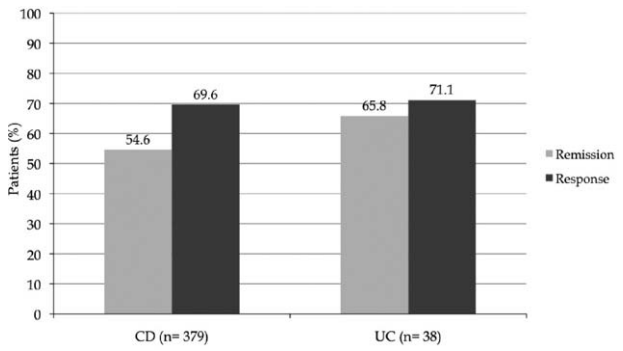

Figure 2. Efficacy in inducing clinical remission or response according to IBD type. In 2 studies,[23,31] the number of patients achieving clinical remission was not specified; for 1 study,[9] the number of responder was considered the same as the patients who achieved remission.

Table 4

Efficacy of in maintaining of clinical remission in the long term.

Study	Population	Outcome – remission at 6 months (%)	12 months (%)	24 months (%)
Lazzerini et al[10]	33	24 (72.7)	23 (69.7)	18 (54.5)
Lazzerini et al[15]	23	16 (69.6)	12 (52.2)	11 (47.8)
Lazzerini et al[13]	21	21 (100)	20 (95.2)	15 (71.4)
Plamondon et al[14]	18	9/10 (90)	5/5 (100)	1/1 (100)
Leung et al[17]	15	15 (100)	15 (100)	–
Qian and Li[41]	13	12 (92.3)	–	–
Felipez et al[22]	12	9 (75.0)	9 (75.0)	7 (58.3)
Ng et al[27]	8	0	0	0
Zheng et al[33]	6	5 (83.3)	2/2 (100)	–
Lazzerini et al[35]	5	5 (100)	3/3 (100)	3/3 (100)
Hegarty et al[34]	5	3/3	–	–
Kane et al[36]	3	1	0	0
Bauditz et al[38]	3	3 (100)	3 (100)	3 (100)
Scribano et al[43]	3	3 (100)	3 (100)	3 (100)
Fleming et al[39]	2	2 (100)	1 (50)	0
Total	170	128/160 (80.0)	96/133 (72.2)	61/112 (54.5)

Data were reported as on intention-to-treat (ITT), and if available on per-protocol (PP).

In 1 study,[32] outcomes were evaluated on endoscopy findings and in 1 study on intestinal bleeding resolution.[38]

these, 46 (69.7%) showed an improvement in their macroscopic appearance with a reduction of mucosal inflammation and 35 (53.0%) had a complete resolution of their mucosal lesions (Table 8). With a separate analysis for the IBD type, 5 studies[28,32,33,41,42] could be used to evaluate mucosal healing in CD and 1 for UC.[15] In the CD subgroup, 23/33 (69.7%) patients had a macroscopic response, whereas 16/33 (48.5%) showed complete endoscopic remission; among UC patients, 10/17 (58.8) had complete mucosal healing.

3.7. Safety data

Overall 530 AE were reported in 29 studies. Four studies[13,14,19,21] reported the number of AE but not the exact

Table 5

Steroid reduction or suspension.

Study	Population	Steroid reduction or suspension (%)
Gerich et al[11]	20	13 (65.0)
Lazzerini et al[13]	20	16 (80.0)
Lazzerini et al[10]	18	18 (100.0)
Ehrenpreis et al[16]	14	3 (21.4)
Leung et al[17]	12	12 (100)
Vasiliauskas et al[21]	12	10 (83.3)
Felipez et al[22]	12	10 (83.3)
Bauditz et al[24]	10	4 (40)
Plamodon et al[14]	7	4 (57.1)
Lazzerini et al[15]	7	7 (100)
Kam et al[29]	7	2 (26.6)
Ahmed et al[31]	6	3 (50.0)
Zheng et al[33]	3	3 (100.0)
Hegarty et al[34]	1	1 (100.0)
Kane et al[36]	1	1 (100.0)
Lazzerini et al[35]	1	1 (100.0)
Scribano et al[42]	1	1 (100.0)
Total	152	109 (71.7)

Table 6

Efficacy on fistulizing Crohn's disease.

Study	Population	Outcome	
		Improvement (%)	Cure (%)
Plamondon et al[14]	15	14 (82.4)	4 (23.5)
Gerich et al[11]	17	2 (11.8)	0 (0)
Ehrenpreis et al[16]	13	10 (76.9)	6 (46.2)
Sabate et al[19]	7	5 (71.4)	5 (71.4)
Vasiliauskas et al[21]	6	2 (33.3)	1 (16.7)
Kane et al[36]	2	2 (100)	2 (100)
Gupta et al[26]	3	3 (100)	2 (66.7)
Felipez et al[22]	7	6 (85.7)	5 (71.4)
Ng et al[27]	8	4 (50.0)	1 (12.5)
Scribano et al[43]	2	2 (100)	2 (100)
Total	81	49 (60.5)	28 (34.6)

One study[11] reported the number of patients with penetrating behavior (11) and perianal disease (6) but not specified the number of patients who had both conditions, so the total number reported may be overestimated. Type of fistulizing disease was as follows: 50 perianal, 18 enteric, 5 both perianal and enteric, 8 not specified.

number of patients involved; due to this uncertainty, the total number of patients who experienced an AE during thalidomide treatment can be estimated in a number ranging between 258 and 338. Table 9 describes the AE and the cumulative AE incidence rate/1000 patient-months; the type and number of AE that required the drug suspension is reported.

Neurological disturbances account for 64.3% of the AE reported. Peripheral neuropathy was the most common side effect observed (109 cases, incidence 15.6/1000 patient-months) and led to drug withdrawal in 56.8% patients who suffered from it.

Sedation or somnolence, of various degrees, were reported in ~25% of the patients and were usually complained of in the first period of therapy. To prevent these symptoms during the day time, some authors administered the drug in the evening before sleeping or managed them by reducing the drug dosage.[16,18,19,21,34]

Mood disturbances and anxiety were rare but in the reported cases severe enough to interfere with daily activities.[13,18,23,25]

Acute severe neurological events like seizure and stroke-like episodes were reported overall in 3 cases (incidence rate 0.3: 1000 patient-months) and determined immediate drug suspension in 2 (0.2: 1000 patient-months).

Cutaneous manifestations were the second most common category of AE reported and account for 15.8% of the AE overall.

Table 7

Efficacy of thalidomide after biological therapy failure.

Study	Population	Outcome	
		Response (%)	Remission (%)
Lazzerini et al[10]	17	8 (47.1)	8 (47.1)
Scribano et al[18]	16	6 (37.5)	5 (31.3)
Felipez et al[22]	12	12 (100)	10 (83.3)
Plamondon et al[14]	12	9 (75.0)	2 (16.7)
Lazzerini et al[15]	8	6 (75.0)	6 (75.0)
Kane et al[36]	4	3 (75.0)	3 (75.0)
Lazzerini et al[35]	2	2 (100)	2 (100)
Ehrenpreis et al[16]	2	1 (50)	1 (50)
Total	73	47 (64.4)	37 (50.7)

The series by Gupta and colleagues[26] was not considered in the analysis as response to thalidomide was reported as mean PCDAI reduction.

Table 8

Efficacy of thalidomide on endoscopic remission.

Study	Population	Response (%)	Remission (%)
Lazzerini et al[15]	17	10 (58.8)	10 (58.8)
Qian et al[41]	17	7 (41.2)	7 (41.2)
Bariol et al[23]	9	7 (77.8)	4 (44.4)
Macumber et al[25]	7	6 (85.7)	5 (71.4)
Trebble et al[32]	5	5 (100.0)	2 (40.0)
Zheng et al[33]	4	4 (100)	4 (100)
Facchini et al[42]	4	4 (100)	4 (100)
Scribano et al[43]	3	3 (100)	3 (100)
Total	66	46 (69.7)	35 (53.0)

These include dry dermatitis and rashes and were generally mild; xerostomia was also reported quite commonly.

Constipation was reported by ~10% of patients (incidence rate 3.0:1000 patient-months) but caused thalidomide suspension only in 2 cases. Ocular abnormalities accounted for 2% of all AE.

Secondary amenorrhea was reported in a 6 female patients and had a cumulative incidence rate in the female sex of 1.8/1000 patient-months; in half of the reported cases, the events led to immediate drug withdrawal.

Few patients reported potentially severe AE such as myelosuppression (2 cases), venous thrombosis (2 cases), infarct (1 case), or cardiac rhythm disturbances (7 cases) but none of the patients died as a result of thalidomide treatment.

4. Discussion

With the present review, we aimed at systematically evaluating existing evidence on the efficacy and safety of thalidomide in patients with either CD or UC. The effects of thalidomide were reported in 31 studies (2 RCTs and 29 case series), for a total of 489 patients. Overall, thalidomide appeared to be a promising therapy for IBD: thalidomide induced clinical remission in 51.4% of 427 cases (25 studies), whereas in 69.3% a clinical response was observed in the first months of treatment (27 studies). In almost 50% of the cases in which endoscopy was performed, complete mucosal healing was observed and a further 15% of patients showed a macroscopic mucosal improvement (8 studies). IBD remission was maintained in 72.2% after 12 months (13 studies) and in 54.5% of patients after 2 years of treatment (11 studies). AE leading to drug suspension had a cumulative incidence of 19.7/1000 patients-months, with neurological disturbances being the most frequent cause of drug withdrawal.

Limitations of this review are mostly related to the quality of the existing evidence. The review identified 31 primary studies for inclusion, but only 2 randomized controlled trials. Additionally, there was a certain degree of case selection by type of disease (over 80% of patients were affected by CD), and by disease severity (patients refractory to standard medical therapies and in some case to biological drugs). No comparative study was available which evaluated thalidomide versus other treatment strategies. Clearly, more RCTs are needed to further evaluate the effects of thalidomide in patients with IBD, in particular, in those with UC, as well as in patients in mild or moderate activity and/or at early stages of the disease. Comparative studies would also help to clarify the role of thalidomide in relation to other treatment strategies.

Despite these limitations, the review has the merit of synthesizing all available evidence on thalidomide for treating

Table 9

Safety data.

	Number of AEs	Number of AEs that caused drug withdrawal	Incidence rate/1000 patients-months (withdrawal)
Patients with AEs	258 (338)*		
Mean duration of exposure-months (SD)	241.7 (345.9)		
Total patients-months	7009.6		
Neurologic			
Peripheral neuropathy	109	62	15.6 (8.8)
Abnormal EMG	17	2	2.4 (0.3)
Sedation	76	11	10.8 (1.6)
Somnolence/ drowsiness	61	2	8.7 (0.3)
Numbness	18	0	2.6 (0)
Headache	17	5	2.4 (0.7)
Fatigue	13	0	1.9 (0)
Vertigo	6	3	0.9 (0.4)
Anxiety	5	4	0.7 (0.6)
Difficult concentrating	3	0	0.4 (0)
Seizures	2	1	0.3 (0.1)
Disorientation	1	1	0.1 (0.1)
Acute neurologic event	1	1	0.1 (0.1)
Depression/mood Disturbance	2	1	0.3 (0.1)
Amnesia	1	0	0.1 (0)
Asthenia	3	0	0.4 (0)
Muscle weakness	2	0	0.3 (0)
Dizziness	2	1	0.3 (0.1)
Agitation	1	1	0.2 (0.1)
Myelitis	1	1	0.2 (0.1)
Gastrointestinal			
Constipation	21	2	3.0 (0.3)
Xerostomia	21	0	3.0 (0)
Liver enzymes abnormalities			
Anoxeria	3	1	0.4 (0.1)
Nausea	2	0	0.3 (0)
Cutaneous	2	0	0.3 (0)
Dermatitis			
Rash	50	2	7.1 (0.3)
Seborrhoea	25	10	3.6 (1.4)
Alopecia	2	0	0.3 (0)
Hair loss	1	0	0.1 (0)
Psoriasis	1	0	0.1 (0)
Urticaria	1	0	0.1 (0)
Acne	2	1	0.3 (0.1)
Perianal itching	1	0	0.1 (0)
Hematological	1	0	0.1 (0)
Deep venous thrombosis			
Leukopenia	2	0	0.3 (0)
Myelosuppression	7	0	1.0 (0)
Cardiac	2	2	0.3 (0.3)
Myocardial infarction			
Conductance disturbances	1	1	0.1 (0.1)
Hypertension			
Ocular	7	2	1.0 (0.3)
Hemianopsia	2	0	0.3 (0)
Amaurosis			
Decreased visual acuity	2	0	0.3 (0)
Emeralopia	1	1	0.1 (0.1)
Scotomas	1	1	0.1 (0.1)
Congiuntivitis	1	0	0.1 (0)
Optic neuritis	1	0	0.1 (0)
Photophobia	1	0	0.1 (0)
Swollen eyes	1	0	0.1 (0)
Hormonal	1	0	0.1 (0)
Amenorrhea	1	1	0.1 (0.1)
Dysmenorrhea			
Gynecomastia	6	3	0.9 (0.4)
Loss of libido	1	0	0.1 (0)
Other	1	0	0.1 (0)
Noncardiac thoracic pain	2	1	0.3 (0.1)
Edema			
Myalgia	2	1	0.3 (0.1)
Dyspnoea	4	0	0.6 (0)
Hoarsness	2	0	0.3 (0)
NS	2	0	0.3 (0)
Patients in whom the AEs	1	0	0.1 (0)
Leading to drug withdrawal	4	0	0.6 (0)
Was NS	–	13	– (1.9)
TOTAL – Aes	530	138	75.6 (19.7)

* Four studies[13,14,19,21] reported the number of AEs but not the number of patients with AEs. The first number refers to the patients with AEs specified. The number in brackets includes the patients of the 4 studies considered if as all the patients had AE.

Sabate (15 patients)[19] e Plamondon (25 patients)[14] did not specify the number of patients with AEs but reported the number of AEs.

Kam and colleagues[29] made explicit that 1 patient stopped thalidomide after 8 wk because of decreased libido and reported that other patients had mild and transient AEs (sedation, pruritus, numbness, dry skin, and decreased libido): because the number of patients involved and the number of AEs were not specified, they were not included in the table.

To calculate the total follow-up time: the sum of follow-up for each patient were used when possible; when mean follow-up time was reported, it was multiplied for the number of patients included; when median follow-up time was reported,[9,19,30] it was considered as a mean follow-up. For 1 study,[37] follow-up was not available.

AEs = adverse events; EMG = electromyographic; NS = not specified; SD = standard deviation.

IBD. A very comprehensive search strategy was used to identify relevant studies, and efforts were made at all steps of the process to reduce possible bias in data synthesis.

Overall this review shows that evidence is accumulating on the use of thalidomide in patients with IBD. The efficacy of thalidomide appears to be not negligible, and worth investing in future research.

This review highlighted that thalidomide was effective even when used after the failure of biological therapies, with response and remission rates similar to biologically naive patients. These results can be explained by the different mechanism of action of thalidomide compared to other anti-TNF alpha biological agents, and supports the use of thalidomide in patients refractory/ intolerant to other anti-TNF alpha agents.

This review confirms to a great extent what is already known about the safety of thalidomide, but also provides a more detailed insight into observed AE in patients with IBD. Adverse events were the most common cause of thalidomide withdrawal in the long-term, whereas the drug's loss of efficacy accounted for only 12% of the drug suspensions. Neurological AE are the most frequent complain during thalidomide treatment. Thalidomide was first commercialized as a sedative drug and it is therefore not surprising that sedation is a common AE. Sedation/somnolence

are generally observed in the first weeks of treatment and are subsequently tolerated probably with a mechanism of tachyphylaxis.[45] The degree of sedation is usually proportional to the daily dose and can be further decreased by assuming the drug late in the evening, before going to sleep at night.[16,21,45]

On the opposite, as reported in studies in multiple myeloma patients or in other inflammatory diseases,[46–49] peripheral neuropathy is generally detected after several months of treatment, as it seems to be associated more with thalidomide cumulative dose, rather than with the daily dosage. The frequency of thalidomide-induced peripheral neuropathy varies in the current literature depending on the age of patients, the primary disease, the drug doses, the concomitant treatments, and the length of follow-up. In 135 adult patients with various dermatological conditions treated with thalidomide at daily dosages comparable to those used in the studies included in the present review (mean thalidomide starting dose 97.5 ± 25.6 mg/d), clinical signs of peripheral neuropathy accompanied by electromyographic signs were observed in 25.2% of cases during a median 11 month follow-up.[47] Data for children are limited: *Priolo* and colleagues evaluated 13 patients treated with thalidomide for rheumatological conditions or for Crohn's disease and found a clinical neuropathy in 35.8% of cases and the presence of electromyographic subclinical alterations in 53.8% of cases.[49] Thalidomide-induced peripheral neuropathy is a predominantly sensory polyneuropathy affecting mainly long and large fibers;[39,49,50] it has been described as reversible although few cases presented persistent clinical and electrophysiologic alterations after thalidomide suspension during a short follow-up time.[49] Nerve conduction studies are useful to monitor the development and the evolution of neurotoxicity once it has become clinically apparent, although it is not fully clear if electromyographic abnormalities in the absence of symptoms are predictive of a developing clinical neuropathy.[45] While awaiting further safety data in patients treated with IBD with low doses of thalidomide, it remains important to warn patients of the need to report symptoms suggestive of neuropathy (tremors, numbness and tingling), and to perform careful routine neurological evaluations including sensitivity to vibration. In cases of mild symptoms or in the case of persistent nerve conduction abnormalities without clinical signs/symptoms, reducing the daily dose may be used as a strategy to arrest or slow down the progression of clinical neuropathy.[10]

This review highlighted that amenorrhea due to hypergonadotropic hypogonadism was a relatively frequent AE in female patients with IBD treated with thalidomide. A previous review highlighted that the risk of amenorrhea in patients with different inflammatory diseases under thalidomide treatment may be higher than in the general population of woman treated with thalidomide.[44] Though in most cases amenorrhea has been described as reversible, patients need to be carefully informed and strictly monitored.

Despite the fact that thalidomide is known to increase the risk of deep vein thrombosis in patients with multiple myeloma,[50] and despite IBD with active diseases having *per se* a higher risk of venous and arterial thromboembolism compared to the general population,[51] only 2 cases of deep venous thrombosis were identified by this review. This may be explained by the fact that the risk of thrombosis associated with thalidomide is low, if the drug is used alone (and not in association with the other drugs used in multiple myeloma) and at a low dosage. Additionally, it is possible that the increased pro-thrombotic risk associated with thalidomide is balanced by the capacity of the drug to control the inflammatory response. More studies on large samples of patients are needed to further evaluate the real risk of thrombosis in patients with IBD at different stages of disease activity.

Interestingly, no infection was reported under thalidomide treatment, even when thalidomide was used at high dosages (>150 mg/d). This highlights that the immunomodulatory effects of thalidomide are not, or are only slightly, immunosuppressive, as compared with anti-TNF alpha biologics.

Most of the other AE reported in this review were mild and did not require the drug to be withdrawn. However, larger studies are needed to detect rare although potentially severe AE.

Toxicity is certainly the main concern of thalidomide treatment. Reducing thalidomide dose to a minimum effective dose, after achieving stable remission, may potentially be a successful strategy to reduce long-term AE and to delay the onset of neuropathy. Despite the fact that at present there is no evidence on efficacy of lenalidomide,[52] in the future, the development of other thalidomide analogs with a lower incidence of AE may further improve the risk and benefit profile of this therapy.

In conclusion, according to the results of this review, thalidomide appears to be a valuable treatment option for patients with CD refractory to other first- and second-line treatments.

Further randomized controlled trials are needed to adequately explore the efficacy and safety of thalidomide in patients with UC, as well as to evaluate thalidomide in comparison with other therapies for patients with less severe diseases or at earlier stages of their natural course.

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