**Name of journal: *World Journal of Meta-Analysis***

**ESPS Manuscript NO: 32747**

**Manuscript Type: META-ANALYSIS**

**Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis**

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**Author contributions:** Sami Ullah KR and Xiong YL contributed equally to this study;

DaiWand MiaoYL supervised this study; UmmairS also contributed in this study.

**Conflict-of-interest statement:** The authors assured no confliction of interest.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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**Received:** January 21, 2017

**Peer-review started:** January 22, 2017

**First decision:** March 8, 2017

**Revised:** May 5, 2017

**Accepted:** June 30, 2017

**Article in press:**

**Published online:**

**Abstract:**

***AIM***

To examine the efficacy and safety of thalidomide and thalidomide analogues in induction and maintenance of remission in patients with inflammatory bowel disease (IBD).

**METHOD**

A literature search was performed in the following databases: PubMed, EMBASE, Web of Science, Ovid and the Cochrane Library, and Chinese databases such as the China National Knowledge Infrastructure, China Science and Technology Journal Database (VIP), wanfang Data. The randomized controlled analysis was performed to assess the effects of thalidomide therapy on inflammatory bowel disease for patients who did show good response with other therapies.

***RESULTS***

Three studies (*n* = 212) met the inclusion criteria were used in this Meta –analysis. No difference was found between thalidomide/thalidomide analogues and placebo in the induction of remission (RR = 1.36, 95%CI: 0.83-2.22, *P* = 0.22), the induction of clinical response (RR = 1.14, 95%CI: 0.75-1.72, *P* = 0.54) and the induction of adverse events (RR = 1.41, 95%CI: 0.99-2.02, *P* = 0.06).

***CONCLUSION***

Currently, there is not enough evidence to support use of thalidomide or its analogue for the treatment in patients of any age with IBD. However, it warrants a reanalysis when more data become available.

**Key words:** Inflammatory bowel disease; Thalidomide; Thalidomide analogues; treatment; Efficacy; Safety; Meta-analysis

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**Core tip:** The aim of this meta-analysis is to examine the efficacy and safety of thalidomide and thalidomide analogues for induction and maintenance of remission in patients with inflammatory bowel disease (IBD). The literature was searched in the databases: PubMed, EMBASE, Ovid and the Cochrane Library, and Chinese databases. The Randomized Controlled Trials was performed during this analysis to assess the effects of thalidomide therapy on IBD patients that did show good response with other therapies. Weighted pooled outcomes were synthesized with a fixed-effects model to account for clinical heterogeneity. This meta-analysis showed that there is not enough evidence to support the use of thalidomide or its analogues in the treatment of IBD for patients of any age.

Sami Ullah KR, Xiong YL, Dai W, Miao YL, Ummair SU. Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis. *World J Meta-Analysis* 2017; In press

**INTRODUCTION**

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract with the long period of clinical relapse and remission[1]. Crohn’s disease and ulcerative colitis are two main subtypes of inflammatory bowel diseases[1]. The quality of life of the patients who are suffering from IBD is highly affected. The causes of IBD are still unclear but many researchers believe that environmental factors and microbial triggers might induce IBD[2,3].

The prevalence of IBD varies considerably around the world with diagnostic criteria vary between geological regions. It is believed that IBD is associated with increased industrialization of countries. The highest prevalence of IBD is observed in North America and Europe[4] (2.6 million in Europe and 1.2 million in North America)[5,6] .

There is no cure of IBD to date, aims of the therapy are induction and maintenance of remission[1,2]. Corticosteroids are the mostly used drugs, which shows effectiveness but only in, inducing remission but not in maintenance of remission for IBD[7,8].

There are many drugs that have been used in the treatment of IBD, however, maintaining remission remains a challenge. A safe and effective drug for the treatment of IBD remains to be found Thalidomide was initially used as a sedative and antiemetic drug. It was removed from the market during 1960s because it births related defects[9].

 It was discovered later that thalidomide could inhibit the synthesis of tumor necrosis factor-a by accelerating the degradation of its mRNA[10]. The immune regulatory property of thalidomide raised peoples’ interests in its potential for the treatments of autoimmune diseases in recent years. The efficacy of thalidomide treatment has been demonstrated by a series of clinical trials in a serious clinical disease like human immunodeficiency virus (HIV) associated wasting syndrome, hereditary hemorrhagic telangiectasia[11], refractory cutaneous lesion of lupus erythematous[12] ,multiple myeloma[13] , and Bachet’s disease[14] .

The increased production of tumor necrosis factor-a (TNF-α) in IBD plays a major role in the pathophysiology of IBD[15,16] and TNF-a tends to increase with the disease progression[13,14].

The development of thalidomide analogues was spurred due to emerging clinical evidence supports that the drug has anti-angiogenic and anti-inflammatory properties[17]. So far there have been many thalidomide analogues but the most famous ones are Lenalidomide, Pomalidomide and Apremilast. They all work is similar manner and have similar mechanisms for the treatment of diseases It is believed that they work by different mechanisms in different diseases[18,19]. Apremilast works differently by reducing PDE4 activity and causing an increase in cAMP concentrations, which lead to inhibition of many pro-inflammatory cytokines and increased production of anti-inflammatory cytokines[20]. Literature review shows no evidence to support or deny the use of thalidomide analogues for the treatment of IBD, nor does it show any difference in efficacy compared with thalidomide.

In a Cocranine review of thalidomide analogues for the induction of remission and maintenance of of Crohn’s disease, lenalidomide showed no statistically significant benefits over placebo[21,22].

Thalidomide has the property to suppressing the synthesis of TNF-a[23,24] .Thalidomide can reduce the production of TNF-α by lipopolysaccharide or phytohaemaglutinin-stimulated monocytes and macrophages and mitogen-induced T-cells[25,26] .Although the exact mechanisms by which TNF-a involves in diseases is not clear, thalidomide seems to be effective for the treatment of diseases[10].

The aim of this study was to systematically review the current evidence examining the efficacy and safety of thalidomide and thalidomide analogues for the induction and maintenance of remission in patients with IBD.

**MATERIALS AND METHODS**

***Literature search strategy***

Two authors (Khan Rana Sami Ullah and YuLin Xiong) independently carried out a retrieval of literatures that investigated the association between thalidomide or thalidomide analogues and IBD. A literature search was performed in the following databases: PubMed, EMBASE, Web of Science, Ovid and the Cochrane Library, and chinese databases including the China National Knowledge Infrastructure, China Science and Technology Journal Database, wanfang Data. The Medical Subject Terms (MeSH) and Keywords used for this research were: Thalidomide OR lenalidomide AND “inflammatory bowel disease” OR “Crohn’s disease” OR “Ulcerative colitis”. The last search was performed on April 20, 2015. We performed a further manual search of references from original or review articles on this topic.

***Selection criteria***

The titles and abstracts of published studies were screened independently by two authors (Khan Rana Sami Ullah and YuLin Xiong)to determine whether they met the following inclusion criteria: (1) randomized controlled trials (RCTs), assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD, including UC and CD; (2) participants: Patients with IBD of all age groups, including UC and CD; (3) intervention: Thalidomide and thalidomide analogues (any route, dose, duration); (4) provided sufficient data for estimation of a relative risk (RR) and corresponding 95%CI; and (5) published in the English or Chinese language.

***Data extraction***

The methodological quality of selected trials was assessed independently by two authors (Khan Rana Sami Ullah and YuLin Xiong) using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions[27] and the Jadad scale[28]. The former is based on the evidence of a strong relationship between allocation concealment and direction of effect. The Jadad scale is a validated five point, scale which measures some important factors that impact on the quality of a trial. They are summarized below: (1) was the study described as randomized? (2) was the method of randomization well described and appropriate? (3) was the study described as double blind? (4) was the double blinding well described and appropriate? and (5) were the withdrawals and dropouts described?

A data extraction form was developed and used to extract information on relevant features and results of included studies. The two authors (Khan Rana Sami Ullah and YuLin Xiong) independently extracted and recorded data on the predefined checklist. Differences were resolved by discussion. Extracted data included the following items (Tables 1 and 2): (1) characteristics of patients: author, publish year, age, sex, country, participants, duration of therapy; (2) total number of patients originally assigned to each intervention group; (3) intervention: Thalidomide, Lenalidomide; (4) control: no intervention, placebo or other interventions; and (5) outcomes: Primary outcome: clinical remission as defined by the primary studies and expressed as a percentage of patients with Secondary outcomes: clinical response as defined by the primary studies, and adverse events.

***Statistical analysis***

The Cochrane Collaboration review manager software (RevMan version 5.0) was used for data analysis. Results were analyzed according to the intention-to-treat principle. We assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD by calculating the pooled relative risk (RR) and corresponding 95%CI using meta-analysis. The Cochrane Q-test was used to evaluate the heterogeneity among those studies. I-square was used to quantify the size of heterogeneity. When there was no significant heterogeneity (*I*2 = 50 %), we used the fixed-effects model to analyze the data. Otherwise, we used the random-effects model. In this study, we performed a sensitivity analysis to test the stability of results. Patients with final missing outcomes were assumed to be treatment failures. Funnel plots were not conducted to investigate publication bias as there were not enough studies included in each comparison to produce a meaningful analysis.

**RESULTS**

***Literature retrieval***

The above described search strategy identified 362 citation. There was also additional references added through other approach (7 articles), and the total number of articles used for literature review was 369 (362+7). Out of these 369 articles, 47 duplicates were removed, leaving only 322 primary articles (369-47 = 322). Out of these 322 primary articles, 302 were excluded after reading titles and abstract of articles. The remaining 20 articles assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD, including UC and CD. Only 3 out of the 20 articles were used for the meta-analysis as 17 failed to meet the inclusion criteria. The process of the included articles were shown Figure 1.

***Methodological quality of included studies***

The assessment of the risk of bias for the three studies used in the meta-analysis was summarized in Figures 2 and 3. Overall, the Lazzerini’s study[29] has high quality (Jadad score﹦5). The two studies[30,31] were rated as having high risk of bias (Jadad score = 3) due to not providing sufficient information on the method of randomization and lack of proper blinding controls. All data were analyzed based on the intention-to-treat principle. Due to an insufficient number of studies to produce a meaningful analysis, funnel plots were not used to investigate publication bias.

***Induction of remission***

The frequency of induction of remission for patients treated with thalidomide was studied in 3 trials that consisted of 212 patients. Significant heterogeneity was detected between these trials (*I*2 = 57%, *P* = 0.07). We divided these trials into two subgroups (adults and children), and no significant heterogeneity was detected in the adult’s trials. (*I*2 = 15%, *P* = 0.31). No meta-analysis was performed for Children’s IBD as there was only one trial available. Meta-analysis using a fixed effects model showed no difference between thalidomide and placebo for the maintenance of clinical remission (RR = 1.36, 95%CI:0.83 - 2.22, *P* = 0.22; Figure 4).

***Induction of clinical response***

The frequency of induction of clinical response for patients treated with thalidomide was studied in 3 trials that consisted of 212 patients. No significant heterogeneity was detected between these trials (*I*2 = 0%, *P* = 0.98). We divided these trials into two subgroups, adults and children. Meta-analysis using a fixed effect model showed no difference between thalidomide and placebo for the maintenance of clinical remission (R.R = 1.14, 95%CI: 0.75-1.72, *P* = 0.54; Figure 5)

***Induction of adverse events***

Adverse events were reported in two out of the three trials (one trial is not clear) which consisted of 69 patients, therefore the Meta analysis included only two trials. No significant heterogeneity detected between the two trials (*I*2 = 49%, *P* = 0.14), Meta- analysis using a fixed effects model showed no difference between thalidomide and placebo for the occurrence of serious side effects (RR = 1.41, 95%CI: 0.99-2.02, *P* = 0.06; Figure 6)

***Sensitivity analysis and publication bias***

All of the outcomes were re-analyzed using a random effects model to estimate the stability of the meta-analysis. W excluded either one study at a time and analyzed the remaining studies to assess whether a particular study had an excessive influence on the results. Most of the results were consistent, as described above.

**DISCUSSION**

The treatment of IBD is quiet challenging in clinical practice for gastroenterologists. There is no cure for IBD; the main goals of therapy are induction and maintenance of remission. Many drugs have been used to treat IBD, but only corticosteroids are commonly used. However, corticosteroids are only effective in inducing remission, but not in maintain remission.

IBD is chronic inflammation of the gastrointestinal tract with a long period of clinical relapse and remission[1]. A wide range of drugs have been used for the treatment of IBD, such as amino salicylic acids, thiopurines, immunomodulators such as azathioprine (AZA), mercaptopurine, methotrexate, infliximab, adalimumab. And corticosteroids. However, the effective rates of these drugs are low and they are associated with many adverse side effects[32,33]. It has now been recognized that the treatment goals should go beyond just controlling the symptoms of IBD. Rather, IBD treatments should aim to rapidly induce steroid-free remission, while minimizing serious complications and side effects[34] .The side effects that have been reported including an increased risk of infections, occurrence of autoimmune disorders[35] ,and risk of lymphoma or other malignancy[36] .

The efficacies of thalidomide and thalidomide analogues for the treatment of IBD are of interest. Three published studies (*n* = 212) were included in the meta-analysis. No statistically significant difference was found between thalidomide/thalidomide analogues and placebo in terms of frequency of clinical remission and clinical response.

The main side effects that have been reported including Peripheral neuropathy, bradycardia, amenorrhea, and so on. Adverse events were reported in two out of three trials. They were not reported in one trial was not clear. We tried to contact the author by e-mail, but we were unsuccessful in retrieving the full data of these studies. Meta-analysis of the two studies did not show any statistically significant benefits from the use of thalidomide and thalidomide analogues.

Despite strict inclusion criteria have been used to reduce heterogeneity, there are still several limitations within this study. First, the degree of IBD of the patients of the trials included in this study vary considerately, ranging from mild-to-moderate to moderately severe. Second, evaluation of response was not uniform upon trial initiation, some trials enrolled patients with PCDAI ≤ 10, response: reduction in PCDAI of ≥ 25%, while others enrolled those with CDAI < 150, reduction in CDAI by ≥ 100, and response: reduction in CDAI by ≥ 70. Third, dosage of thalidomide and thalidomide analogues used differ between trials. All of these variability could affect the results of our analysis.

In summary, this meta-analysis has shown that there is not enough evidence to support the use of thalidomide or its analogues for the treatment of IBD for patients of any age. Many studies published so far on the use of thalidomide and thalidomide analogues for the treatment of IBD are handicapped by their small sample sizes and debatable interpretation. There were no case–control or cohort study and there were only three RCTs in publications. Therefore, it will be necessary to perform a re-analysis when more data become available.

**COMMENTS**

***Background***

Inflammatory bowel disease (IBD) is chronic inflammation of the gastrointestinal tract with a long period of clinical relapse and remission. A wide range of drugs have been used for the treatment of IBD. However, the effective rates of these drugs are low and they are associated with many adverse side effects. The increased production of tumor necrosis factor-α (TNF-α) in IBD plays a major role in the pathophysiology of IBDand TNF-α tends to increase with the disease progression.

***Research frontiers***

The treatment of IBD is quiet challenging in clinical practice for gastroenterologists. There is no cure for IBD, the main goals of therapy are induction and maintenance of remission. Many drugs have been used to treat IBD, but only corticosteroids are commonly used. However, corticosteroids are only effective in inducing remission, but not in maintain remission. The efficacies of thalidomide and thalidomide analogues for the treatment of IBD are of interest. Three published studies (*n* = 212) were included in the meta-analysis. No statistically significant difference was found between thalidomide/thalidomide analogues and placebo in terms of frequency of clinical remission and clinical response.

***Innovations and breakthroughs***

In this meta-analysis, we examined the efficacy and safety of thalidomide and thalidomide analogues for induction and maintenance of remission in 53 patients with IBD. No difference was found between thalidomide and placebo in the induction of remission (*P* = 0.22), clinical response (*P* = 0.54) and adverse events (*P* = 0.06). Therefore, it is concluded that there is not enough evidence to support the use of thalidomide or its analogues in the treatment of IBD patients of any age.

***Applications***

This meta-analysis has shown that there is not enough evidence to support the use of thalidomide or its analogues for the treatment of IBD for patients of any age. Many studies published so far on the use of thalidomide and thalidomide analogues for the treatment of IBD are handicapped by their small sample sizes and debatable interpretation.

***Peer-review***

The authors submitted a meta-analysis article entitled “Thalidomide and thalidomide analogues in treatment of patients with inflammatory Bowel Disease”. As a pediatric gastroenterologist for more than 35 years, I agree that maintaining remission for IBD remains a challenge. In our past limited experience, we also doubted the effect of thalidomide in treatment for IBD. This article, after making the meta-analysis, concluded that no enough evidence to support use of thalidomide or its analogue for the treatment in patients of any age with IBD. Although there are still several limitations within this study as the authors mentioned in the discussion, the study design, methodology and statistical analysis were all under the principle of preciseness. This article may be beneficial to the clinicians.

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**P-Reviewer:** Lee HC **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Specialty type:** Medicine, Research and Experimental

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Summary of included studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  **Study/yr** | **Country** | **Patients NO.****(Intervention/Control)** |  **Mean Age****(Intervention/Control)** | **Gender****(Male/Femal)**  | **Participants** |    |
| Luo/2008Lazzerini/2013Mansfield/2007  | ChinaItalyUnited Kingdom  | 23/2328/2623/2833/28 |  37.2/36.5 14.0/15.0 41.5/41.337.5/41.3 |  27/19 32/22 21/3033/29 | aged 18 to 70 years, with mild-to-moderate CDaged 2 to 18 yr with active CDaged 18 to 75 yr with moderately severe CD |  |

CD: Crohn’s disease.

**Table 2 Summary of included studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  **Study/yr** | **Intervetion** |  **Control** |  **Remission****(Intervention/Control)** | **Response****(Intervention/Control)** | **Adverse effects****(Intervention/Control)** |    |
| Luo/2008Lazzerini/2013Mansfield/2007  | Thalidomide100 mg/d Thalidomide50, 100 and 150 mg/d lenalidomide 25 mg ⁄d,lenalidomide 5 mg ⁄d | SASP 4 g/d UknownUnknown | 6/513/32/710/7  | 15/135/54/46/4 | 10/9Unknown/ 118/1012/10 |  |

Records identified through database searching
(n = 362 )

Identification

Eligibility

Included

Screening

Additional records identified through other approach (n = 7)

Records excluded（after reading title and abstract of articles） (n = 302)

Records screened
(n = 322)

Full-text articles excluded, with inclusion criteria
(n = 17)

Full-text articles assessed for eligibility
(n = 20)

Studies included in quantitative synthesis (meta-analysis)
(n = 3)

**Figure 1 PRISMA selection. Study selection process according to the PRISMA statement meaningful analysis, funnel plots were not used to investigate publication bias.**



**Figures 2 Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.**



**Figure 3 Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.**



**Figure 4 Remission: fixed effects model forest plot of weighted pooled estimate.**



**Figure 5 Clinical response: fixed effects model forest plot of weighted pooled estimate.**



**Figure 6 Adverse events: Fixed effects model forest plot of weighted pooled estimate.**