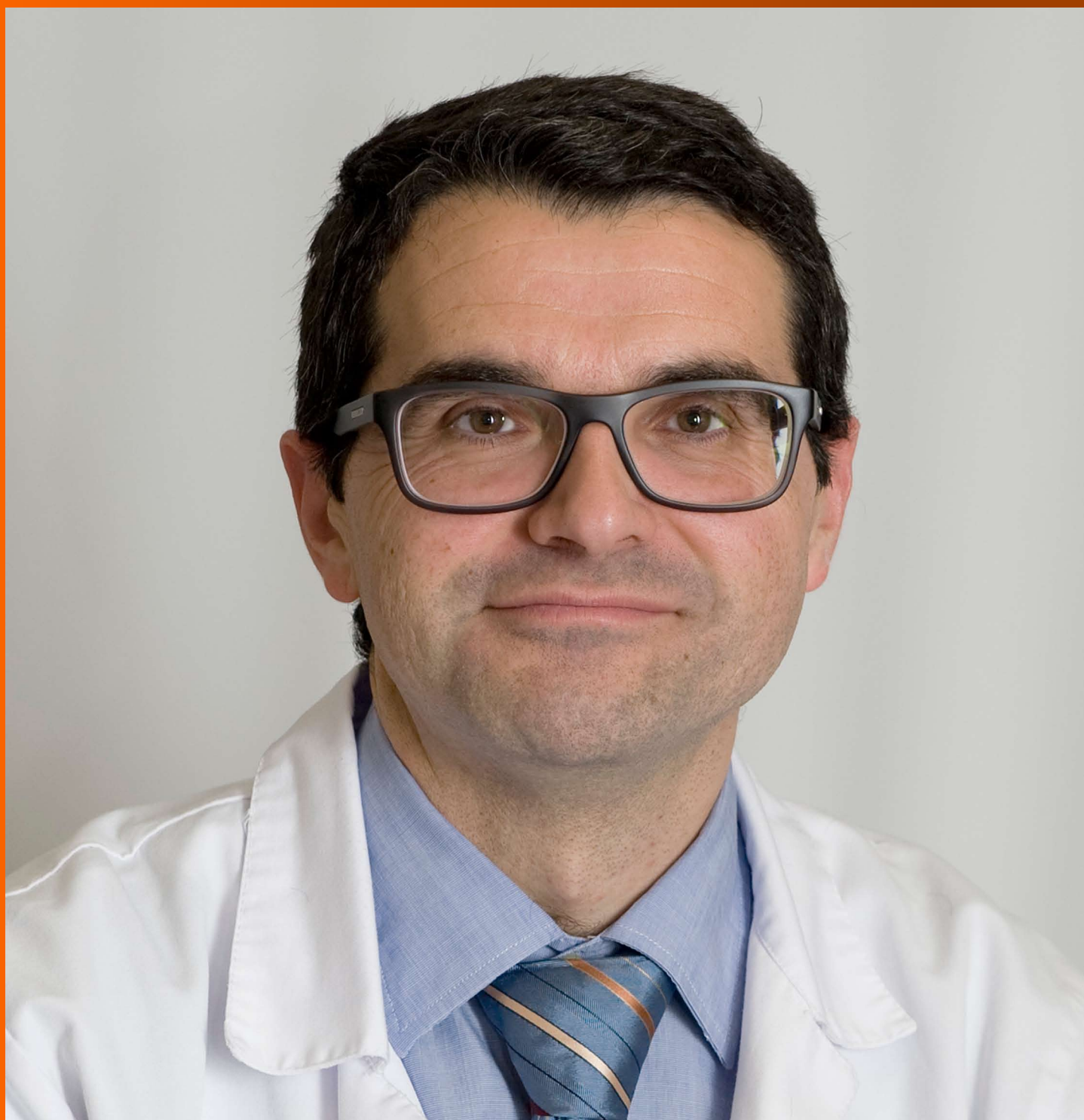


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Sami Ullah KR, Xiong YL, Miao YL, Ummair S, Dai W

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

Khan Rana Sami Ullah, Yu-Lin Xiong, Ying-Lei Miao, Saeed Ummair, Wei Dai

Khan Rana Sami Ullah, Ying-Lei Miao, Wei Dai, Department of Gastroenterology, First Affiliated Hospital of Kunming Medical University, Yunnan Institute of Digestive Disease, Kunming 650032, Yunnan Province, China

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Saeed Ummair, Department of Dermatology, First Affiliated Hospital of Kunming Medical University, Kunming 650032, Yunnan Province, China

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Telephone: +86-871-65324888

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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).

METHODS

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, Miao YL, Ummair S, Dai W. Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis. *World J Meta-Anal* 2017; 5(5): 124-131 Available from: URL: <http://www.wjgnet.com/2308-3840/full/v5/i5/124.htm> DOI: <http://dx.doi.org/10.13105/wjma.v5.i5.124>

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 geographical 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- α (TNF- α)

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 erythematosus^[12], multiple myeloma^[13], and Bachel's disease^[14].

The increased production of TNF- α in IBD plays a major role in the pathophysiology of IBD^[15,16] and TNF- α 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- α ^[23,24]. Thalidomide can reduce the production of TNF- α by lipopolysaccharide or phytohaemagglutinin-stimulated monocytes and macrophages and mitogen-induced T-cells^[25,26]. Although the exact mechanisms by which TNF- α 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 Yu-Lin 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

Table 1 Summary of included studies

Study/yr	Country	Patients No. (intervention/ control)	Mean age (intervention/ control)	Gender (male/ female)	Participants
Luo/2008	China	23/23	37.2/36.5	27/19	Aged 18 to 70 yr, with mild-to-moderate CD
Lazzerini/2013	Italy	28/26	14.0/15.0	32/22	Aged 2 to 18 yr with active CD
Mansfield/2007	United Kingdom	23/28	41.5/41.3	21/30	Aged 18 to 75 yr with moderately severe CD
		33/28	37.5/41.3	33/29	

CD: Crohn's disease.

Table 2 Summary of included studies

Study/yr	Intervention	Control	Remission (intervention/ control)	Response (intervention/ control)	Adverse effects (intervention/control)
Luo/2008	Thalidomide 100 mg/d	SASP 4 g/d	6/5	15/13	10/9
Lazzerini/2013	Thalidomide 50, 100 and 150 mg/d	Unknown	13/3	5/5	Unknown/1
Mansfield/2007	lenalidomide 25 mg/d, lenalidomide 5 mg/d	Unknown	2/7 10/7	4/4 6/4	18/10 12/10

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 Yu-Lin 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 Yu-Lin 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 Yu-Lin 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 RR and corresponding 95%CI using meta-analysis. The Cochrane Q-test was used to evaluate the heterogeneity among those studies. I^2 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

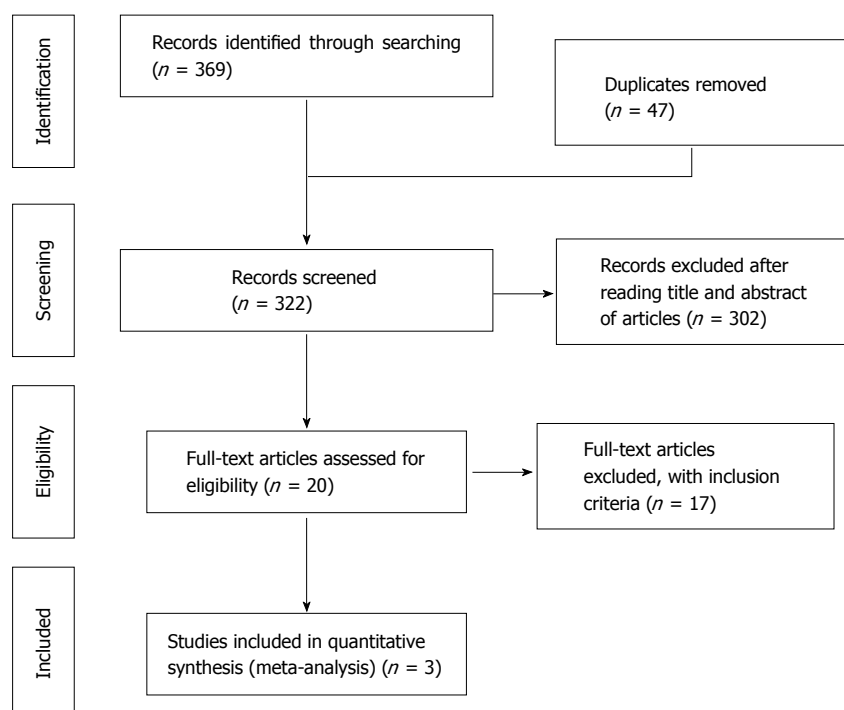


Figure 1 PRISMA selection. Study selection process according to the PRISMA statement meaningful analysis, funnel plots were not used to investigate publication bias.

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

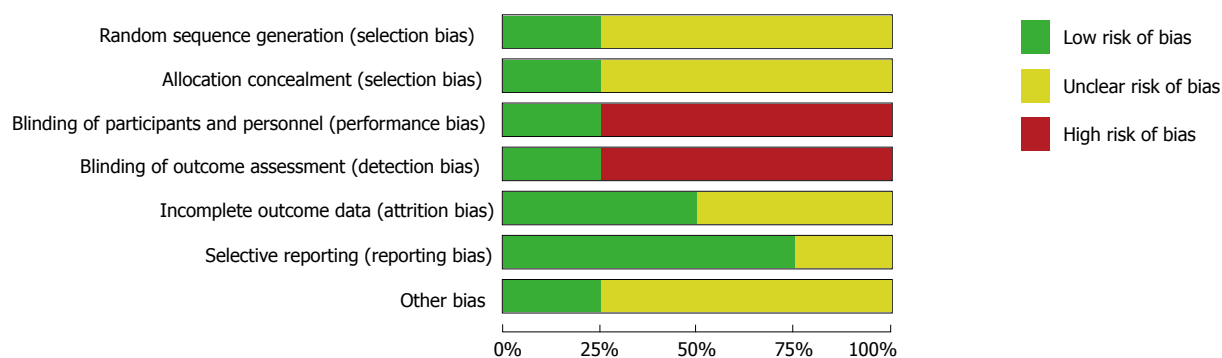


Figure 2 Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

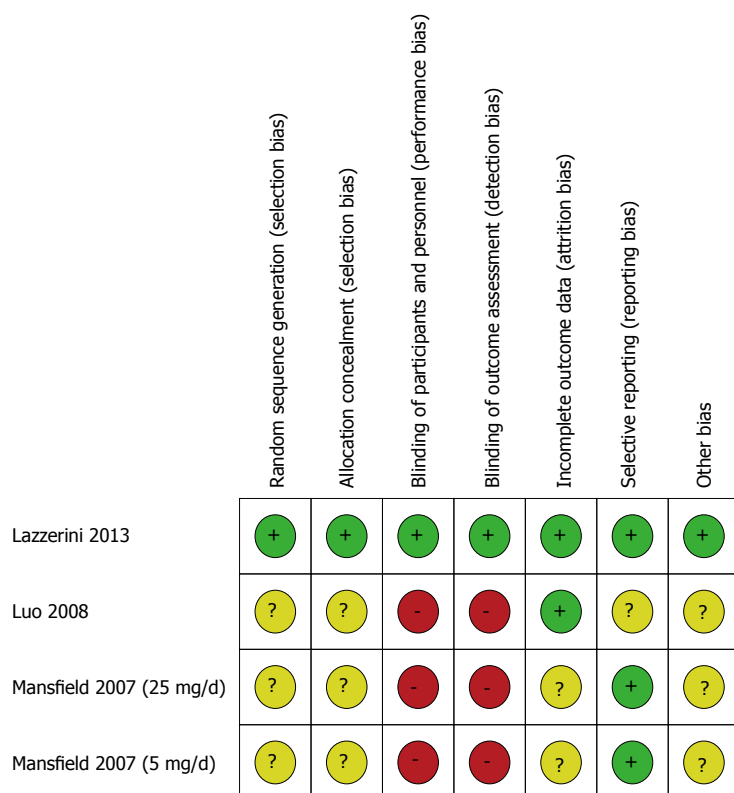


Figure 3 Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

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. We 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 quite 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

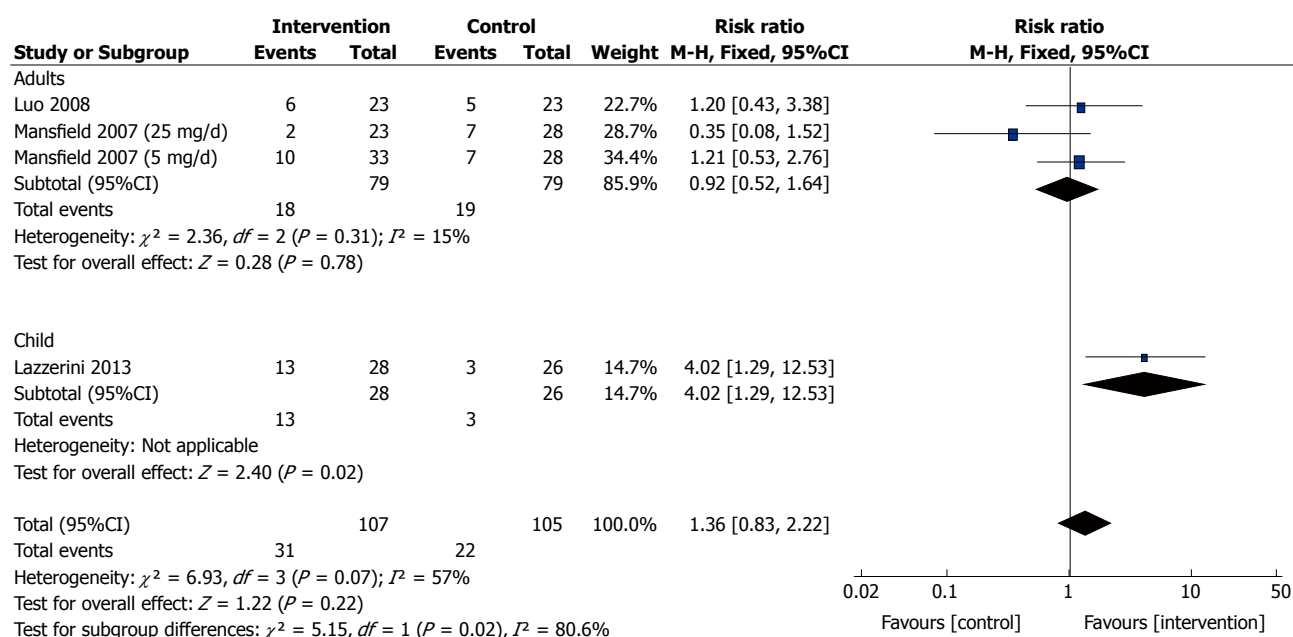


Figure 4 Remission: Fixed effects model forest plot of weighted pooled estimate.

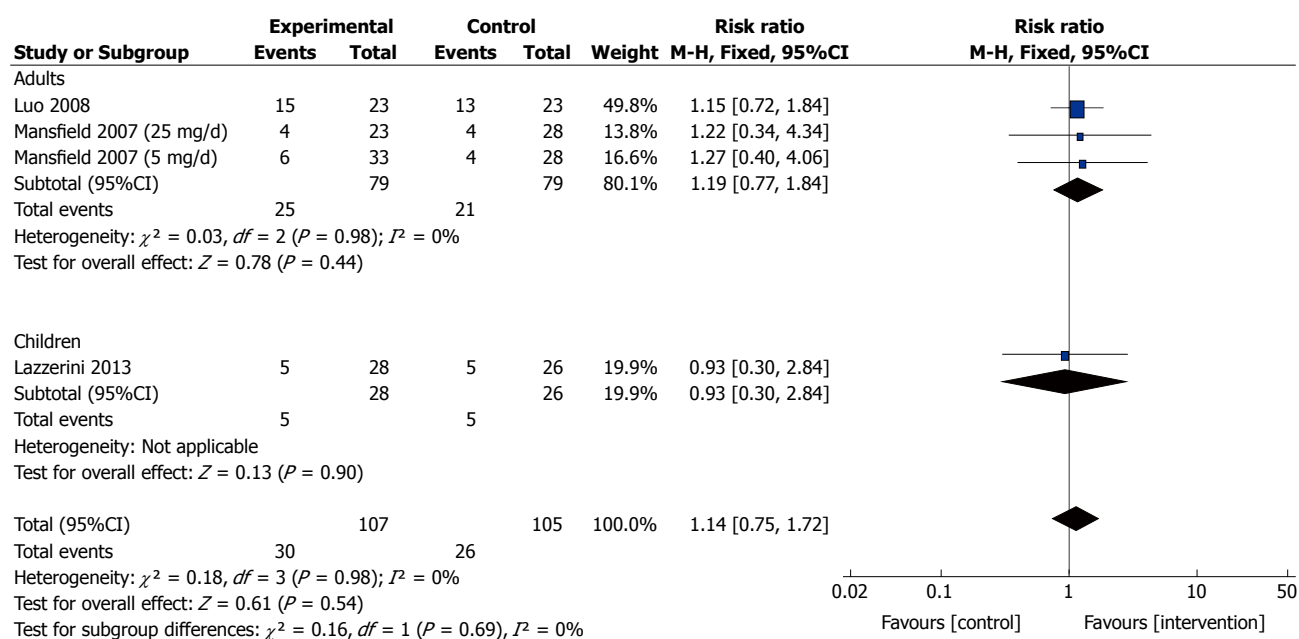


Figure 5 Clinical response: Fixed effects model forest plot of weighted pooled estimate.

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.

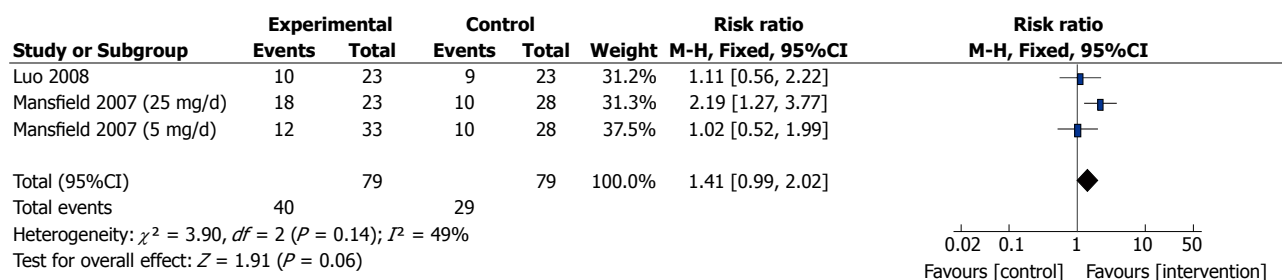


Figure 6 Adverse events: Fixed effects model forest plot of weighted pooled estimate.

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 considerably, 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 $\geq 25\%$, 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 IBD and 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, the authors 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

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. This article may be beneficial to the clinicians.

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