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[Intervention Review]

Thalidomide and thalidomide analogues for maintenance of remission in Crohn's disease

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ABSTRACT

Background

Maintenance of remission is a major issue in the management of Crohn's disease. Thalidomide, a tumour necrosis factor-alpha (TNF- α) inhibitor and its analogue, lenalidomide, may have a role in the management of Crohn's disease, but it is not clear whether it is an effective maintenance therapy.

Objectives

To conduct a systematic review to evaluate the efficacy and safety of thalidomide and lenalidomide for the maintenance of remission in Crohn's disease.

Search methods

MEDLINE (1966 to September 2008), EMBASE (1984 to September 2008), the Cochrane Central Register of Controlled Trials from the Cochrane Library (Issue 3, 2008) and the IBD/FBD Review Group Specialized Trials Register were searched to identify relevant studies.

Selection criteria

Randomised controlled trials which compared thalidomide with either placebo or an active comparator were considered for inclusion.

Data collection and analysis

No trials met the inclusion criteria.

Main results

No studies that satisfied the inclusion criteria were found. In the absence of any suitable randomised controlled trial in this area, no analysis was performed.

Authors' conclusions

There is no evidence to support or refute the use of thalidomide or its analogue, lenalidomide, as maintenance therapy for patients with Crohn's disease. Given the teratogenic nature of thalidomide its use for maintenance therapy is difficult to justify. Well designed clinical trials are needed to evaluate the efficacy and safety of lenalidomide in Crohn's disease and its use is not recommended until these data are available.

PLAIN LANGUAGE SUMMARY

Thalidomide for maintenance of remission in Crohn's disease

Prevention of relapse is a key objective in the management of Crohn's disease. There is no current treatment available that completely maintains remission and is without significant side-effects. Thalidomide is sometimes used in clinical practice to attempt to maintain remission in Crohn's disease. This review found no randomised controlled trial that had investigated the role of thalidomide or a similar drug lenalidomide, for the maintenance of remission in Crohn's disease. There is currently no evidence to support or refute the use of these agents as maintenance therapy for Crohn's disease. However, given the well known risk of severe birth defects the use of thalidomide is not recommended. Lenalidomide has a much lower risk of causing birth defects and well designed randomised controlled trials are needed to investigate the effectiveness and side effects of this drug for maintenance of remission in Crohn's disease. The use of lenalidomide is not recommended until data from a well designed study are available to support its use.

BACKGROUND

There is no cure for Crohn's disease and treatment is mainly directed toward induction and maintenance of remission. Maintenance of remission is a major issue in the management of Crohn's disease. Corticosteroids, the mainstay of treatment of acute exacerbations are not effective for maintenance of remission and chronic use is limited by numerous adverse events. Recent studies suggest that tumour necrosis factor- α (TNF- α) antagonists such as infliximab (Rutgeerts 1999; Hanauer 2002; Sands 2004;), certolizumab (Schreiber 2007) and adalimumab (Colombel 2007; Sandborn 2007) are effective for maintenance of remission in Crohn's disease. An uncontrolled study suggests that thalidomide, a TNF- α production inhibitor, may have a role in the management of Crohn's disease (Ehrenpreis 1999), but it is not clear whether it is an effective maintenance therapy.

Thalidomide is best known for its role in the history of drug development when it caused an epidemic of severe birth defects in the mid twentieth century (McBride 1961). At that time it was already known that thalidomide also displayed favourable effects on erythema nodosum leprosum. Consequently the drug has been used for various diseases including Behçet disease, graft-versus-host disease, rheumatoid arthritis and inflammatory bowel disease (Sands 1999).

The therapeutic effect of thalidomide is mediated via suppression of tumour necrosis factor- α (TNF- α) synthesis by means of an enhanced degradation of messenger RNA (Bauditz 2002; Meierhofer 2003). In this regard, thalidomide may be an alternative to expensive TNF- α antagonists currently used for the treatment of Crohn's disease. As a small chemical compound it lacks the disadvantage of monoclonal antibodies that are immunogenic and have to be administered parenterally. Other effects of thalidomide such as decreasing levels of interleukin-12 (2) and blockade of leukocyte transmigration (Meierhofer 1999) provide additional rationale for studying its use in Crohn's disease.

In addition to case series (Bariol 2002; Kane 2002; Plamondon 2007), open label clinical trials in refractory Crohn's disease have been published, suggesting a beneficial effect of thalidomide (Ehrenpreis 1999; Gupta 2003; Vasiliukas 1999). In some of these studies, steroids could be tapered and symptoms of fistulae were reduced. A retrospective chart review of six paediatric patients who did not respond to infliximab therapy suggests that thalidomide may allow tapering of steroids and improve fistula healing (Gupta 2003).

Teratogenicity, peripheral neuropathy, and drowsiness are well known adverse effects of thalidomide that may preclude its long term use. Patients receiving thalidomide are required to use two effective contraceptive methods due to the highly teratogenic nature of the drug. These aspects are of particular interest when the drug is used as maintenance therapy. The aim of this systematic review is to summarize the efficacy and safety of thalidomide maintenance therapy for Crohn's disease.

OBJECTIVES

To evaluate the efficacy and safety of thalidomide and its analogue lenalidomide for maintenance of remission in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with treatment duration of at least 3 months.

Types of participants

Patients of any age with Crohn's disease whose disease was in remission at the time of entry into the study. Remission should have been defined with a recognised Crohn's disease activity index.

Types of interventions

Studies comparing thalidomide to placebo or active comparator.

Types of outcome measures

The primary outcome measure was the occurrence of clinical or endoscopic relapse as defined by the primary studies and expressed as a percentage of the number of patients randomised (intention to treat analysis). Secondary endpoints would include the occurrence of adverse events such as birth defects, peripheral neuropathy and drowsiness.

Search methods for identification of studies

A. Electronic search

The following electronic databases were searched for relevant studies:

1. MEDLINE (1966 to September 2008);
2. EMBASE (1984 to September 2008);
3. Cochrane Central Register of Controlled Trials (Issue 3, 2008) and
4. Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Group Specialised Trial Register.

The search strategy was not limited by language.

B. Reference searching

The references of all identified studies were inspected for more trials.

C. Personal contacts

Leaders in the field were contacted to try and identify other studies.

D. Drug companies

Manufacturers of thalidomide were contacted for additional information.

MEDLINE on PUBMED was searched using the following search strategy:

1. Crohn* disease
2. crohn disease (MESH)
3. regional enteritis
4. ileitis
5. ileitis (MESH)
6. inflammatory bowel disease
7. inflammatory bowel diseases (MESH)
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. thalidomide
10. thalidomide (MESH)
11. thalidomid

12. lenalidomide
13. lenalidomide (MESH)
14. 9 OR 10 OR 11 or 12 OR 13
15. remission OR relapse
16. disease-free survival (MESH)
17. 15 OR 16
18. 8 AND 14 AND 17

The above search strategy was adapted and used to search the other electronic databases.

Data collection and analysis

Step 1. Potentially relevant papers were identified by the two authors using the above search strategy.

Step 2. The authors, after reading the full texts, independently assessed the eligibility of all trials identified based on the inclusion criteria above.

Step 3. The methodological quality of selected trials was to be assessed independently by the two authors using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005) and the Jadad scale (Jadad 1996).

DATA COLLECTION

Data extraction was to be performed independently by the two authors. The authors aimed to separately extract and record data on the predefined checklist. Data to be extracted were to include the following items:

- a. characteristics of patients: age, sex, disease distribution, disease duration, disease activity index;
- b. total number of patients originally assigned to each intervention group;
- c. intervention: thalidomide or lenalidomide and dose;
- d. control: no intervention, placebo or other interventions;
- e. concurrent medications; and
- f. outcomes: time of assessment, length of follow up, type of Crohn's disease activity index used, definitions of remission and relapse, relapse rates, time to relapse, quality of life assessment, adverse events.

STATISTICAL ANALYSIS

The Cochrane Collaboration review manager (RevMan 5.0.17) was to be used for data analysis. Data were to be analysed according to the intention to treat principle, using as the denominator, the total number of patients randomised. The presence of significant heterogeneity among studies was to be assessed using the chi-square test. As the chi-square test has low power in the situation of a meta-analysis when trials have small sample size or are few in number, a P value of 0.10 was to be regarded as statistically significant. The effect of heterogeneity was to be quantified using the I^2 value. For pooled data, summary test statistics were to be derived using the odds ratio and 95% confidence intervals. A fixed effects model was to be used for pooling of data when statistical heterogeneity was not present.

Subgroup analysis

When possible, subgroup analyses were to be performed based on the following:

- a. age of participants {adults (>16 years) versus children};
- b. disease distribution;

- c. dose of thalidomide or lenalidomide;
- d. duration of treatment;
- e. concurrent medications (especially immunosuppressive agents such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine and mycophenolate mofetil); and
- f. length of follow up.

Sensitivity analyses

When necessary, sensitivity analyses were to be conducted based on the following:

- a. only including patients whose outcome is known (i.e. number of patients who completed the study used as denominator);
- b. random effects versus fixed effects models; and
- c. study quality.

RESULTS

Description of studies

After inspecting the titles and abstracts of articles, one study was initially thought to be potentially relevant (Sabate 2002). However, after reading the full text, this paper was excluded as it was not a randomised controlled trial.

Risk of bias in included studies

No suitable trials were identified for inclusion.

Effects of interventions

In the absence of any suitable randomised placebo-controlled trials in this area, no analyses were performed.

DISCUSSION

A systematic search of the medical literature did not identify any randomised controlled trials on the use of thalidomide or its analogue, lenalidomide for maintenance of remission in Crohn's disease. It therefore appears that the use these agents as maintenance therapy for Crohn's disease has not been subjected to appropriate randomised controlled trials. A number of uncontrolled studies and case reports suggest that thalidomide may offer some benefit in Crohn's disease, but the lack of comparison groups in these reports makes it impossible to evaluate the effects of this intervention. In a retrospective single centre study Plamondon and colleagues described the use of thalidomide in 25 patients with refractory Crohn's disease (Plamondon 2007). Although the patients in this study initially received the drug due to active disease, the data are of some interest for this review because the median follow up was 12 months fulfilling the criterion of treatment duration of at least 3 months. At the time of last follow-up (range 1 to 60 months) the median reduction in estimated CDAI from baseline was 212 points. Nine of 11 patients with active fistulizing disease responded to thalidomide (6 responses and 3 remissions). The authors concluded that thalidomide may be effective for the treatment of active Crohn's disease, although its long-term use is limited by toxicity. Adverse events were frequent, and twelve patients discontinued therapy due to adverse events such as neuropathy and drowsiness. In another uncontrolled study, Sabate et al investigated the role of thalidomide for the maintenance of infliximab-induced response in refractory Crohn's disease (Sabate 2002). Fifteen adults with severe, refractory Crohn's disease were started on thalidomide (100 mg daily) after they had responded to infliximab infusions. Patients

were followed up for a median of 238 days (range, 10-458 days). Remission rates on thalidomide were 92%, 83% and 83% at 3, 6 and 12 months, respectively, after the last infliximab infusion. Four patients stopped thalidomide for suspected adverse effects. The authors reported that adverse events which included drowsiness, rash and peripheral neuropathy were mild and mostly transient.

Whilst the results of these reports may be promising, it is important for thalidomide and lenalidomide to be subjected to appropriate clinical trials in order to allow a proper evaluation of efficacy and long-term safety. One known adverse effect of thalidomide that may make its use as a long term maintenance therapy problematic is teratogenicity. Whereas short-term use may be acceptable and safe in some patients when the strict need for contraceptive use is stressed, long-term use could become problematic in young adult patients with Crohn's disease.

AUTHORS' CONCLUSIONS

Implications for practice

The efficacy and safety of thalidomide or its analogue, lenalidomide, for the maintenance of remission in Crohn's disease have not been evaluated with randomised controlled trials. There is no evidence to support or refute the use of thalidomide or lenalidomide as maintenance therapy for Crohn's disease. Nonetheless, given the adverse effects of thalidomide including teratogenicity, its use for maintenance therapy is difficult to justify. The use of lenalidomide for maintenance therapy is not recommended until data from a definitive randomised controlled trial are available.

Implications for research

There are no randomised controlled trials on the safety and efficacy of thalidomide or its analogue, lenalidomide, for the maintenance of remission in Crohn's disease. Well-designed trials are needed. Given the teratogenic nature of thalidomide, randomised controlled trials of this agent may not be justified. However, the study of thalidomide analogues, such as lenalidomide, that have a low teratogenic risk are justified. Such trials should have adequate statistical power and adequate follow up period to allow long term assessments of benefits and harms. Outcome measures such as relapse prevention and health-related quality of life should be evaluated and attention should be paid to long-term adverse events.

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Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund.

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References to studies excluded from this review

Sabate 2002 {published data only}

Sabate JM, Villarejo J, Lemann M, Bonnet J, Allez M, Modigliani R. An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. *Aliment Pharmacol Ther* 2002;**16**(6):1117-24.

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Bauditz 2002

Bauditz J, Wedel S, Lochs H. Thalidomide reduces tumour necrosis factor alpha and interleukin 12 production in patients with chronic active Crohn's disease. *Gut* 2002;**50**(2):196-200.

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Meierhofer 1999

Meierhofer C, Dunzendorfer S, Wiedermann CJ. Protein kinase C-dependent effects on leukocyte migration of thalidomide. *J Infect Dis* 1999;**180**(1):216-9.

Plamondon 2007

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Rutgeerts 1999

Rutgeerts P, D'Haens G, Targan S, Vasiliauskas E, Hanauer SB, Present DH, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**(4):761-9.

Sabate 2002

Sabate JM, Villarejo J, Lemann M, Bonnet J, Allez M, Modigliani R. An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. *Aliment Pharmacol Ther* 2002;**16**(6):1117-24.

Sandborn 2007

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Sands 1999

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Sands 2004

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Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**(3):239-50.

Vasiliauskas 1999

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dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* 1999;**117**(6):1278-87.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Sabate 2002	Not a randomised controlled trial

WHAT'S NEW

Date	Event	Description
20 July 2009	Amended	Contact details updated

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 2, 2009

Date	Event	Description
17 February 2009	New citation required and conclusions have changed	Substantive amendment
2 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Anthony Akobeng conceived the idea for the review and coordinated the review. Anthony Akobeng and Pieter Stokkers jointly wrote the protocol for the review, independently applied the search strategy and prepared the final manuscript of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Crohn Disease [*drug therapy]; Immunosuppressive Agents [*therapeutic use]; Lenalidomide; Remission Induction; Thalidomide [analogs & derivatives] [*therapeutic use]; Tumor Necrosis Factor-alpha [antagonists & inhibitors]

MeSH check words

Humans