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REVIEW

A Systematic Review of Adverse Drug Reactions associated with Thalidomide in the treatment of Erythema Nodosum Leprosum

MARIAMA MAHMOUD* & STEPHEN L. WALKER**
**Lakka Government Hospital, Ministry of Health and Sanitation, Sierra Leone*
***Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London*

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Summary
Background: Erythema nodosum leprosum (ENL) is a painful, multisystem immune mediated complication of borderline lepromatous and lepromatous leprosy. The management of ENL may be complex and often requires prolonged administration of immunomodulatory drugs including thalidomide.
Thalidomide is very effective in controlling ENL although its mode of action in ENL is not well understood. Teratogenicity and cost limit its use in many settings. In addition to teratogenicity, thalidomide is reported to have a wide range of adverse drug reactions including neurotoxicity. The non-teratogenic adverse drug reactions associated with thalidomide in patients with ENL have not been systematically reviewed. We have reviewed the literature to determine the adverse drug reactions attributable to thalidomide in the management of ENL.
Methods: Several databases were searched using the relevant terms. Articles found were reviewed according to the PRISMA protocol. The eligibility of the articles was agreed by both authors.
Results: A total of 45 papers from 1965–2017 were systematically reviewed. Eight of these were randomised control trials (RCTs), nine non-randomised clinical trials, three prospective studies, five retrospective studies and 20 case reports.
The papers included 1,673 participants with 1,017 (61%) receiving thalidomide. The most frequent adverse drug reaction encountered was drowsiness, in 13·5%. The frequency of constipation was 13·4% and dizziness 6·8%. Other events were reported in less than 5% of participants. Severe adverse reactions such as pulmonary embolism and peripheral neuropathy were uncommon. Only one fatality was reported, the cause of which was uncertain. Thalidomide had to be withdrawn in 67% of individual case reports but only in four patients in the clinical studies.

Correspondence to: Mariama Mahmoud, Lakka Government Hospital, Ministry of Health and Sanitation, Sierra Leone (e-mail: m_mahmoud85@yahoo.com)

 0305-7518/19/064053+19 $1.00

Conclusions: Thalidomide is a potentially safe and effective drug for use in the management of ENL. There is limited information about thalidomide-induced neurotoxicity in patients with ENL and this needs further study.

Thalidomide is an effective alternative to long-term corticosteroids which have significant adverse effects. It must be administered in a closely supervised way and requires adherence to robust guidelines by prescribers.

Introduction

Erythema nodosum leprosum (ENL) or leprosy Type 2 reaction is an immune mediated inflammatory reaction which occurs in approximately 5–10% of people with borderline lepromatous (BL) leprosy and in up to 50% of individuals with lepromatous leprosy (LL).[1] The odds of LL patients developing ENL are 8·4 times greater than of individuals with BL leprosy. The odds for BL patients with bacteria index ≥ 4 are 5·2 times greater than BL patients with bacterial index < 4.[1]

ENL is a very painful condition.[2] It is characterised by the occurrence of crops of painful new cutaneous and subcutaneous nodules, which are often associated with fever. ENL is a multisystem disorder and may also affect the eyes, bones, kidneys, testes, joints, lymph nodes and peripheral nerves.[2]

The pathophysiology of ENL is not well understood. A large systematic review of the immunological studies of ENL found little evidence for immune complexes which are often cited as causing ENL. Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), IFN-γ and Interleukins 1 and 6 (IL-1, IL-6) may be increased in ENL patients but their role is unclear. The infiltration of high numbers of neutrophils and polymorphonuclear cells (PMN) into the lesions and throughout the dermis and subcutis is characteristic of ENL.[3,4] The recruitment of large numbers of neutrophils leads to their adhesion to endothelial cells and TNF-α production.

ENL is usually chronic and is often treated with high dose oral corticosteroids. The use of corticosteroids is associated with significant morbidity and mortality.[5]

Tachyphylaxis to corticosteroids occurs in ENL patients and necessitates increasing doses to control symptoms. Other agents such as thalidomide, clofazimine, minocycline, ciclosporin and methotrexate are used as alternatives or for "steroid-sparing".[6]

Thalidomide (α-phthalimido glutarimide) is a glutamic acid analogue first developed in 1954 in West Germany by the Chemie Grünenthal drug company. It was sold as an anti-emetic and a sedative.[7] It was widely used in Europe, Australia and Canada for treating anxiety, insomnia, gastritis, and for the management of morning sickness in pregnant women, before being found to be teratogenic.

Teratogenicity occurs between days 20–36 post-conception.[6] Phocomelia is the most commonly recognised feature of thalidomide embryopathy and is characterised by reduced or missing long bones, with the distal elements of the limb spared. Other structures affected include the eyes, external ear, the spine, palate, heart, kidneys, gastrointestinal tract and genitals. Thalidomide suppresses the insulin-growth-factor 1 (IGF-1) and fibroblast growth factor (FGF), which together stimulate limb initiation in utero.[8,9] A more recent study in 2013 identified cerebron (CRBN) as the primary target of thalidomide and its analogues, leading to teratogenicity.[10]

Thalidomide is used in a variety of dermatological, oncological and inflammatory conditions such as Behcet's disease, metastatic prostate cancer, lupus erythematosus, graft-vs-host disease, pyoderma gangrenosum, and sarcoidosis. Thalidomide and its analogues are used in the treatment of myeloma. In myeloma they exert their effect by binding to the CRBN complex promoting substrate degradation necessary for the management of myeloma and other B-cell malignancies.[10]

The anti-ENL effect of thalidomide was discovered serendipitously by Sheskin in 1964. He reported dramatic clinical improvement of individuals with ENL who were given thalidomide for sedation.[11]

A Cochrane review published in 2006 showed some evidence of benefit of thalidomide in the management of ENL.[12] More recently a prospective longitudinal study reported thalidomide to be superior to prednisolone in managing first episodes of ENL.[13] A randomised trial also reported a more rapid response of ENL to thalidomide than prednisolone, lower recurrence rates and longer remission periods.[14]

In a retrospective study of patients with ENL treated with thalidomide at the Hospital for Tropical Diseases, London, the doses used ranged from 12·5 mg–500 mg/day with a maximum effective median dose of 400 mg/day.[15]

A major concern about the use of thalidomide is its neurotoxicity and this is particularly the case in individuals with a pre-existing peripheral nerve disorders such as leprosy. Thalidomide induced peripheral neuropathy, diagnosed using nerve conduction studies, is frequently seen during the first year of treatment in dermatological conditions and has been reported to affect up to 20% of individuals.[16] It occurs as a painful paraesthesia, numbness, or weakness, affecting the feet and hands in a glove-and-stocking like distribution.[6] Nerve function impairment associated with ENL does not appear to respond to thalidomide and is usually managed with oral corticosteroids.[6] There are no tests which differentiate between thalidomide-induced neuropathy and nerve function impairment (NFI) due to leprosy.[17]

Thromboembolism is associated with thalidomide monotherapy in 3% of myeloma patients[18] but can increase to 14% when used in combination with corticosteroids.[6]

Other common adverse drug reactions (ADRs) listed in the summary of product characteristics for thalidomide include drowsiness or somnolence, dizziness, neutropenia and increased HIV viral load. Rarer ADRs of the drug include constipation, cardiac disturbances, peripheral oedema, rash, raised liver enzymes and amenorrhea. These unwanted effects do not always warrant the withdrawal of the drug and may be managed effectively during therapy.[19]

There are large systematic studies of the ADRs of thalidomide in patients with myeloma[29,16,18,20] but there are no such studies in individuals with ENL. We wished to conduct a systematic review of the ADRs associated with thalidomide therapy in ENL to determine their frequency and to inform clinical practice.

Methods

The World Health Organization defines an adverse drug reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[21]

All randomised control trials (RCTs), and cohort studies of thalidomide in patients with ENL and case reports of ENL managed using thalidomide after 1965 were included in this systematic review. Articles reporting adverse drug reactions with thalidomide in ENL were eligible for inclusion. The eligibility of the articles was agreed upon by the authors. Reference bibliographies from all reviewed publications were also examined to identify further relevant studies. There were no restrictions made based on the language in which the studies were reported. Reports of teratogenicity of thalidomide were not included in this study.

The following databases were searched up until the 13th August 2017 using the search strategy in Appendix 1: CINHAL plus, Cochrane, EMBASE, Global health, LILACS and PUBMED. Similar articles of relevant searches were also reviewed.

Google scholar database was searched using a combination of "leprosy or lepromatous", "leprosy reactions or type 2 reactions or ENL" and "adverse reactions of thalidomide". The first 100 relevant items from this search were selected for review.

The contents of issues of the Indian Journal of Leprosy (http://www.ijl.org.in/index.html), International Journal of Leprosy and Other Mycobacterial (http://www.leprosy-ila.org/leprosyjournal/gn1/default.php?ed=MTY1), and Leprosy Review (https://www.lepra.org.uk/leprosy-review-index) hosted on the journals' websites were searched manually to identify additional articles.

CRITICAL APPRAISAL

The quality of the included studies and reports was assessed based on: appropriate randomisation method; mode of allocation concealment; method of blinding; number of participants lost to follow-up; collection of adverse reaction data properly described; bias adequately minimised in recruitment, similar comparison groups or differences accounted for; appropriate sampling and measurement. Each criterion grouped as applicable to the type of study. Criterion were labelled Yes for adequate, No for inadequate, and U for unclear. See Appendix 2.

Results

A total of 808 papers were collected from all searches and from references. After removal of duplicates, 505 papers were excluded by screening of title and abstract, with 244 screened via full text review (Figure 1).

45 papers were included in this review of which, eight were randomised control trials (RCTs), nine non-randomised clinical trials, three prospective and five retrospective studies, 20 were case reports.

ANALYSIS OF 25 CLINICAL STUDIES

25 clinical trials were assessed during this study. 14 studies were published between 1965–1990, and 11 between 2005–2016. A total of 1,671 participants were recruited with 1,015 (61%) of these cases reportedly treated with thalidomide. The number of cases in the thalidomide group was unclear in one study and therefore not included in this percentage.[22] Studies with un-quantified adverse effects will not be included in the following quantitative analysis and will be discussed separately.

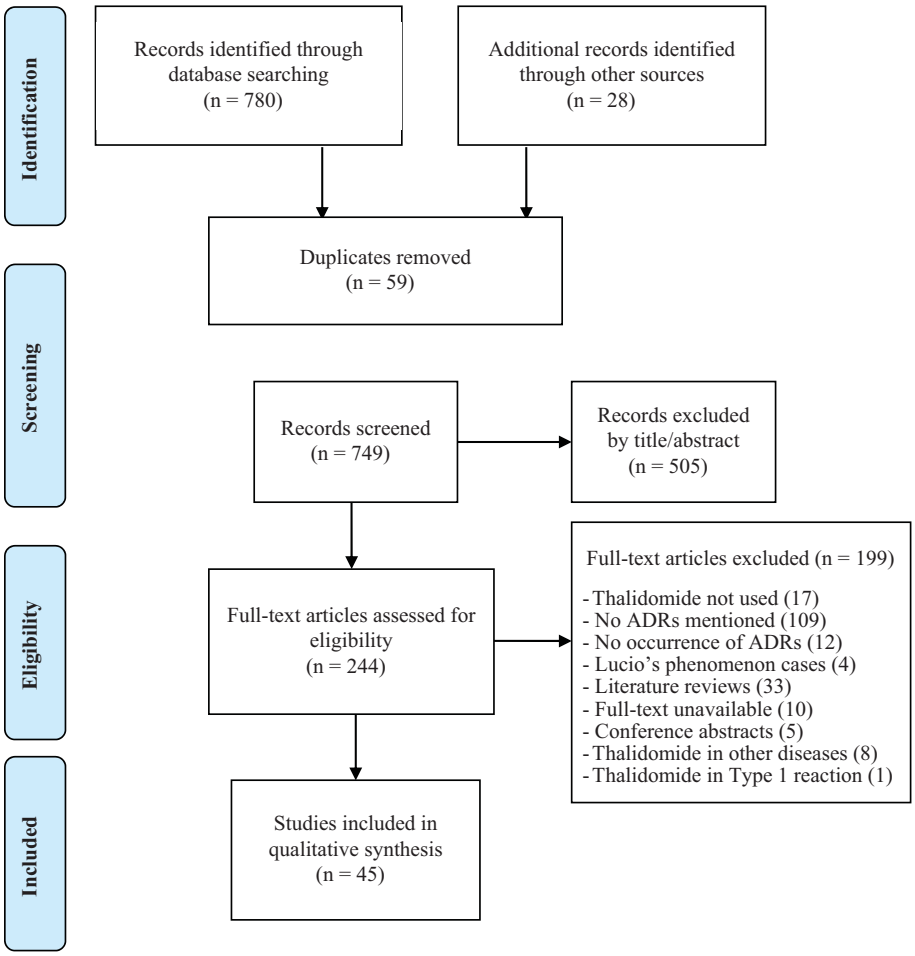

Figure 1. PRISMA flow diagram.

RANDOMISED CONTROLLED TRIALS

Eight of the 45 studies reviewed (18%) were randomised controlled trials, published between 1965 and 2009 (Table 1). The adverse drug reactions from thalidomide could not be quantified in one RCT and therefore it was not included in this analysis.[23]

In the seven studies where adverse reactions could be quantified, 268 participants were enrolled with 196 (73%) receiving thalidomide therapy. The male to female ratio was 7:1. Five of these studies were reported to be double-blinded,[24–28] Kaur's trial was not blinded (14) and the allocation concealment technique was unclear in one study.[29]

The daily dose of thalidomide ranged from 50 mg to 400 mg. Treatment with thalidomide varied between 7 days and 1 year. Four trials documented concomitant corticosteroid use in all or some of the patients.[25,26,28,29] Other studies either failed to mention the use of oral corticosteroids or prohibited its use during the trial period. In a double-blind, double-dummy, dose comparison RCT done by Villahermosa in 2005, patients who had taken corticosteroids

Table 1. Summary of RCTs

Author/Year of publication	Type of Study	Number of participants	Patients who received thalidomide	Daily dose of Thalidomide	Duration of therapy	Co-interventions	Side effects attributable to thalidomide
Kaur *et al*. 2009 [14]	RCT Not blinded	N = 60	N = 30 26M; 4F	300 mg tapered by 50 mg every 2 weeks	1 year	Prednisolone	Somnolence (30%) Pruritus (20%) Constipation (17%) Tremors (10%) Inability to concentrate (2 cases) Rash (1 case) Leukocytoclastic vasculitis (1 case) Amoebic dysentery (1 case)
Villahermosa *et al*. 2005 [27]	RCT Double-blind, double-dummy	N = 22	N = 12 N = 10 All male	0–100 mg tapered down 50–300 mg tapered down	7 weeks 7 weeks	None	Somnolence (75%) Rash (47%) Pruritus (38%) Vertigo (28%), Headache (20%) Nausea (1 case) Tremor (1 case) Constipation (1 case)
Iyer *et al*. 1971 [24]	RCT Double-blinding	N = 92	N = 50 All Male	100–400 mg	7 days or max of 2 weeks at a time, some for >5 years	Acetylsalicylic acid	Dizziness (34%) Mucosal dryness (26%) Headache (26%) Constipation (15%) Leucopoenia (14%) Drowsiness (13%) Oedema (11%) Nausea (9%) Rash (9%) Paraesthesia (6%) Itching (4%) Vomiting (1case) Urticaria (1 case) “Numbness” (1 case)

Table 1. *Continued*

Author/Year of publication	Type of Study	Number of participants	Patients who received thalidomide	Daily dose of Thalidomide	Duration of therapy	Co-interventions	Side effects attributable to thalidomide
Waters 1971 [28]	RCT Double blinding	N = 10	N = 10 All male	300 mg	7 weeks & 11 weeks	Prednisolone ACTH Dapsone	Sleepiness (20%) Allergic dermatitis & eosinophilia (20%) Transient rash & eosinophilia (20%) Perifollicular thickening of skin & eosinophilia (1 case) Constipation (1 case) Giddiness (1 case)
Pearson & Vedagiri 1969 [25]	RCT Double-blinding	N = 12	N = 12 11M; 1F	200–300 mg	6 weeks	MDT, Prednisolone, Stibophen	Drowsiness (2 cases) Mild dermatitis (1 case) Intestinal obstruction (1 case)
Sheskin & Convit 1969 [26]	RCT Double blinding	N = 59	N = 59 37M; 15F 7 patients doubly registered	100 mg or 6 mg/kg/d	129 days; one week at a time	Placebo (Sulfones & Corticosteroids continued in some cases)	Drowsiness (34%) Dizziness (14%) Nausea (12%) Increased appetite (10%), Urticaria (3%) Headache (1 case)
Sheskin 1965 [29]	RCT Blinding unclear	N = 13	N = 13 10M; 3F	200–400 mg	9 months	Dapsone Placebo Prednisolone	Drowsiness (77%) Constipation (69%) Dryness of oral & nasal mucosa (54%), Erythema of face & chest (38%), Pitting oedema (38%) Erectile dysfunction (31%) Vesiculobullous eruption (23%) Ravenous appetite for 6 months (1 case) Eczematous rash (1 case)

less than two weeks prior to the study were excluded.[27] MDT for leprosy had been initiated in majority of the trials done after 1982 and was continued after commencement of thalidomide.

Neurological ADRs reported in the RCTs

The studies reported rates of drowsiness/somnolence/sleepiness between 13 and 77%. Overall, 58 (29·6%) of 196 patients treated with thalidomide had drowsiness. Dizziness (including "giddiness" and "vertigo") was experienced by 1–28% of participants, with an overall of 28 (14·3%) of the 196 participants reporting this symptom. The proportion of headaches reported in the individual studies ranged from 2–26%. 15 (7·7%) patients reported headaches. There were three reports of "paraesthesia" and a case of unspecified "numbness" documented.[24] Kaur encountered two cases complaining of "inability to concentrate" during therapy.[14] One case of tremor was documented in an RCT done in 2005.[27]

Vascular ADRs

Peripheral oedema was reported in a total of nine (4·6%) of the 196 individuals on thalidomide treatment, with proportions between 11–38% per trial. A case of leukocytoclastic vasculitis occurred ten days into therapy and thalidomide was stopped.[14]

Gastrointestinal ADRs

Chronic or intermittent constipation was documented in 23 (11·7%) of the total 196 patients and either resolved spontaneously or was managed symptomatically with laxatives. The prevalence of constipation ranged from 1–69% in the studies. 19 (9·7%) patients were reported to have experienced oral and nasal mucosal dryness in two studies. Other gastrointestinal symptoms reported include six cases of increased appetite in one study, one case of vomiting and an account of ravenous appetite for six months. The only female patient enrolled in an RCT in 1969 developed intestinal obstruction of uncertain cause after nine weeks of thalidomide and was withdrawn from the study.[25] A patient with amoebic dysentery within two weeks of starting therapy also warranted withdrawal of the drug.[14]

Cutaneous ADRs

Of the 196 patients on thalidomide during the trial period, 22 (11·2%) had a cutaneous problem. 13 patients developed a "rash", three had dermatitis, three had urticaria and three were found to have vesiculobullous eruptions. The frequency of skin ADRs was highly variable. Some studies documented only one case of skin lesions whilst in other studies skin lesions occurred in 8–47% of participants. 12 (6·1%) other patients complained of itching or pruritus without skin lesions. There were five cases of erythema of the face and chest in a single study, and one case of "perifollicular skin thickening".

Genitourinary ADRs

Three patients complained of erectile dysfunction after 2 months of thalidomide therapy, whilst one participant reported to have not been able to have an erection for 7 months after commencement of the drug.[29]

NON-RANDOMISED CLINICAL TRIALS

Three of these nine clinical trials will be analysed with the studies with un-quantifiable adverse reactions of thalidomide. The rest of the trials included a total of 248 participants, all of which were on treatment with thalidomide in doses of 50 mg–400 mg daily (Table 2). The male to female ratio was 25:1.[30] The exposure to thalidomide was between 12 and 738 days.[30,31] The administration of oral corticosteroids to all or some groups of participants was documented in all but one trial.[32]

Neurological ADRs

The adverse drug reactions associated with thalidomide, drowsiness was reported by 25 (10·1%) of the 248 patients on therapy. One study reported only one case of drowsiness whilst in another it affected all the participants.[30,32] A total of ten reports of giddiness (11%) were documented in one trial.[33]

Vascular ADRs

Pedal oedema was found in a combined total of 23 cases (9·3%) from the 248 patients on thalidomide therapy.

Gastrointestinal ADRs

Constipation was the most frequently reported amongst the 248 patients on thalidomide. 24 patients (9·7%) complained of sustained or occasional constipation during therapy. All but two trials listed constipation as an ADR of thalidomide. Seven participants (2·8%), in one study, reported experiencing symptoms of "gastrointestinal upset". There was one case each of diarrhoea, oral mucosal dryness and flushing, and two cases of nausea. Two cases of abdominal pain warranted the reduction of the dose of thalidomide.[34]

Nine reports of ADRs were labelled "miscellaneous" in a trial done by Parikh in 1986.[31]

PROSPECTIVE STUDIES

Three prospective studies were included in this review. The male to female ratio more than 20:1. 87 out of a total of 203 participants (42·9%) in these studies were treated with thalidomide. Patients were started on thalidomide at doses between 100–400 mg daily (Table 3). The duration of therapy but spanned four months to less than three years in others was unclear in one study.[36]

Neurological ADRs

The most common adverse reaction mentioned was drowsiness/somnolence in 24 (27·6 %) of 203 cases. It was documented in 31% of individuals in one trial and in 95% of individuals in another. Six participants (3%), reported headaches, four patients complained of paraesthesia and dysesthesia (2%) and four patients encountered dizziness (2%) whilst on the drug. Guillain-Barre syndrome was diagnosed in one patient after three weeks of thalidomide

Table 2. Summary of non-randomised clinical trials

Author/Year of publication	Type of Study	Number of participants	Patients who received thalidomide	Daily dose of Thalidomide	Duration of therapy	Co-interventions	Side effects attributable to thalidomide
Dipak *et al*. 2012 [35]	Clinical trial	N = 21	N = 21 14M; 7F	100–300 mg tapered down	Unclear	Prednisolone	Nausea (10%) Drowsiness (38%)
Chaudhry *et al*. 2009 [30]	Clinical trial	N = 15	N = 15 Including 3F	50–300 mg tapered down	80–738 days	MDT Corticoteroids	Constipation (20%), Pedal oedema (20%), Drowsiness (1 case)
Jadhav *et al*. 1990 [33]	Clinical trial	N = 90	N = 90 All male	200–400 mg	25–>100 days	Corticosteroids NSAIDs Clofazimine	Giddiness (11%), Gastrointestinal upset (8%)
Parikh *et al*. 1986 [31]	Clinical trial	N = 94	N = 94 All male	50–400 mg tapered down	12–643 days	Dapsone Corticosteroids Clofazimine, Prednisolone	Pedal oedema (21%), Drowsiness (11%), Constipation (14%), "Miscellaneous" (10%), Diarrhoea, Flushing & Dryness of mouth (1 case each)
Chandorkar *et al*. 1984 [32]	Clinical trial	N = 6	N = 6 All male	100–400 mg tapered down	One month after duration of reaction	DDS, Clofazimine	Fatigue & Drowsiness (100%), Occasional constipation (100%)
Ramu & Girdhar 1979 [34]	Clinical trial	N = 22	N = 22 All male	100–300 mg tapered down	4 months	Clofazimine (Dapsone and corticoteroids in some cases)	Abdominal pain (1%) Constipation (1%)

therapy.[37] Symptoms of Guillain-Barre resolved completely after three months of withdrawal of thalidomide and did not recur on re-introduction of the drug for over a year.[37]

Vascular ADRs

There was one report of deep venous thromboembolism (DVT) in a patient receiving thalidomide and prednisolone, in a prospective longitudinal study.[13] Thalidomide therapy was discontinued after the occurrence of DVT.

Gastrointestinal ADRs

Constipation was documented in five of the 203 patients on treatment (2·5%), occurring in 10% of cases in one trial and in 19% of cases in another, whilst four patients experienced gastric fullness (2%). There was only one case of nausea documented in these studies.[36]

RETROSPECTIVE STUDIES

291 participants were reported in these three retrospectives studies. The male to female ratio was 7:1. The number of participants treated with thalidomide was 287 (98·6%). The lowest dose administered was 12·5 mg daily[15] (Table 4).

In De Las Aguas' study, the participants had stopped taking oral corticosteroids before starting thalidomide, but oral corticosteroids had to be restarted in a few patients because of "rebound" reactions.[38]

Neurological ADRs

6 and 15% of patients in two studies had documented drowsiness/sedation/sleepiness. 16 (61%) of patients had tiredness in one study.[39] Reported rates of dizziness of 10% and 15% in two trials. There was one report of peripheral neuropathy diagnosed following thalidomide therapy.[40]

Gastrointestinal ADRs

Constipation was the most frequently reported gastrointestinal adverse reaction associated with thalidomide therapy. The prevalence in the three studies was 3%, 15% and 50%. Two women in De Las Aguas' study experienced abdominal "tympanism".[38] Withdrawal of therapy was not necessary for these conditions.

STUDIES IN WHICH THE FREQUENCY OF THALIDOMIDE ASSOCIATED ADVERSE DRUG REACTIONS WERE NOT QUANTIFIED

ADRs attributable to thalidomide were mentioned in six studies but the numbers of patients experiencing these effects was not reported or was unclear.[23,41–45] The studies consisted of 661 patients with more than 197 on thalidomide therapy (29·8%). These groups comprised patients with a history of long-term usage of oral corticosteroids, patients who failed to respond to oral corticosteroids or patients with corticosteroid-dependency.[33,41,45] Convit did his trial amongst patients with history of corticosteroid treatment and without, but none was

Table 3. Summary of Prospective Studies

Author/Year of publication	Type of Study	Number of participants	Patients who received thalidomide	Daily dose of Thalidomide	Duration of therapy	Co-interventions	Side effects attributable to thalidomide
Kar & Gupta 2016 [13]	Prospective study	N = 80	N = 40 All male	400 mg tapered to 50 mg	20 weeks	MDT Prednisolone Clofazimine	Drowsiness (31%), Constipation (19%), DVT (1 case)
Valente & Vieira 2010 [36]	Prospective study	N = 20	N = 20 16M; 4F	100–200 mg	Unclear	Prednisolone MB-MDT	Somnolence (95%), Headache (30%) Gastric fullness (20%), Dizziness (20%), Paraesthesia and dysesthesia (15%), Constipation (10%), Nausea (1 case),
Magora *et al*. 1970 [37]	Prospective study	N = 103 61M; 42F	N = 27	300–500 mg tapered to 50–100 mg	>4 months to >3 years	Sulfones Prednisolone	Guillain-Barre syndrome (1 case)

Table 4. Summary of Retrospective Studies

Author/Year of publication	Type of Study	Number of participants	Patients who received thalidomide	Daily dose of Thalidomide	Duration of therapy	Co-interventions	Side effects attributable to thalidomide
Nabarro *et al*. 2016 [15]	Retrospective study	N = 30	N = 27 17M; 10F	12·5–500 mg	Median of 16 months	Prednisolone Clofazimine Azathioprine	Tiredness (61%), Constipation (15%), Dizziness (15%)
Rivett A.L.J. (Unpublished) 2010 [40]	Retrospective Study	N = 102	N = 101	100–300 mg tapered down to once every 10 or 15 days in some cases	Mean 14·9 months	Prednisolone MDT Clofazimine	Constipation (50%), Dizziness (10%), Sedation (6%), Peripheral neuropathy (1 case)
De Las Aguas 1971 [38]	Retrospective study	N = 159	N = 159 Including 26F	100–500 mg	45–85 days Average of 1 month	Corticosteroids	Sleepiness (15%), Constipation (3%), Abdominal tympanism (2 women)

administered throughout the trial period.[45] 80% of the subjects included in Darlong's study were already corticosteroid-dependent. Even though the adverse effects of the prolonged use of corticosteroids were seen to decline during treatment with thalidomide, 8 patients were reported to have died from its sequelae.[41]

In the retrospective study by Feuth NFI deteriorated in 25% of 36 ENL patients who received thalidomide and 14% of individuals who received corticosteroids. The authors found no significant difference but did suggest the possibility of thalidomide contributing to the deterioration.[42]

Other complaints included increased drowsiness, asthenia and somnolence. One study documented incidence(s) of peripheral oedema which was controlled by reduction of thalidomide dosage.[45] Constipation was documented in two of these studies whilst other studies had reports of nausea, mucosal dryness, and loss of appetite.

Case reports

The age range of individual cases was 19–70 years with only three reports of female patients aged 33, 37 and 61 years.[46–48] Two women of childbearing age were treated with thalidomide. The contraceptive means employed in these cases was unclear, but no report of pregnancy was recorded.[46–48] The maximum dose of thalidomide recorded was 400 mg.[49,50] All but two cases reported co-intervention with corticosteroids, one of which oral corticosteroids were discontinued before initiation of thalidomide.[51] Thalidomide was withdrawn as a consequence of its adverse effects in 12 cases.[48–50,52–60]

Vaso-occlusive disease was the most frequent ADR described in the case reports. All 12 reports of DVT occurred during joint therapy with corticosteroids, further strengthening the evidence of increased risk of DVT during combined thalidomide and corticosteroid therapy.[6] In one case DVT occurred as early as 6 days into therapy.[61] Sharma's case with adherent venous thrombosis had been on thalidomide for 3 weeks but developed DVT 5 days after co-intervention with pulsed dexamethasone-cyclophosphamide.[48] Cases were adequately managed using thromobolytics and a vena cava implant was administered in one case.[56] In four cases of thromboembolism, thalidomide therapy was restarted without any further issues following introduction of anticoagulants.[46,56,61]

Peripheral neuropathy was the second most common ADR reported in three patients, all of which resolved on withdrawal of the drug.[52,55,62] Neuropathy manifested in the form of new glove-and-stocking distribution sensory neuropathy or worsening of ENL induced neuropathy. One case of neuropathy was undoubtedly associated with thalidomide use by confirmation from nerve conduction studies.[62]

In addition to the ADRs reported in larger studies a patient with ENL who developed chromoblastomycosis and mucormycosis during corticosteroid and thalidomide therapy was reported.[63] Sudden unexplained death of a 70-year-old male patient on MDT and thalidomide was reported.[51]

Discussion

Thalidomide was introduced for use as a sedative; therefore, somnolence is expected to be commonly associated with use of the drug. It is therefore unpleasant for patients to perform daily

work-related as well as social activities whilst on thalidomide. This therefore limits its use in outpatients especially in severe ENL where high doses at increased frequencies will be required.

Management of cutaneous manifestations may be challenging due to the large spectrum of lesions manifested. Symptoms should therefore be monitored for and individualised for each patient.

Constipation is also frequently encountered and could have been missed or omitted in case reports in favour of more severe adverse events. Constipation can prove uncomfortable for patients. Patients should preferably be informed of the likelihood of this and managed appropriately if it occurs.

Peripheral neuropathy has been associated with thalidomide owing to demyelinatory and inflammatory changes observed via nerve conduction studies of patients on thalidomide.[16,64] In this review however, neuropathy recorded could not always be confidently associated with thalidomide. Differentiating between NFI of thalidomide and that caused by ENL is difficult.

The most commonly recorded ADR in the case reports was vasculo-occlusive disease. Thrombo-embolism was reported in one-third of the documented thrombosis cases.[52,53,65,66] Thrombosis in thalidomide therapy in other diseases is common especially when co-administered with glucocorticoids.[67] A project undertaken by the research on adverse drug events and reports (RADAR) documented the occurrence of 695 cases of venous thromboembolism among cancer patients treated with thalidomide, chemotherapy, and/or dexamethasone over a period of 8 years.[68] DVT has been reported in 30% of patients treated for myeloma in doses as low as 100 mg and without corticosteroid use,[20] in this review however, thromboembolic events ranked low on the list of ADRs associated with thalidomide therapy. Aspirin was used as a prophylaxis for thrombosis in a retrospective study involving 73 participants for a period of one year.[41]

Limitations of the study

Most trials either failed to include women of childbearing age or non-randomly assigned women to groups excluded from thalidomide.

Another drawback encountered is the quality of the papers reviewed (Appendix 2). Some of the best described and most recent studies were small and/or had a short duration of follow up. Studies without quantifiable ADRs were difficult to include in the review due to the constraints they pose for analysis. There was immense variability in data collection methods employed by the researchers making data extraction challenging.

ADR of thalidomide was not the primary point of any of the studies and were not always clearly defined. Concomitant administration of other drugs such as MDT and corticosteroids may influence the outcome of the treatment. ADRs reported could be due to other drugs administered or even due to the ENL reaction itself. As such, the ADRs reported in these studies cannot be entirely attributable to thalidomide.

Recommendations

IMPLICATIONS FOR PRACTICE

Thalidomide is a potentially safe and effective drug for use in the management of ENL episodes. Thalidomide can be used to decrease the adverse effects of long-term

corticosteroids and as an alternative to its use. Thromboembolism is a potentially fatal event and the role of prophylaxis in patients on both steroids and thalidomide requires further research.

Patients should be monitored closely for thalidomide related adverse effects. A programme similar to the STEPS programme should be followed for all patients on thalidomide. The possibility of subsidies from leprosy programmes should be considered in order to reduce the costs of thalidomide therapy borne by the patients.

IMPLICATIONS FOR RESEARCH

Large, prospective longitudinal studies of thalidomide use in ENL need to address the ADR profile of thalidomide in patients with ENL. Patient perceptions of the drug and its tolerability would be an important component of this.

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1. APPENDICES

1.1. Appendix 1: Search strategy

#1. Leprosy OR lepromatous OR lepra* OR "Hansen* disease"
#2. "Leprosy reaction" OR "lepr* reaction" OR "borderline leprosy" OR "type 2 reaction" OR "ENL" OR "erythema nodosum leprosum" OR "erythema nodosum" "lepromatous leprosy"
#3. Thalidomide OR thalidomide* OR immunoprin OR "α- (N-phthalimido) glutarimide
#4. "Adverse effects" OR "side effects" OR "harmful effects" OR "adverse events" OR "AE" OR "drug reaction" OR reaction OR "complications of" OR "adverse drug reaction"
#5. (#1 AND #2 AND #3 AND #4)

1.2. Appendix 2: Critical appraisal tables

RCTs	Appropriate randomization?	Concealment allocation?	Outcome data complete?	Dropout rate low?
Iyer *et al*. 1971	Yes	Yes	Yes	Yes
Kaur *et al*. 2009	Yes	Unclear	Yes	Yes
Pearson & Vedagiri 1969	Yes	Yes	Yes	Yes
Ramanujam *et al*. 1975	Yes	No	Yes	No
Sheskin & Convit 1969	No	Yes	Yes	Unclear
Sheskin 1965	Unclear	Yes	Yes	Yes
Villahermosa *et al*. 2005	Yes	Yes	Yes	Yes
Waters 1971	Unclear	Yes	Yes	Yes

Non-RCTs	Bias minimized?	Measurement appropriate?	Groups similar (or differences analysed)?	High response rate/appropriate follow-up
Chandorkar *et al*. 1984	No	Yes	Unclear	Yes
Convit *et al*. 1967	Unclear	Yes	Yes	Yes
Jadhav *et al*. 1990	No	Yes	Unclear	Yes
Parikh *et al*. 1986	No	No	No	Yes
Ramu & Girdhar 1979	No	Yes	Yes	Yes

Descriptive studies	Sampling appropriate?	Sample representative of population?	Measurement appropriate?	Complete data/high response rate?
Ahamed Riyaz *et al*. 2011	Unclear	Yes	Yes	Yes
Rivett A.L.J. 2010	Yes	Yes	Yes	Yes
Basilio *et al*. 2012	Unclear	Unclear	Yes	Yes
Brito *et al*. 2010	Unclear	Yes	Yes	Unclear
Budania & Kar 2014	Yes	Yes	Yes	No
Burdick & Ramirez 2005	Yes	Yes	Yes	Yes
Chaudhry *et al*. 2009	Unclear	Yes	Yes	Yes
Chhabria *et al*. 2017	Yes	Yes	Yes	Yes
Darlong *et al*. 2016	Yes	Yes	Unclear	Yes
De Las Aguas 1971	Yes	Yes	Unclear	Yes
Dipak *et al*. 2012	Unclear	Yes	No	No
Ferrari *et al*. 2002	Unclear	Yes	No	Yes
Feuth *et al*. 2008	Unclear	Yes	No	No
Forno *et al*. 2010	Unclear	Yes	No	No
Kar & Gupta 2016	No	Yes	Yes	Yes
La Rosa & Casciano 1968	Unclear	Yes	Unclear	No
Leon *et al*. 2015	Unclear	Yes	Unclear	No
Magora *et al*. 1970	Unclear	Yes	Yes	Yes
Medeiros *et al*. 2009	Unclear	Yes	Yes	Yes
Mehta 2008	Unclear	Yes	Yes	No
Nabarro *et al*. 2016	Yes	Yes	Yes	Yes
Petiti-Martin Hebe *et al*. 2013	Unclear	Yes	Yes	Yes
Ramien *et al*. 2011	Unclear	Yes	Yes	Yes
Salafia & Kharkar 1988	Unclear	Yes	No	No
Sharma *et al*. 2004	Yes	Yes	No	Yes
Sharma *et al*. 2005	Yes	Yes	Yes	Yes
Valente & Vieira 2010	Yes	Yes	Yes	Yes
Vetrichevvel *et al*. 2008	Yes	Yes	Yes	Yes
Yamaguchi *et al*. 2012	Yes	Yes	Yes	Unclear