A PROSPECTIVE STUDY OF SAFETY AND EFFICACY OF THALIDOMIDE IN DERMATOLOGY IN A TERTIARY CARE CENTRE - TAMILNADU

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INTRODUCTION

Thalidomide, an effective drug, once abandoned because of devastating teratogenic effects, has now re-emerged as an alternative treatment in many dermatologic conditions (1). In 1998, thalidomide became FDA approved for the treatment of the cutaneous manifestations of Erythema nodosum leprosum (ENL), Pyoderma gangrenosum (PG), Discoid Lupus erythematosus (DLE). Aims: The use of thalidomide in relation to dermatology is well-known. Enough data is available in the literature about various aspects of thalidomide. Our study aims to assess the safety and efficacy of Thalidomide in patients with ENL, PG, DLE and psoriasis who were refractory to conventional treatment.

Settings and Design: The study was done in the Dermatology Department, Govt. Stanley medical college hospital using a prospective study design.

Methods and Material: The study was an open label, prospective interventional study. The study population included 20 patients each of ENL, Pyoderma gangrenosum, psoriasis and 10 DLE patients. Inclusion and Exclusion criteria were fulfilled.

Statistical analysis used: not mentioned.

Results: The response to thalidomide was excellent in 3 of the 4 conditions we studied. Our study implies that Thalidomide can be safely and effectively used in the treatment of ENL, Pyoderma gangrenosum, DLE, though the clinical response to treatment in Psoriasis is not much satisfactory.

Conclusions: Thalidomide with its excellent tolerability can be used for many dermatological conditions as an alternative when other modalities are contraindicated or ineffective.

Key-words: Thalidomide, ENL, DLE, Pyoderma gangrenosum, Psoriasis.

Key Messages: Thalidomide is safe and effective.

SUBJECTS AND METHODS

Patients were included in the study after a written and informed consent was obtained. The age of the patient, sex and duration of disease and a detailed history was taken. Clinical examination to assess the extent of skin/mucosal involvement was done. All exclusion criteria were ruled out. The diagnosis was confirmed clinically and histopathologically. Patients were then evaluated for their baseline parameters such as complete blood count, renal and liver function tests. Pregnancy test was done for all females in the reproductive age group. For ENL, thalidomide was started at a dosage of 200 mg/day given for 3 weeks and tapered by 50 mg every 3 weeks and maintained at 50 mg for 6-8 weeks. Patients with Pyoderma gangrenosum were started with 200 mg/day for 4 weeks and tapered by 50 mg every 2 weeks and maintenance dose of 50 mg for 4-6 weeks. DLE patients were started with 200 mg/day for 4 weeks, given in tapering doses and maintained at 50 mg for 2 months. For psoriatic patients, 200 mg/day was given for a month, tapered by 50 mg every
month and maintained at 50 mg/day for 6 weeks. The response to thalidomide was assessed and the time taken for initial improvement till complete resolution of lesions was recorded. We also observed the side effects occurred during treatment. The patients were regularly followed up with pregnancy tests weekly for first 4 weeks, then monthly for women of child bearing potential, CBC including absolute neutrophil count, LFT monthly till dose is stable, then every 2–3 months. Neurologic examination was done monthly for the first 3 months, then once in every 6 months. They were followed up for a period of 24 weeks.

RESULT
(Table 1,2)
Patients with pyoderma gangrenosum showed symptomatic resolution in 1 week and ulcer started to shrink in size by 2-4 weeks. Marked decrease in the size of ulcer was noted around 6-8 weeks. In the follow-up period of 24 weeks there was no recurrence. DLE cases symptomatically improved by 1-2 weeks. Erythema, size and thickness of the lesions started to come down by 3-6 weeks and markedly improved by 12 weeks. They had no recurrence in follow-up period of 24 weeks. Symptomatic resolution in ENL patients was noted in 2-3 days. Resolution of lesions began by 1-2 weeks and markedly improved by 6-10 weeks. There was no subjective response in plaque type of psoriasis. Only 20% of patients showed reduction in erythema and scaling by 4 weeks. Moderate response with 50% reduction in PASI score was seen in 20% of cases by 12 weeks of therapy.

DISCUSSION
Most of the biological effects of thalidomide are related to its anti-inflammatory, immune-modulator and anti-angiogenic properties (15, 16). It decreases the polymorphonuclear cell chemotaxis and mono-

<table>
<thead>
<tr>
<th>DERMADES</th>
<th>IMPROVEMENT</th>
<th>COMPLETE RESOLUTION OF LESIONS</th>
<th>FOLLOW UP</th>
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</thead>
<tbody>
<tr>
<td>Poderm gangrenosum(fig.1,2,3,4)</td>
<td>Shrinkage of the ulcer size noted by 2-4 weeks</td>
<td>Marked reduction in size around 6-8 weeks</td>
<td>For 24 Weeks. No recurrence</td>
</tr>
<tr>
<td>DLE (fig.5,6)</td>
<td>Decrease in erythema, size and thickness of the lesion by 3-6 weeks</td>
<td>Complete resolution by 10-12 weeks</td>
<td>For 24 weeks. No recurrence</td>
</tr>
<tr>
<td>Erythema nodosum Leprosum(fig.7,8)</td>
<td>Resolution of ENL nodules begins within 1-2 weeks</td>
<td>By 6-10 weeks</td>
<td>For 24 weeks. No recurrence</td>
</tr>
<tr>
<td>Plaque type psoriasis(fig.9,10)</td>
<td>Erythema &amp; scaling persisted after 6 weeks in 80% patients. Remaining 20% response seen after 4 weeks</td>
<td>Poor response to therapy even after 12 weeks in 80% of patient. Moderate response in remaining 20%</td>
<td>PASI score: 20% reduction in 80% patients. 50% reduction in 20% patients</td>
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Table 1: Clinical response to thalidomide therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Subjective Response (symptomatic resolution)</th>
<th>Objective Response (clinical resolution)</th>
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<tbody>
<tr>
<td>Erythema nodosum</td>
<td>2-3 days</td>
<td>6-10 weeks</td>
</tr>
<tr>
<td>Leprosum</td>
<td>1 week</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLE</td>
<td>1-2 weeks</td>
<td>10-12 weeks</td>
</tr>
<tr>
<td>Plaque type psoriasis</td>
<td>Persistence</td>
<td>Poor response</td>
</tr>
</tbody>
</table>

Table 2: Subjective and objective response

<table>
<thead>
<tr>
<th>Side effects</th>
<th>No: of patients (%)</th>
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</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Tremor</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
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Table 3: Side effects observed
cyte phagocytosis. (4) Thalidomide can selectively decrease tumor necrosis factor α (TNF-α) production, possibly by reducing TNF-α messenger RNA levels. Antagonism of inflammatory mediators such as histamine, acetylcholine, prostaglandins and serotonin has been demonstrated. Studies by Sheskin in 1965 and Iyer et al in 1971 showed significant superiority of thalidomide in the treatment of Erythema Nodosum Leprosum (13, 14). There have been many anecdotal reports of the use of thalidomide to treat recalcitrant Pyoderma gangrenosum. Eight previous cases have been reported in the medical literature. (5-12) Two of these patients (8, 9) had coincidental Behçet syndrome and two (6, 11) had significant mucosal involvement (penile and pharyngeal). In all the reported cases, Pyoderma gangrenosum was recalcitrant to treatment with corticosteroids, although specific dosages were not always reported. Dosages of thalidomide ranged from 100 to 400 mg/d. In most cases, the cutaneous lesions were reported to have responded within few weeks of the initiation of therapy. The studies in the treatment of psoriasis with thalidomide are not convincingly sufficient. Thalidomide in treatment of psoriasis is not much satisfactory as evident by our study. Studies regarding thalidomide on chronic cutaneous lupus erythematosus suggest that thalidomide is effective in the treatment of severe skin manifestations of lupus refractory to other treatment. Many patients noticed improvement within 2 weeks of starting thalidomide and in all maximum benefit was achieved within 16 weeks.

Only physicians and pharmacists registered with the STEPS (System for Thalidomide Education and Prescribing Safety) are permitted to prescribe and dispense the product. Female patients of childbearing potential must have a negative pregnancy test within 24 hours of treatment initiation. Patients must use reliable contraception for a period of at least 1 month before initiating therapy and must continue this practice during and for 1 month after therapy is completed. Male patients are required to use latex condoms, even in patients who have had a vasectomy.

Adverse effects of thalidomide are teratogenicity, peripheral neuropathy, drowsiness, nausea, constipation, thromboembolism, neutropenia, hypoglycaemia, bradycardia, SJS, TEN, erythroderma, brittle fingernails, xerostomia, xerosis, pruritus etc. Our experience suggests that thalidomide can be effectively used in the treatment of ENL, Pyoderma gangrenosum, DLE. Though not much satisfactory response is obtained in the treatment of psoriasis, future studies regarding this may be a necessity. Thalidomide is a double-edged weapon. The adverse effects particularly teratogenicity effect should be given due consideration. If used judiciously, it can work miracles in many recalcitrant conditions. The response is good with respectable remission period. Lower starting doses appear to be effective in the majority of patients and may improve drug tolerability. The risk of symptomatic drug induced neuritis can be minimized by careful follow-up. Thalidomide with its excellent tolerability can be used for many dermatological conditions as an alternative when other modalities are contraindicated or ineffective.
Fig 4: Pyoderma gangrenosum after thalidomide

Fig 5: Discoid lupus erythematosus (DLE) before thalidomide

Fig 6: DLE after thalidomide

Fig 7: Erythema nodosum leprosum (ENL) before thalidomide

Fig 8: ENL after thalidomide
REFERENCES