Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behçet’s disease: use of neurophysiological studies to detect thalidomide neuropathy

J M M Gardner-Medwin, N J Smith, R J Powell

Abstract

Objective—To examine the efficacy, dose, and safety profile, including neurophysiological testing of thalidomide used in 59 patients (including 23 with Behçet’s disease) to treat severe oral or genital ulceration (OGU).

Methods—We identified prospectively subjects (including women of childbearing potential) who had persistent OGU over periods lasting one to 40 years and whose active ulceration was not controlled by other therapies. They were treated with thalidomide. Retrospectively, we identified the number of subjects with complete resolution of the ulcers at one and two months of thalidomide therapy, and the dose required to maintain that improvement in those individuals who relapsed after stopping thalidomide. The decrease from the baseline sensory nerve action potential (baseline SNAP) amplitude value (derived from median, radial and sural nerve SNAPs) at which the development of paraesthesiae was likely to occur was also determined.

Results—Complete resolution of the ulcers occurred in 81% of patients within one month of thalidomide therapy at doses of 200 mg/day. No further thalidomide was required by 20% of patients responding and in the remainder improvement was maintained with smaller doses (7–200 mg/day). Using an approximate 50% decrease from baseline SNAP as an indication to discontinue thalidomide, the incidence of symptomatic neuropathy was 13-5%. No patients with a decrease of less than 42% developed neuropathy, and a further 13-5% were asymptomatic with a decrease in SNAP between 42 and 69%. Other side effects were seen in 44% of patients. There were no pregnancies and no requirement for urgent pregnancy testing.

Conclusions—Thalidomide provided a useful therapeutic option in severe oral and genital ulceration which had not responded to other therapies. The physician must remain vigilant to the continuing danger of axonal neuropathy and teratogenesis at all times during thalidomide therapy.

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Thalidomide was given in smaller doses of 100 mg/day until the ulcers cleared. The total doses of thalidomide received were in the range 0.56–152 g over periods of 8–3369 days.

NEUROPHYSIOLOGICAL STUDIES

To detect early changes suggestive of axonal neuropathy, SNAP amplitudes of the median, radial, and sural nerves were recorded by standard techniques in a temperature controlled environment by the same observer for all readings in 46 subjects. After baseline readings, studies were repeated every six months or after each 10 g of thalidomide if this occurred earlier.

In the early phase of our thalidomide usage, nerve conduction studies were not performed before treatment in 14 patients. Although all 14 had received less than 7 g before their first study, it became apparent that this could be misleading, as one patient had evidence of axonal neuropathy on his first recording despite only receiving 2.8 g of thalidomide. Subsequently, recordings of SNAP before treatment was begun became mandatory.

In normal subjects the radial nerve has a significantly larger SNAP amplitude than both the median and sural nerves. Consequently, when the baseline SNAP value was calculated for each patient, the amplitudes of the three nerves (median, radial, and sural) required equal weighting. For this purpose the SNAP amplitude for each individual nerve at the initial reading was deemed to be 100%, and the three summed. A decrease of approximately 50% from this baseline total percentage SNAP (baseline SNAP) was prospectively selected as an indication of subclinical neuropathy, and thalidomide was discontinued.

SUBSET ANALYSIS

Data from a group of 12 patients who had required long term thalidomide treatment necessitating more than four SNAP measurements during their therapy, were analysed further. The amplitudes of the individual nerves and their total SNAPs were calculated and plotted against the cumulative dose of thalidomide, the daily dose of thalidomide, and the duration of thalidomide therapy to determine if the clinical development of peripheral neuropathy could be predicted.

Results

THERAPEUTIC EFFICACY

The efficacy of thalidomide in the whole cohort was such that 81.3% were ulcer free at one month, and 84.7% ulcer free at two months. Of those with idiopathic OGU, 91.6% were ulcer free at one and two months, and in Behçet’s disease 73.9% were ulcer free at one month and 82.6% at two months. For the other diagnoses, 72.7% patients were ulcer free within two months. A further two patients improved but never became ulcer free, and seven stopped thalidomide because of side effects before improvement was noted. Of the
Table 1  Relationship between dose and duration of thalidomide therapy (time between the first and last dose of thalidomide) and the degree of deterioration in sensory nerve action potential amplitudes (SNAP)

<table>
<thead>
<tr>
<th>Decrease from total SNAP</th>
<th>Cumulative dose (g)</th>
<th>Duration of therapy (days)</th>
<th>Cumulative dose with time (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50% (n = 34)</td>
<td>50-46 (15-2-89-8)</td>
<td>464 (8-25-55)</td>
<td>0.147 (0.004-0.378)</td>
</tr>
<tr>
<td>≥50% (n = 16)</td>
<td>47-82 (17-3-115)</td>
<td>1079-5 (28-3369)</td>
<td>0.08 (0.013-0.2)</td>
</tr>
</tbody>
</table>

Values are mean (range); n = number of patients.

50 patients who responded to thalidomide, 36 (Behçet’s 16, idiopathic OGU 14, other six) required either a single further course, or low dose continuous thalidomide therapy for recurrence of the ulcers. The range of doses required to maintain control of the ulcers was 7–200 mg/day. Of the five patients who could not tolerate thalidomide because of side effects, three nevertheless showed a sustained reduction in both severity and duration of ulcers after receiving thalidomide. Thalidomide had no obvious effect on the other features of these patients’ diseases.

Table 1 shows the doses of thalidomide.

SIDE EFFECTS
Symptomatic neuropathy
Eight of 59 individuals (13.5%) developed paraesthesia of hands and feet; only one of them developed a painful neuropathy classically associated with thalidomide (patient with SLE, tuberculosis and metastatic carcinoma of the breast). Four of the eight had Behçet’s disease (two of whom were the only patients taking cyclosporin A concurrently with thalidomide), a single patient had idiopathic OGU and the remaining three comprised the

Table 2  Individual percentage decreases from the total sensory nerve action potential amplitudes (SNAP) at the time of stopping thalidomide because of deterioration in the nerve conduction tests, in eight patients who were symptomatic and eight who showed symptoms of neuropathy

<table>
<thead>
<tr>
<th>Decrease in total SNAP (%)</th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-0</td>
<td>51-4</td>
<td>48-4</td>
</tr>
<tr>
<td>49-0</td>
<td>48-4</td>
<td>48-2</td>
</tr>
<tr>
<td>57-4</td>
<td>62-7</td>
<td>67-1</td>
</tr>
<tr>
<td>53-7</td>
<td>53-7</td>
<td>57-4</td>
</tr>
<tr>
<td>42-6</td>
<td>47-4</td>
<td>47-2</td>
</tr>
<tr>
<td>59-4</td>
<td>64-3</td>
<td>67-1</td>
</tr>
<tr>
<td>52-6</td>
<td>64-3</td>
<td>67-1</td>
</tr>
<tr>
<td>54-3</td>
<td>51-4</td>
<td>64-3</td>
</tr>
</tbody>
</table>

Table 3  Percentage decrease from the baseline total sensory nerve action potential amplitudes (SNAP) in all patients with a >40% decrease from baseline, in whom subsequent SNAP measurement was made after stopping thalidomide, and time interval between the two measurements, in patients with and without paraesthesia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Decrease from baseline total SNAP</th>
<th>Time between measurement (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At time of stopping thalidomide (%)</td>
<td>At subsequent measurement (%)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>51-4</td>
<td>26-0</td>
</tr>
<tr>
<td>2</td>
<td>48-4</td>
<td>38-6</td>
</tr>
<tr>
<td>3</td>
<td>62-7</td>
<td>42-2</td>
</tr>
<tr>
<td>4</td>
<td>53-7</td>
<td>28-0</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>69-0</td>
<td>31-2</td>
</tr>
<tr>
<td>2</td>
<td>49-8</td>
<td>25-8</td>
</tr>
<tr>
<td>3</td>
<td>42-6</td>
<td>13-0</td>
</tr>
</tbody>
</table>

individuals with SLE and metastatic carcinoma of the breast, mixed cryoglobulinaemia, and Hodgkin’s disease with pyoderma gangrenosum. In patients who developed neuropathic symptoms the total SNAP amplitudes had decreased by 47-4-64-3% from the initial baseline readings (table 2).

Four of these eight patients with paraesthesia had further measurements after stopping thalidomide and these showed an improvement in baseline SNAP, albeit within the 30% variability (table 3). No further deterioration was noted in the total SNAP amplitude of any patient after thalidomide withdrawal. Six patients reported an improvement in their symptoms, one indicated no change and one died (patient with SLE, tuberculosis and metastatic carcinoma of the breast) before reassessment.

The patient with Behçet’s disease and co-existent diabetes mellitus had no demonstrable peripheral neuropathy at any time.

Asymptomatic deterioration in baseline SNAP: putative subclinical neuropathy
Eight individuals without paraesthesia (five with Behçet’s disease and three with idiopathic OGU) had a decrease of 42-6-69% from baseline SNAP (table 2) and their thalidomide was discontinued. Subsequently, three of these individuals had further SNAP recordings after stopping therapy; two showed improvement of >30%, and one showed an improvement of less than 30% (table 3). None of these patients became symptomatic after stopping thalidomide.

Comparison of the 16 patients with clinical and putative subclinical neuropathy with the 34 patients with a decrease of less than 42% showed that the duration of thalidomide treatment was longer in those with ‘neuropathy’, but there was no difference between the total cumulative doses of the two groups. These data are summarised in table 1. The daily average dose per patient was less in the neuropathic group, reflecting the low doses of thalidomide in those receiving long term therapy, as opposed to the greater dose in those receiving intermittent courses. Within the group of 16 neuropathic individuals, asymptomatic subjects (n = 8) received a larger cumulative dose for longer (mean 51-42 g over a mean of 1221-1 days) than did symptomatic subjects (n = 8) (mean 44-23 g over a mean of 937-9 days). For the complete cohort, the rate of deterioration for a given patient could not be predicted.

Serial SNAP in long term treatment
 Twelve patients received thalidomide treatment for longer than two years and consequently had undergone more than four nerve conduction studies; their data were analysed further. In seven of these patients thalidomide was withdrawn because of a >50% reduction in amplitude from baseline SNAP (range 51-69%, mean 57-24%); two of the seven developed symptoms suggestive of peripheral neuropathy. All seven stopped thalidomide. Only three of them subsequently
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SNAP amplitudes were measured as indication of axonal neuropathy because conduction velocities would not be expected to show significant early changes. In 1991 the poor reproducibility of SNAP in documenting progressive neuropathy was described by Chaudry et al. and detailed by Bleasel et al. The latter report demonstrated a wide range of variability in the individual nerve sensory amplitudes between serial measurements in normal subjects at constant temperature: median 26-9%, ulnar 32-1%, sural nerves 31-2%. We noted a similar variability in the amplitude for the individual nerves (figure) and chose to use the sum of the amplitudes of the three nerves, to minimise the dominant contribution of the radial nerve. If patients had a decrease of >30% from baseline SNAP, we repeated the test sooner than planned.

Our observations and a study of thalidomide in discoid lupus erythematosus by Knop et al. highlight the importance of baseline studies in the interpretation of changes in SNAP. Our experience suggests that a single baseline SNAP recording may create difficulties in the interpretation of the significance of SNAP changes, and that two studies before the commencement of treatment are needed to improve the interpretation of subsequent change, by allowing the calculation of confidence limits for each patient. Alternatively, to control for the analytical and biological variation, a large normal population should be studied so that critical differences can be established.

All patients demonstrated an overall decrease from baseline SNAP values whilst taking thalidomide. Prospectively, we decided to repeat SNAP measurements every six months or after 10 g of thalidomide if this was sooner. We also selected a decrease of approximately 50% as an indication to stop thalidomide. In retrospect, this was a reasonable estimate of the critical level of deterioration in SNAP associated with paraesthesia; however, it was too high, as it failed to predict symptoms in all patients. No patient with a decrease in total SNAP of less than 42% developed symptoms. Thus any patient with a >30% decrease in SNAP from baseline (which therefore exceeds the expected variability) should be considered to have demonstrated a significant deterioration in SNAP, and should have their treatment with thalidomide monitored even more closely.

In the literature the reported incidence of peripheral neuropathy in patients taking thalidomide appears to vary between conditions. In prurigo nodularis it approaches 100%, contrasting with discoid lupus erythematosus in which the incidence is approximately 28%. Leprosy may be a special case, confounded by lepromatous neuropathy; however, the incidence does seem genuinely to be low. In idiopathic OGU/Behçet’s disease, the reported incidence of neuropathy, albeit in small numbers, lies between 23 and 50%.

Careful monitoring with regular neurophysiological studies has resulted in lower incidence of symptomatic neuropathy (13-5%) in our...
patients. Even in those patients with paraesthesiae, an improvement in symptoms was seen after thalidomide was stopped.

Differences between the OGU patients developing neuropathy and those who did not included concurrent cyclosporin A therapy and underlying malignancy. We suggest that patients with additional risk factors for the development of neuropathy should be monitored with increased vigilance, including more frequent SNAP measurements. The importance of warning patients to stop thalidomide with the development of paraesthesiae must be stressed, as electrophysiological testing in our protocol failed to anticipate the clinical symptoms in eight of the 59 patients. The need to stop thalidomide before the development of symptoms, or immediately they develop, is emphasised. After stopping thalidomide, six of the eight patients with symptoms of peripheral neuropathy showed an improvement in their symptoms, but these did not resolve in all. This contrasts with the work of Fullerton et al., who observed individuals with longstanding painful neuropathy secondary to thalidomide and noted some improvement or recovery in 50% and no change in the remainder. In addition, we have shown that those patients considered to have subclinical neuropathy also demonstrated an improvement in the SNAP after stopping thalidomide.

The rate of deterioration from baseline SNAP for a given patient could not be predicted accurately from their dose or duration of therapy. Consequently, individual patients must be monitored regularly for the duration of thalidomide therapy with baseline and regular electrophysiological testing. Prospectively we chose the criteria 10 g of thalidomide or six months of therapy, whichever was earlier, as the intervals for repeating nerve testing. This was not sufficiently frequent in all patients as neuropathy did develop, and shorter periods between tests would be required to prevent the onset of neuropathy in all patients.

We observed a lower incidence of clinical neuropathy, particularly painful neuropathy, than previously described with thalidomide therapy, and suggest that regular monitoring with SNAP contributed to this outcome. However, peripheral neuropathy did occur in this cohort, and we present our observations to highlight the complex issues arising from the management of patients treated with thalidomide, which would benefit from further clinical studies.

The continued, albeit limited, use of thalidomide must recognise the significant neuropathic and teratogenic potential of this drug. Special clinical vigilance is demanded to maintain the safest possible use of thalidomide for disabling conditions such as severe OGU which have failed to respond to conventional medication. Its safe use should be assisted by this description of our clinical experience over 10 years, and the recent development of a clinical guideline to promote the safest possible use of thalidomide.21

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