**Letter to the Editor**

**PULSE DEXAMETHASONE, ORAL STEROIDS AND AZATHIOPRINE IN THE MANAGEMENT OF ERYTHEMA NODOSUM LEPROSUM**

We describe here therapeutic results of intravenous dexamethasone pulse therapy given at 4-week intervals, together with azathioprine 50 mg daily, in three patients with severe and recurrent ENL having poor control even with 80 mg of prednisolone daily.

A 43-year-old male patient was hospitalized in October 2000 with recurrent crops of generalised erythematous, tender nodulo-plaque lesions associated with high grade fever, chills, rigors and arthralgia for the last 3 years. The symptoms would subside temporarily with analgesics, antibiotics and rest. He also had a history of ulceration and burning sensation over the lesions and extremities, nasal stuffiness, crusting and epistaxis.

On admission he was afebrile, had bilateral pitting pedal edema and tender, firm to soft generalized lymphadenopathy. Systemic examination was normal. Cutaneous examination revealed multiple, erythematous, warm and tender nodulo-plaque lesions of variable size. Some of these were annular shaped and others showed ulceration, particularly on extremities. There was lesional as well as glove and stocking hypoaesthesia. The ulnar, radial cutaneous, lateral popliteal and posterior tibial nerves were bilaterally thickened and tender but no motor deficit was seen. Slit smear showed 6+ BI and smear from the pre auricular lymphnode aspirate was highly positive for acid-fast bacteria. Except for raised erythrocyte sedimentation rate (130 mm in first hour) haemogram was normal. Other laboratory parameters including blood biochemistry, urinalysis and chest X-ray were normal. With the diagnosis of lepromatous leprosy with erythema nodosum leprosum (ENL), he was started on MDT-MB, ampicillin and ibuprofen.

After 2 weeks, he developed a fresh crop of ENL lesions, fever (100–101°F), arthralgia and increase in the size and tenderness of lymph nodes. At this stage, indomethacin (25 mg tid) was added and clofazimine was increased to 100 mg thrice daily. As the patient continued to have fresh ENL lesions, high fever (103–104°F), increased nerve tenderness and arthralgia, 40 mg prednisolone daily was added. After an initial improvement for a week he had fresh exacerbation of his signs and symptoms and his general condition deteriorated further. Addition of chloroquin 250 mg twice daily to the existing regimen of steroids did not help, and due to vertigo it had to be discontinued after a week. The dose of prednisolone was increased to 80 mg daily but even after 12 days of this treatment, the patient continued to have high fever (104–105°F), tender lymphadenopathy, nerve tenderness without motor deficit and poor general condition. At this point it was decided to give him dexamethasone pulse therapy, which was already being used successfully for the treatment of pemphigus. The regimen consisted of giving 100 mg dexamethasone in 500 ml 5% glucose by a slow intravenous infusion over 2 h and repeating this dose on 3 consecutive days. In addition azathioprine 50 mg daily was added for its steroid sparing effect. The MDT-MB was continued and the dose of prednisolone was reduced to 60 mg daily after the dexamethasone pulse.

By day 3 after completion of the first dexamethasone pulse, he became afebrile and his general condition improved. The subsequent course of therapeutic response is shown in Table 1. The patient is

Correspondence to: V. K. Mahajan (e-mail: nandlals@hotmail.com)
presently on MDT-MB, azathioprine 50 mg daily and prednisolone 10 mg on alternate days. He is asymptomatic and general condition is improved, with weight gain. The only side effect seen was diarrhoea during the initial two dexamethasone pulses, which could be controlled with ciprofloxacin and tinidazole.

The second patient, a 50-year-old female having lepromatous leprosy with BI 6+, developed ENL after starting MDT-MB in August 2000. She was given MDT-MB with clofazimine 300 mg daily and analgesics along with any one of colchicine, zinc sulphate, pentoxifyllin or chloroquine initially but without much relief. Her symptoms could only be ameliorated by prednisolone 80 mg daily. She continued to have flare-ups whenever the dose of prednisolone was reduced below 80 mg daily. She had already developed iatrogenic glaucoma and osteoporosis of the spine.

In January 2001, dexamethasone pulse therapy and azathioprine 50 mg daily along with MDT-MB was started after the encouraging response seen in case 1 (Table 1). She is currently on MDT-MB, azathioprine 50 mg daily and 20 mg prednisolone on alternate days.

Another 40-year-old female patient with lepromatous leprosy, BI 6+, had recurrent ENL for more than 1 year since August 1999. She was under treatment with MDT-MB, analgesics, clofazimine 300 mg daily, zinc (as sulphate) and 80 mg prednisolone daily. On five or six occasions in the past, whenever the dose of prednisolone was reduced to less than 60 mg daily, she would get fresh ENL lesions, often pustular, along with systemic symptoms. She had already developed iatrogenic cushingoid features and was under treatment for glaucoma. She was operated for bilateral cataract during this period in May to June 2001.

After our experience of other two cases, she was started on intravenous dexamethasone pulse therapy and azathioprine 50 mg daily in consultation with ophthalmologist. She became asymptomatic after the sixth pulse. The dose of prednisolone was reduced after each dexamethasone pulse. At present, she was on MDT-MB, azathioprine 50 mg daily and 20 mg prednisolone on alternate days at the time of her last visit (Table 1).

**Discussion**

The management of ENL is guided by the need to control the acute inflammation and neuritis, to provide pain relief, save the eye and prevent further attacks. All the currently available treatment modalities have some or the other drawback and are not always effective in all the patients.

Prednisolone is the anti-inflammatory of choice in moderate, severe and recurrent ENL, being easily available, and having a definite and early therapeutic action. A starting dose of 60 mg is recommended by most workers, but doses as high as 200 mg/day may be needed. Patients with chronic and recurrent ENL on steroids are at greater risk of becoming steroid dependant. The higher immunosuppressive doses of steroids for prolonged periods often result in side effects. More or less all these factors were observed in all the three of our patients.

Intravenous methylprednisolone is now well established in the treatment of various disorders. Its role in ENL has only been speculated on recently, and no clinical trial/study is available. We have good clinical experience and data available in the use of dexamethasone intravenous pulse therapy in the treatment of pemphigus patients. Its use in our three ENL patients has shown early subsidence of ENL, thus reducing morbidity, hospital stay and the side effects seen with conventional use of steroids.

Azathioprine has been used in various dermatological conditions in the past. It is a purine antagonist derived from 6-mercaptopurine by the addition of an imidazole ring. It mainly affects rapidly dividing cells, especially of the bone marrow. Thus the principal side effects are bone marrow depression, gastrointestinal upsets and oral ulcerations. Cutaneous infections, neoplasia and haematopoietic tumours are the other side effects seen on its long-term use. It has been found to be effective along with prednisolone, both as an immunosuppressive and steroid sparing agent, for the treatment of reversal reaction in a small study. All our ENL patients had less severe or no ENL as therapy with
<table>
<thead>
<tr>
<th>Time period</th>
<th>Dose of prednisolone (mg/day)</th>
<th>Before dexamethasone pulse</th>
<th>After dexamethasone pulse</th>
<th>No. of dexamethasone pulses</th>
<th>Clinical response</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td></td>
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<tr>
<td>0 days</td>
<td>80</td>
<td>60</td>
<td>1st pulse</td>
<td></td>
<td>Poor general condition, neuritis, generalized lymphadenopathy (LAP) and severe ENL lesions</td>
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<td>2 weeks</td>
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<td>50</td>
<td></td>
<td></td>
<td>Afebrile, neuritis and LAP lessened, new ENL lesions stopped</td>
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<tr>
<td>3 weeks</td>
<td></td>
<td>40</td>
<td></td>
<td></td>
<td>Above features improved further</td>
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<tr>
<td>4 weeks</td>
<td></td>
<td>40</td>
<td>2nd pulse</td>
<td></td>
<td>Further improvement continued</td>
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<tr>
<td>8 weeks</td>
<td></td>
<td>30</td>
<td>3rd pulse</td>
<td></td>
<td>For mild recurrences of ENL with systemic symptoms</td>
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<td>12 weeks</td>
<td></td>
<td>20</td>
<td>4th pulse</td>
<td></td>
<td>Mild recurrences of ENL, mild nerve tenderness</td>
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<tr>
<td>16 weeks</td>
<td></td>
<td>20 and 10 on alternate days</td>
<td>5th pulse</td>
<td></td>
<td>Asymptomatic/discharged from hospital</td>
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<tr>
<td>20 weeks</td>
<td></td>
<td>10</td>
<td>6th pulse</td>
<td></td>
<td>Mild recurrences of ENL, no nerve tenderness</td>
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<td>24 weeks</td>
<td></td>
<td>10 and 5 on alternate days</td>
<td>7th pulse</td>
<td></td>
<td>Asymptomatic/no nerve tenderness</td>
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<td>Case 2</td>
<td>5 months</td>
<td>80</td>
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<td></td>
<td>Recurrent ENL, systemic symptoms, nerve tenderness, iatrogenic glaucoma and spine osteoporosis. After initial mild recurrences patient became fully asymptomatic after 11th dexamethasone pulse</td>
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<tr>
<td>Case 3</td>
<td>20 months</td>
<td>80</td>
<td></td>
<td></td>
<td>Recurrent ENL, often purpuric, nerve tenderness, systemic symptoms, iatrogenic cushingoid, glaucoma, premature cataract. Moderate recurrences. Asymptomatic after 6th dexamethasone pulse</td>
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Prednisolone reduced by 10 mg/day after each dexamethasone pulse (as above) till 20 mg on alternate days.
dexamethasone pulse and azathioprine progressed. Their disease could be controlled on low doses of prednisolone when combined with azathioprine. In fact, the general condition of the first patient had deteriorated so much before starting dexamethasone pulse therapy that we, as well as his family, had almost lost hope of his survival.

We make no attempt to speculate the mechanism of this approach in treating ENL. The suprapharmacological, immunosuppressive doses of dexamethasone given at regular intervals probably inhibit proliferation and regeneration of antibody producing cells (J. S. Pasricha, personal communication). Azathioprine is known to inhibit B-cell proliferation and antibody production and diminish T-cell mediated responses such as cytokine production. It probably also inhibits monocytic and polymorphic nuclear function and suppresses prostaglandin synthesis via inhibition of cyclo-oxygenase activity.\(^{7}\) The involvement of all these immunological components of inflammation in ENL is well elucidated.\(^{11}\) However, azathioprine acts slowly and has no effect on intraneural edema and its use is only recommended as an adjunct with corticosteroids.\(^{12}\)

The only side effect seen with this mode of treatment was diarrhoea during the initial two pulses in case 1. The exact reasons for this are unknown, but it is considered to be due to bacterial or candidal overgrowth and stops after two or three pulses (J. S. Pasricha, personal communication). None of the patient had haematological or other adverse effects due to azathioprine.

In view of the limited number of patients, it is too early to comment on the efficacy of this treatment modality. More trials are needed to reach any definite conclusion, find its full potential and devise a schedule.

Department of Dermatology
I.G. Medical College
Shimla 171001 (H.P.)
India

VIKRAM K. MAHAJAN
N. L. SHARMA
R. C. SHARMA
ASHOK SHARMA

References