Lepr Rev (2013) **84,** 105–112

LETTER TO THE EDITOR

Using Methotrexate to treat patients with ENL unresponsive to steroids and clofazimine: A Report on 9 patients

DELWAR HOSSAIN
Professor and Head, Department of Dermatology and Venereology, University of Science and Technology Chittagong, Foy's Lake, Pahartoli, Chittagong, Bangladesh

Accepted for publication 21 December 2012

Summary
Introduction: Erythema nodosum leprosum (ENL) is a chronic recurrent systemic complication of multi-bacillary leprosy frequently associated with the development of neuritis, iritis, orchitis, arthritis and dactylitis. It is well managed by thalidomide, but thalidomide is not available in Bangladesh. The World Health Organization recommends high doses of clofazimine and prednisolone. About 19% of patients do not respond completely to this regimen or experience relapse when reducing steroid dosage.
Objective: We undertook this study to determine whether oral prednisolone combined with methotrexate was an effective and safe treatment regimen for individuals with ENL resistant to clofazimine and prednisolone.
Methodology: Between September, 2006–June, 2011, we treated nine resistant ENL patients with a combination of prednisolone and methotrexate for 24–36 months with a mean duration of 30 months.
Result: We observed improvement leading to persistent remission of ENL in all our patients. Adverse effects were mild weight gain, weight gain with facial swelling, folliculitis and extensive *Pityriasis versicolor* infection in one patient and crusted scabies in another.
Conclusion: A combination of prednisolone and methotrexate was safe and effective in managing ENL not controlled by clofazimine and prednisolone.

Introduction

Erythema Nodosum Leprosum (ENL) is a chronic recurring complication of multi-bacillary leprosy particularly lepromatous leprosy (LL) and borderline lepromatous leprosy (BL). It is an immune complex mediated systemic complication having potential for damaging skin

Correspondence to: (e-mail: Delwar_ustc@yahoo.co.uk)

0305-7518/13/064053+08 $1.00

and mucous membrane, peripheral nerves, liver, spleen, kidneys, eyes, testes, lymph nodes, small muscles and bones of hands and feet. There is an acute inflammatory infiltrate composed mainly of, neutrophils, eosinophils and mast cells in the early stage together with oedema in the dermis and sub-cutis. There may also be features of vasculitis and panniculitis[1] in some patients.

Thalidomide[2–3] is the drug of choice for the management of ENL unresponsive to prednisolone. However, the government of Bangladesh has banned the drug due to its teratogenicity.

The Bangladesh national committee for leprosy control has adopted the guidelines of World Health Organization (WHO) in treating leprosy and managing its complications including ENL. Consequently, we treat all ENL with the combination of a high dose of clofazimine e.g. 100 mg three times daily for 3 months followed by 100 mg twice daily for 3 months and 100 mg once daily for 3–6 months and prednisolone, 1 mg/kg/day (40–60 mg) as an initial dose and then tapering the dose to end the course within 3 months. The regimen is effective in 81% of all ENL-reactions (our data). However, 19% of patients with severe ENL reaction do not respond completely to this regimen and experience relapse during attempts to reduce their steroid below 15–20 mg/day. In 25% of individuals, treatment has to be stopped because of adverse effects of prednisolone. In 15% treatment has to be stopped because of abdominal pain and unacceptable generalised pigmentation from high doses of clofazimine (our data). Our experience of tailoring the clofazimine and prednisolone regimen for individual patients has been disappointing.

In 2004 Kar BR and Babu R[4] reported a case of steroid resistant severe Type 2 reaction that they managed with methotrexate and high dose prednisolone. Here we report on the treatment on nine patients with severe ENL that did not respond to treatment with long term prednisolone and clofazimine.

Methods

The study was approved by the Institutional Review Board of the University of Science and Technology Chittagong and was undertaken in the leprosy clinic of the university.

Nine patients with ENL not controlled by prednisolone and clofazimine were enrolled between September 2006 to June 2011.

Each patient was examined their neuromuscular function was charted. Slit skin smears (SSS) for acid-fast bacilli were made and mean bacteriological index (BI) calculated. Routine blood, urine and stool examination, liver and kidney function tests and serum electrolytes were recorded.

Patients were treated with prednisolone and methotrexate. The initial dose of prednisolone was either 30 mg/day (for patients with body weight <45 kg) or 40 mg/day (for patients with body weight $>$ 45 kg). This initial dose was continued for 3–6 months, then reduced by half and then very slow tapered to end the course of prednisolone after 30–36 months. In addition methotrexate was given in a dose of 2·5 mg twelve hourly three doses weekly for first 24–30 months (Table 1).

Patients were followed up monthly for the first year and quarterly for next 2 years. Follow up included clinical examination, measurement of blood pressure, fasting blood sugar, routine blood and urine test, vision test and body weight.

Table 1. Our study regimen

Drugs	Dose	Duration
Prednisolone	Body wt 45 kg: 30 mg/day and above 45 kg: 40 mg/day	
	30 mg or 40 mg/day as initial dose	3–6 months
	15 mg or 20 mg/day	6–9 months
	10 mg or 15 mg/day	3 months
	5 mg or 10 mg/day	3 months
	or 5 mg/day	3 months
	5 mg alternate day	3–6 months
	5 mg twice weekly	3 months
	5 mg once weekly	3 months
	2·5 mg once weekly	3 months
		30–36 months
Methotrexate	2·5 mg (one tab) 12 hourly three doses every week	24–30 months
Total duration: 2–3 years		

Results

Patients were adults aged 23–52 years (mean 34 years). Seven were male and two female weight 42–65 kg (Table 2). All had MB leprosy (LL-5, BL-4) with BI $1{\cdot}45^{+}$–$4{\cdot}32^{+}$. Their ENL reactions developed before starting MDT in four cases, during MDT in two cases and after stopping MDT in three cases. They all gave histories of multiple hospital admissions and at least two WHO-recommended anti-ENL regimens. They had taken MDT (MB) regularly and had been suffering from reaction for 12–18 months with an average of 16·66 months while they were on WHO recommended prednisolone and clofazimine. All had characteristic painful and tender papules and nodules associated with fever, body ache, joint pain, weakness and anorexia. Two patients had ulcerated skin lesions, two had neuritis (painful, tender enlarged nerve with function loss), one had a nerve abscess, one iritis, two orchitis and one arthritis/dactylitis. The mean BI of slit skin smears ranged from 1·45–4·32.

In response to treatment, systemic symptoms of fever, body ache and joints pains resolved within 2–4 weeks; skin lesions improved within 4–8 weeks and resolved completely within 9–15 months. Iritis, orchitis and arthritis/dactylitis, resolved in 2–2·25 years. Neuritis took 2–3 years to resolve completely. There was some recovery of lost function. Slit skin smears became negative in all patients within 2·5 years. Patients were able to resume a normal enjoyable life within 2–3 years of starting treatment (Table 3). No patient relapsed during 12–15 months after stopping treatment.

Early attempts to reduce the dose of prednisolone from 15 mg or 20 mg per day led to the appearance of new small skin nodules. The problem was overcome by prolonging the duration of the maintenance dose from 3 to 6 or even 9 months, sometimes with the addition of paracetamol 500 mg twice daily for two weeks. Later, attempts to wean the patients off prednisolone led to mild joint pains, muscles cramps and discomfort, perhaps from steroid dependency. We overcame this by prolonging the duration of 5 mg/alternate day regimen from 3 months to 6 months, and the addition of 2 weeks courses of paracetamol.

We did not note any serious clinical or laboratory adverse effects attributable to treatment. However one patient gained weight, one developed facial swelling, 2 had attacks of multiple folliculitis and one an episode of extensive *Pityriasis versicolor* infection.

Table 2. Patient profile at enrollment in our study

	P-1	P-2	P-3	P-4	P-5	P-6	P-7	P-8	P-9
Age (in years)	28	29	32	39	31	23	45	28	52
Sex	M	F	M	M	M	M	M	F	M
Weight (in Kg)	65	55	48	57	49	45	65	42	52
Type of Leprosy	LL	BL	LL	LL	LL	BL	BL	BL	LL
Average BI	2·66	2·16	3·89	4	4·32	2·93	1·45	2·89	3
Category of ENL reaction	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Organs other than skin involved	Nerve abscess	Dactylitis	Orchitis	Orchitis	Iritis	–	Neuritis	Neuritis	–
MDT (MB) received	1 year	1 year	1 year	1 year	1 year	1 year	1 year	1 year	1 year
WHO anti- ENL regimen received	1·5 yrs	1·5 yrs	1·5 yrs	1·5 yrs	1·5 yrs	1·5 yrs	1 yr	1·5 yrs	1 yr
Maintenance dose of Prednisolone found	20 mg daily	15 mg daily	20 mg daily	20 mg daily	20 mg daily	20 mg daily	20 mg daily	20 mg daily	20 mg daily

P: Patient; M: Male; F: Female; LL: Lepromatous Lepromatous leprosy; BL: Borderline Lepromatous leprosy; BI: Bacteriological Index; and MDT (MB): Multi Drug Therapy (Multi Bacillary).

Table 3. Outcome of anti-ENL treatments

Symptom/Sign	Duration	Frequency	Response to Prednisolone and Methotrexate (Observed by the author)	Response to Prednisolone and Clofazimine (As per record)
Patient, 1–9 Fever Body ache Joint pain Discomfort Anorexia Weakness	4–6 weeks with each attack of ENL	2–3 attacks yearly	Quick relief within 2–4 weeks	Quick relief within 2–4 weeks
Patient, 1–9 Painful/Tender skin lesion Papule Nodule Pustule Ulcer	4–12 weeks	2–3 episodes per year	Apparent disappearance by 4–8 weeks and complete and persistent disappearance by 9–15 months	Apparent disappearance by 4–8 weeks
Patient, 1, 7–8 Nerve lesion Pain Tenderness Enlargement Firmness Abscess Autonomic function loss Sensory function loss Motor function loss	≥1–1·5 years	Continuous and worsening with new attacks of ENL reaction	Severity reduces by 4–12 weeks and persistent remission with improved function by 2–3 years	Severity reduced by 4–12 weeks
Patient, 5 Eye lesion Painful red eye Watering Reduced light reflex Reduced vision	1·5 years	Continuous and worsening with new attacks of ENL reaction	Improvement by 4–8 weeks but persistent remission by 2 years	Improvement by 4–8 weeks

Table 3. *Continued*

Symptom/Sign	Duration	Frequency	Response to Prednisolone and Methotrexate (Observed by the author)	Response to Prednisolone and Clofazimine (As per record)
Patient, 3–4				
Testicular lesion Painful tender testes Enlargement Testicular atrophy Nodular testes Nodular vas	1·5 years	Continuous and worsen with new episodes of ENL reaction	Gradual improvement by 4–12 weeks and persistent remission by 2·25 years	Gradual improvement by 4–12 weeks
Patient, 2				
Arthritis / Dactylitis Painful tender joints Difficulty in movement Swelling of joints Function loss	1·5 years	Continuous and worsen with new episodes of ENL reaction	Gradual improvement by 8–12 weeks and persistent remission by 2·25 years	Gradual improvement by 8–12 weeks
Patient 1–9				
Average BI	Positive for 3·5–6 years	Remained positive	Reduced gradually and became negative by 1·5–2·5 years	Reduced in value but did not become negative
Patient 1,2 and 7				
Side effects	≥1 year	3 patients out of 9	Mild abdominal pain, mild weight gain and Norwegian scabies from Prednisolone and no side effects of from Methotrexate	Abdominal pain, swollen face, weight gain, infection and striae from Prednislone and abdominal pain and generalized brown pigmentation from Clofazimine, warranted patients to be non-compliant
Patient 1–9				
Reaction free Period	4–8 weeks when patients were on higher doses of Prednisolone		Observed in all after 15 months with our treatment	Relapse experienced at an attempt to reduce Prednisolone from 15–20 mg/day
Patient 1–9				
Resuming normal work			All resumed normal work and are happy at the end of treatment	Not observed in any of the study patients

These subsided within six months of stopping treatment. One patient developed crusty scabies that responded to a topical scabicide.

Discussion

The nine patients in this study had been suffering from severe ENL, which was unresponsive to conventional treatment with clofazimine and prednisolone, and which had relapsed when the daily dose prednisolone was reduced below 15–20 mg. Using a combination of prednisolone and methotrexate for a period of 30–36 months we observed a steady, gradual improvement leading to persistent remission of ENL in all the patients. No serious adverse effects were seen. Till now (December, 2012), we have not seen any relapse in treated patients. That means they remained free from relapse for last 30–33 months since completion of our regimen.

In managing this special group of patients, we targeted the chronic nature of ENL and monitored slit skin smear positivity. Hence the initial doses of drugs were maintained till the reaction was well controlled. Prolonged maintenance dose of prednisolone and subsequent very slow tapering prevented further relapses and managed the more chronic complications of iritis, orchitis, arthritis and neuritis. Slit skin smear results fell to zero during the treatment period.

Treatment of non-responsive ENL is challenging. Infliximab[5] and etanercept[6] have been found useful, but they are prohibitively expensive and their long term complications have not been assessed. Oral zinc,[7] azathioprine[8] and high dose clofazimine[9–10] have also been found helpful but are far from ideal and have their own limitations.

Non-availability of thalidomide forced us to look for more effective and less hazardous regimens. Prednisolone inhibits chemotactic function of polymorphs, T-lymphocytes, monocytes, basophils and eosinophils and impairs mediator release from T-lymphocytes, mast cells and macrophages.[11] Methotrexate can suppress primary and secondary antibody responses[12] and has potential as a steroid sparing agent. Thus, both the drugs have mechanism-based anti-ENL activities and their combination could be additive and useful. We therefore combined reducing doses of prednisolone with a low dose methotrexate to minimise dose related complications, while maximising benefit in controlling ENL. It was our strategy to reduce prednisolone by 5 mg decrements every 3 months (as compared with every 2 weeks as recommended by WHO), with quarterly extensions of the duration of a particular dose if necessary, to achieve at least three consecutive problem-free months.

The mean duration of ENL while under treatment with prednisolone and methotrexate was 13 (range 9–15) months for cutaneous features and 28 (range 24–36) months for other organs involved. These figures illustrate the chronicity of ENL, especially of ENL in the eye, testis, bones and joints of the hands and the peripheral nerves. And bring into question the current WHO recommendations for relative short courses of treatment. It is also interesting that despite the long duration of anti-inflammatory drugs, there was also a role for a simple analgesic, such as paracetamol, to complete the weaning process.

One could hypothesise that it takes up to 15 months for prednisolone to bring complex ENL under control, and that a similar period of treatment is required to prevent later relapse. The possible role of methotrexate in controlling ENL and preventing relapse is unknown.

Ours was an outpatient based treatment and although it is a regimen of 2–3 years' duration, it proved to be successful and acceptable to the patients. Although the number of

patients treated was small and the study was uncontrolled, the regimen represents a useful step towards individualisation of treatment in difficult-to-manage ENL in the field. More formal studies are indicated.

Acknowledgements

I would like to thank Sultan Mohammed Elias Uddin, Leprosy Control Officer (LCO), The Leprosy Mission International-Chittagong programme, for referring patients and delivering home visit, and Dr. Virgil Aravinda Thomas, Interne, University of Science and Technology Chittagong, for his help in editing the manuscript.

References

[1] Mabalay MC, Helwig EB, Tolentino JG. The histopathology and histochemistry of erythema nodosum leprosum. *Int J Lepr*, 1965; **33**: 28–49.
[2] Pearson JM, Vedagiri M. Treatment of moderately severe erythema nodosun leprosum with thalidomide-a double blind controlled trial. *Lepr Rev*, 1969; **40**: 111–116.
[3] Iyer CG, Languillon J, Ramanujam K *et al.* WHO coordinated short-term double-blind trial with Thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ*, 1971; **45**: 719–732.
[4] Kar BR, Babu R. Methotrexate in resistant ENL. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 480–482.
[5] Faber WR, Jensema AJ, Goldschmidt WF. Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med*, 2006; **355**: 739.
[6] Ramien ML, Wong A, Keystone JS. Severe refractory erythema nodosum leprosum successfully treated with the tumor necrosis factor inhibitor etanercept. *Clin Infect Dis*, 2011; **52**: e133–e135.
[7] Mahajan PM, Jadhav VH, Pakti AH *et al.* Oral Zinc therapy in recurrent erythema nodosum leprosum: a clinical study. *Indian J Lepr*, 1994; **66**: 51–57.
[8] Verma KK, Srivastava P, Minz A, Verma K. Role of Azathioprine in preventing recurrence of ENL in a patient. *Lepr Rev*, 2006; **77**: 225–229.
[9] Iyer CG, Ramu G. An open trial with clofazimine in the management of recurrent lepra reaction using thalidomide as a control drug. *Lepr India*, 1976; **48**(Suppl-4): 690–694.
[10] Schreuder PA, Naffs B. Chronic recurrent ENL, steroid dependent: long-term treatment with high dose clofazimine. *Lepr Rev*, 2003; **74**: 386–389.
[11] Lester RS. Corticosteroids. *Clin Dermatol*, 1989; **7**: 80–97.
[12] Hersh EM, Carbone PP, Wong VG *et al.* Inhibition of primary immune response in man by anti-metabolites. *Cancer Res*, 1965; **25**: 1997–2001.