MANAGEMENT OF RESISTANT ERYTHEMA NODOSUM LEPROSUM WITH PROLONGED METHOTREXATE AND PREDNISOLONE: A REPORT ON 9 PATIENTS

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Summary

Introduction: ***Erythema Nodosum Leprosum is the chronic recurrent systemic complication of multi-bacillary leprosy particularly Lepromatous Lepromatous Leprosy and Borderline Lepromatous Leprosy. It is frequently associated with the development of neuritis, iritis, orchitis, arthritis / dactylitis of hands and feet, etc. Decades ago, it was well managed with thalidomide but now a high dose of Clofazimine and Steroid are the recommended drugs by the World Health Organization. Unfortunately there are some patients who do not respond to this regimen or experience relapse after they attempt to reduce their steroid below 15- 20mg / day. Objective: We undertook this study to find out an effective and safe treatment regimen for those resistant patients. Methodology: During 2007-2011, we treated 9 resistant ENL patients. They were ENL reaction with (a) Skin Ulcers-2, (b) Neuritis-2, (c) Nerve Abscess-1, (d) Iritis-1, (e) Orchitis-2 and (f) Arthritis/Dactylitis-1. All had comparable clinical and bacteriological features, and almost similar history of incomplete response to courses of conventional treatment in hospital, during last 1-1½ years. We treated them all with a combination of Methotrexate and Predinisolone for 2¼-3¼ years. Results: We observed smooth remission of ENL-reaction in all our patients. No remarkable side effects were seen in our patients, except mild weight gain in one, weight gain and facial swelling in one, two attacks of multiple folliculitis and one attack of extensive P. versicolor in another one and Norwegian scabies in one. Conclusion: A combination of low dose Prednisolone and Methotrexate was found safe and effective in managing resistant ENL reaction and we welcome controlled study in this regard.***

Key words

Erythema nodosum leprosum; methotrexate; prednisolone

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Introduction

Erythema Nodosum Leprosum (ENL) is the chronic recurring complication of multi-bacillary leprosy particularly, Lepromatous Lepromatuous (LL) Leprosy and Borderline Lepromatous (BL) leprosy. In fact, it is an immune complex mediated systemic complication having potential for damaging skin, mucous membrane, liver, spleen, kidneys, eyes, testes, nerves, lymph nodes, small muscles and bones of hands and feet. Histologically there is acute inflammatory infiltrate composed mainly of, Neutrophil, Eosinophil and Mast cells in early stage and chronic inflammatory infiltrate mainly by, Lymphocytes, Histiocytes and Plasma cells in older lesions together with edema in dermis and subcutis, and features of vasculitis and panniculitis[1].

Decades ago, Thalidomide[2-3] was the drug of choice for its management. Unfortunately it's potential for teratogenicity, high cost, unavailability and inadvertent use obliged authority to band it's use in ENL reaction.

International Federation of Anti-leprosy Associations (ILEP), recommended Prednisolone, 30-60 mg daily as initial dose, reduce by 10 mg every week until the daily dose of 20 mg is reached, then reduce by 5 mg weekly until daily dose of 10 mg is reached and finally maintain a daily dose of 5-10 mg for several weeks in patients with chronic ENL with a combination of Clofazimine, in a dose of 300 mg in divided doses for 3-4 months, then 200 mg for 3-4 months and finally 100 mg for 3-4 months. Since, this guideline is not endorsed by our National Guidelines, neither the physicians working in leprosy organizations nor the dermatologists of our country use this regimen even at discretions.

However, our National Guidelines for Leprosy Control has adopted the guidelines of World Health Orngnization (WHO) in treating leprosy and managing its complications including ENL reaction. As such, we treat ENL reaction with the combination of a high dose of Clofazimine e.g. 100 mg thrice daily for 12 weeks followed by 100 mg twice daily for 12 weeks and 100 mg once daily for 12-24 weeks and Prednisolone, 1 mg / kg / day (40-60 mg) as initial dose and then tapering the dose to end the course within 12 weeks. It works in majority cases of ENL-reactions.

However, there are some patients who do not respond completely to this WHO-recommended regimen or experience relapse in an attempt to reduce their steroid from 15-20mg / day or follow a staggering course even while on WHO recommended regimen. These patients usually suffer all through the year and for several years making them unable to enjoy their normal life. Though there is an option for individualization of regimen for those patients in the WHO-guidelines, our experience in this regard is disappointingly minimal.

Having approval from the responsible authority of our university we undertook this study at our out door.

Materials and methods

We treated 9-patients consecutively, who were resistant ENL reaction from January, 2007 to June, 2011. All of them were adults, 7-males and 2-females with weight between 42 kg and 65 kg. They were multi-bacillary, LL-5 and BL-4 with average BI between 2^+ and 3.5^+. All had characteristic painful and tender papules and nodules associated with fever, body ache, headache, joints pain, weakness and anorexia, and categorizing severe ENL-reaction with (a) Skin Ulcers in 2, (b) Neuritis in 2, (c) Nerve Abscess in 1, (d) Iritis in 1, (e) Orchitis in 2 and (f) Arthritis/Dactylitis in 1.

Their reaction developed before MDT in 4, during MDT in 2 and after MDT in 3. All of them had completed MDT (MB) for leprosy regularly in due time and been suffering from reaction for more than 1-year before we enrolled them as our patients. They had multiple hospital admissions and received at least two WHO-recommended anti-ENL regimens. They received 1 mg / kg / day (40-60 mg) of Prednisolone, as initial dose and they also followed the WHO guidelines but were not under controlled. Two of them had weight gain from Prednisolone and one had generalized pigmentation and abdominal pain form Clofazimine. All of them were unable to enjoy normal life for at least 1-year.

We took history carefully, examined thoroughly and did body chart, Sensory Test and Quick Muscle Test (ST and QMT), SSS-test (Slit Skin Smear Test), Routine Blood, Urine and Stool examination, Liver Function Test and Kidney Function Test and Serum Electrolytes for all patients as a baseline record. We scrutinized their previous records carefully to find their maintenance dose of steroid and to determine our approach.

We put them all on Prednisolone, 0.75 mg / kg / day (With an initial dose of 30 mg/ day for patients with body weight 45 kg or 40mg / day for patients with body weight more than 45 kg) at morning, and Methotrexate, 2.5mg, 12 hourly, 3 times weekly as we scheduled (Table-I). We continued Methotrexate for 2 – 2½ years, and Prednisolone for 2¼-3¼ years.

Table I : Our regimen

Drugs	Dose	Duration
Prednislone	Initial: 30 or 40 mg / day (0.75 mg / day).	3-6 months.
	Maintenance: 20 mg / day.	6-9 months.
	15 mg / day	3-months.
	10 mg / day	3-months.
	5 mg / day	3-months.
	5 mg / alternate day	3-months.
	5 mg / twice weekly	3-6 months.
	5 mg / once weekly	3-months.
	2.5 mg / once weekly	3-months
Methotrexate 2.5 mg, 12 hourly, 3-times, weekly		24-30 months.

Duration of our course: 2¼ to 3¼ years.

We delivered monthly follow up for first year and quarterly follow up for next 2 years. Monthly assessment of Blood Pressure, Fasting Blood Sugar, Routine Blood and Urine Test, Visual Test and Weight Measurement was done for first year and then quarterly till patients were released from treatment. Then telephonic casual contacts were made to get information about their health status.

Results

The duration of our treatment was between 27 months and 39 months with an average of 33 months (27 months in 2, 30 months in 4, 36 months in 2 and 39 months in 1)

There were no complaints of fever, body ache, headache, joints pain and skin ulcers etc, after the first three to six months of treatment. Iritis, Orchitis and Arthritis/ Dactylitis took 2-2½ years and Neuritis took 2-3¼ years to resolve completely. Smear became negative by 1½-2½ years. Patient returned back to normal enjoyable life within 2-3 years.

We observed appearance of nodules (though few and mild) in an attempt to reduce dose from 20 mg or 15 mg per day (was their maintenance dose). We were able to overcome the difficulty with prolonging the duration from 3 months to 6 months or even 9 months. Similarly there was difficulty in an attempt to change the dose 5 mg twice weekly to 5 mg once on a week. Patients felt mild joints pain, muscles cramps and discomfort from steroid dependency. Again we overcame it by prolonging the duration from 3 months to 6 months.

We did not find any clinical and investigational side-effects attributable to our low dose Methotrexate. However we observed mild weight gain in one, weight gain and facial swelling in one, two attacks of multiple folliculitis and one attack of extensive P. versicolor in one with initial dose of Prednisolone, 40 mg / day and there was Norwegian scabies in one.

Discussion

We observed extended (3-6 months) initial dose followed by prolonged (6-9 months) maintenance dose and very slow tapering (quarterly decrement) of Prednisolone together with low dose Methotrexate, was safe and effective in 9-patients with otherwise uncontrollable ENL-reaction.

Treatment of resistant ENL is challenging. Pulsed corticosteroid[4] and Immuno-modulators[5-6] were found useful but the former is potentially hazardous and not suitable for the field practice and the later is prohibitively expensive and their long term complication not yet assessed. Oral Zinc[7], Azathioprine[8] and high dose Clofazimine[9-10] were also found helpful but they are far from ideal and have their own limitations.

A combination of high dose Prednisolone and Methotrexate (>1 mg / kg / day and 15 mg / week respectively) was seen synergistic and found helpful in aborting resistant ENL in a patient as reported by Kar BR and Babu R[11]. However we used low dose Prednisolone and Methotrexate (0.75 mg / kg / day and 7.50 mg / week respectively). Even then we found their combination helpful in bringing persistent remission in our patients. They did not mention duration of treatment and outcome after its completion whereas we found patients free of ENL reaction even 8-months to 1½ years after stoppage of our treatment.

Ours was a outdoor based treatment and was the only observation of its kind in our country for those chronic sufferers. However, at the end a regimen of 2¼-3¼ years appeared to be "brow-raising." Even then, our patients had preferably accepted the prolonged helpful treatment than the chronic distressful and incapacitating suffering.

In conclusion, for our Bangladeshi patients, a combination of low dose Prednisolone (0.75 mg / kg per day but not more than 40 mg per day), and Methotrexate (7.50 mg per week) was safe in field situation and at the same time effective in controlling resistant ENL reaction. We welcome controlled study in this regard.

Limitation

Small sample size and uncontrolled nature is the main limitation of this observation.

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Disclosure

All the authors declared no competing interestes

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