

SHORT REPORT

Effectiveness of Methotrexate in prednisolone and thalidomide resistant cases of Type 2 lepra reaction: report on three cases

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Accepted for publication 19 August 2015

Keywords: type 2 lepra reaction, erythema nodosum leprosum, thalidomide, methotrexate, resistant, treatment, prednisolone, leprosy, Hansen disease

Introduction

Type 2 lepra reactions, and its cutaneous manifestation, Erythema Nodosum Leprosum (ENL) are an immune complex mediated systemic condition, often complicating the disease and/or its treatment in cases of the lepromatous spectrum of leprosy.¹ Prednisolone and thalidomide are the mainstay for the treatment of Type 2 lepra reactions.¹

According to the guidelines set out by the WHO and the National Leprosy Elimination Programme (NLEP) of India cases of Type 2 lepra reaction should be managed with prednisolone, clofazimine and thalidomide. NLEP guidelines suggest that prednisolone at 1 mg/kg body wt/day is given to start with as a single morning dose after breakfast, and after the reaction/inflammation is controlled, to taper the prednisolone by 10 mg fortnightly till the dose of 20 mg/day is reached. Thereafter prednisolone is tapered by 5 mg/day, fortnightly till withdrawal. Clofazimine is given with corticosteroids in every case, starting with 100 mgs three times a day, tapering to 100 mgs after every 12 weeks. It is recommended not to exceed clofazimine beyond 12 months. Thalidomide can be used in resistant cases of ENL under strict supervision in tertiary care centres only.

During the years 2009 and 2010, thalidomide was made available to our department through the kind donation of the NGO Lepra Society, India. This thalidomide was used for prednisolone/clofazimine non-responsive patients of Type 2 lepra reaction. The thalidomide schedule that we followed was, to start 100 mgs three times a day, tapered fortnightly

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by 100 mgs till the lowest effective dose was achieved, which should be continued until 6 months thalidomide therapy had been reached. A second similar cycle could be initiated if the need arose.

We follow a routine of extensive history and examination, data recording and charting for cases of leprosy. A general physical examination, neurological examination, ophthalmic references, slit skin smear for acid fast bacilli with recording of bacteriological index, complete blood count, liver function screening, renal function screening, USG abdomen, chest x-ray, and urine routine examinations are routinely performed in cases of leprosy. Also, a skin biopsy is routinely done for leprosy patients. In-patient facility has been utilised for cases of leprosy-induced severe complications.

Most patients of Type 2 lepra reaction respond to prednisolone, clofazimine and thalidomide therapy, but we had received a few patients of Type 2 lepra reaction in whom prednisolone and thalidomide were unable to induce remission. We initiated these patients on low dose methotrexate, and brief accounts of three such patients have been presented here.

Case 1

A 32 year old male patient with lepromatous leprosy, completed multibacillary multidrug therapy (MDT-MB), started developing Type 2 lepra reaction 6 months after initiating MDT-MB. Prednisolone was started in the dose of 40 mg/day along with clofazimine 300 mgs/day accordingly. Both drugs were used in accordance with NLEP guidelines and were tapered down to 15 mgs/day, over a period of about 4 months. Relapse of ENL was observed when the dose of prednisolone was further tapered. So we restarted him on 40 mgs/day with slower tapering reaching 15 mgs/day over a period of 6 months. The patient was not responding favourably below 15 mgs/day, so thalidomide was initiated in above mentioned schedule. After two cycles of thalidomide, it was found that reaction relapses occurred each time thalidomide was tapered below 100 mgs/day. He was put on methotrexate, 15 mgs per week in three divided doses 12 hours apart. Complete remission of reactional state was achieved after 2 months; the methotrexate was continued for a total duration of 6 months.

Case 2

A 27 year old male presented with ENL of 1 month duration. He was started on MDT-MB along with prednisolone 40 mgs/day, and clofazimine 100 mgs three times a day. The dose of prednisolone was tapered down and stopped after 5 months, while clofazimine was continued. After a week, the patient started developing ENL, which prompted us to re-initiate prednisolone in higher doses of 60 mgs/day. This second course of prednisolone was tapered over a period of 6 months; attempts to taper below 15 to 20 mgs/day of prednisolone were unsuccessful and resulted in reappearance of ENL. Similarly two successive thalidomide courses were also found to be ineffective to induce remission. Methotrexate 15 mgs/week in three divided doses, 12 hours apart was started; good clinical response was achieved and remission was seen within 3 months of therapy. Methotrexate was continued for 6 months.

Case 3

A 40 year old man presented with severe Type 2 lepra reaction during 10th-11th month of his MDT-MB therapy. A course of 60 mgs/day prednisolone and 300 mgs/day clofazimine was started; two consecutive tapering courses of prednisolone were unsuccessful and the patient was unable to tolerate tapering below 15 mgs/day of prednisolone. Two following courses of thalidomide also were unable to induce remission. Subsequent methotrexate in the dose of 15 mgs/day was able to induce remission after 3 months of therapy. Methotrexate was continued for 1 year.

All three cases have been under regular follow-up, and are in remission since complete stoppage of their methotrexate therapy. Methotrexate had been able to induce and to maintain remission in these cases for 24 months, 24 months and 18 months respectively. The decision to initiate methotrexate was partly because of the inability to initiate remission and partly because of the unavailability of thalidomide after initial supplies from Lepra Society, India.

We have not found any clinical or laboratory adverse events attributable to methotrexate therapy or to thalidomide therapy; however prednisolone induced cushingoid features, striae distansae, gastritis, and weight gain was present in all the cases. Hypertension and deranged blood glucose level was found in case 1 and case 3 respectively; probably because of oral corticosteroids, as these conditions developed after initiation of prednisolone.

Discussion

Methotrexate has been successfully used in patients of resistant ENL; however to the best of our knowledge it has not been effective in thalidomide non-responsive cases. We had an opportunity to use thalidomide and to use methotrexate in our resistant cases of Type 2 lepra reaction.

Type 2 lepra reaction/ENL is an immune complex mediated response, hence corticosteroids, thalidomide, clofazimine, methotrexate, pentoxifylline, cyclosporine, azathioprine, zafirlukast, infliximab, etanercept, colchicine, chloroquine, and oral zinc have been found to be useful treatment options.¹⁻³

Methotrexate exerts anti-inflammatory and immune-suppressive effects.^{4,5} It has direct inhibitory effects not only on the proliferation and induction of apoptosis in cells involved in immune/inflammatory reaction but also on pro-inflammatory cytokines.⁴ The immunomodulatory activity of thalidomide mainly lies in its capability of altering the secretion and activities of various cytokines including interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 1, and TNF- α ,⁶ same cytokines are also targeted by methotrexate.^{4,5} Methotrexate has been found effective in cases of Type 2 lepra reaction,^{3,7} but here it appears that methotrexate has been providing a boosting effect to the action of thalidomide.

However, more formal studies are required, but methotrexate appears to have a beneficial effect in cases of Type 2 lepra reaction, specifically in resistant cases, as has been pointed out by our cases and that of others.^{3,7} Also, methotrexate may provide a cheaper and convenient option in management of Type 2 lepra reaction, as dermatologists have greater experience of using methotrexate than thalidomide.

Acknowledgements

Authors wish to thank Lepra Society, Indore (address: C-16, H I G Colony, Indore - 452001, Opp Christian Eminent School) and Dr. Bhandarkar, State Coordinator, Lepra Madhya Pradesh for their kind donation of thalidomide for the treatment of Type 2 leprosy reaction patients.

References

- ¹ Pandhi D, Chhabra N. New insights in the pathogenesis of type 1 and type 2 lepra reaction. *Indian J Dermatol Venereol Leprol*, 2013; **79**: 739–749.
- ² Kaur I, Dogra S, Narang T, De D. Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe erythema nodosum leprosum: a randomized study. *Australas J Dermatol*, 2009; **50**: 181–185.
- ³ Hossain D. Using methotrexate to treat patients with ENL unresponsive to steroids and clofazimine: a report on 9 patients. *Lepr Rev*, 2013; **84**: 105–112.
- ⁴ Cutolo M, Sulli A, Pizzorni C *et al.* Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. *Ann Rheum Dis*, 2001; **60**: 729–735.
- ⁵ van der Heijden JW, Assaraf YG, Gerards AH *et al.* Methotrexate analogues display enhanced inhibition of TNF α production in whole blood from RA patients. *Scand J Rheumatol*, 2014; **43**: 9–16.
- ⁶ Zhou S, Wang F, Hsieh TC *et al.* Thalidomide—a notorious sedative to a wonder anticancer drug. *Curr Med Chem*, 2013; **20**: 4102–4108.
- ⁷ Kar BR, Babu R. Methotrexate in resistant ENL. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 480–482.