

Tacrolimus in the management of large facial patch with recurring reversal reaction: Outcome of a pilot clinical trial study on 5 patients

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Abstract: Background: Inflamed large facial patch, being compromising the appearance and beauty of a patient, is a source of embarrassment and distress, and affects anti-leprosy drive adversely in many ways in the field situation. Its management with oral prednisolone alone, the mainstay of treatment for reversal reaction, proved disappointing. Objective: To see whether topical tacrolimus will be helpful in managing those patients. Methodology: We treated five adult patients with recurring reversal reaction in large facial patch with tacrolimus 0.1% ointment, twice daily and lower dose oral prednisolone for twelve months during March, 2012-February, 2013. Result: Complete remission was achieved in all cases. No side effects of whatsoever was seen in any patient. No recurrence of reaction is seen in any patient till to date. Conclusion: Tacrolimus ointment and lower dose prednisolone was found helpful in managing patients with recurring reversal reaction in large facial patch.

Keywords: Leprosy, Reversal Reaction, Reacting Facial Patch, Management, Tacrolimus and Prednisolone

1. Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. The disease may be complicated by immunological adverse reactions called reversal reaction and erythema nodosum leprosum reaction. Reversal reaction is a cell mediated immunological reaction directed against *M. leprae* in the dermal macrophages and Schwann cells leading to inflammation of skin and nerve lesions.

Reversal reaction predominantly occurs in borderline leprosy¹. Its frequency varies from 8.8%² to 47%³. It may be recurrent in one-third of cases⁴.

Facial patch is self-expressive. It easily attracts others attention and incurs harm to the patient in the form of embarrassment, anxiety and mental distress. Moreover, reacting angry looking patch affects anti-leprosy drive in many ways in the field situation particularly where the disease is associated with intense psychosocial stigma like ours.

Oral prednisolone is the mainstay of treatment of reversal reaction. However, its management with only

prednisolone may be disappointing. In that case, methotrexate⁵, cyclosporine⁶ and azathioprine⁷ were also tried. Gilles Safa⁸ et al reported a case managed by topical tacrolimus with oral prednisolone. Here, we report outcome of five patients with recurring reversal reaction in large facial patch treated with topical tacrolimus and lower dose prednisolone for twelve months.

2. Methods

The study was undertaken in a university run clinic during March, 2012- February, 2013. Our project proposal for limited pilot clinical trial study was approved by the Institutional Review Board (IRB) of the University of Science and Technology Chittagong (USTC). We gathered five patients in a leprosy clinic in February, 2012. A health education talk was arranged to identify the problem and to discuss the action plan of management. They were on prednisolone maintenance dose (20 mg/day) and facial patch was at quiescent. At this stage, we asked them to taper prednisolone, 5 mg weekly to end the course within

next four weeks and report to clinic again.

One month later (March, 2012) they returned back with full blown reversal reaction on their facial lesions. They were red to pink in color, swollen, shiny and angry looking with impaired cotton touch sensation. After thorough clinical evaluation, we did sensation test of facial patch and eyes with the wisp of cotton and routine sensory test for hands and feet with the help of monofilament nylon as designed for field practice by the World Health Organization (WHO). We did quick muscle test of eyes,

hands and feet as per WHO guidelines, routine blood, urine and stool test and individual baseline record was made.

We put them on tacrolimus (0.1%) ointment, twice daily for twelve months and oral prednisolone for twelve months (20 mg/day for first three months, 15 mg/day for next three months, 10 mg/day for next three months and 5 mg/day for last three months and then stop) and asked them to report to clinic monthly.

3. Results

Table 01. Patient profile at enrollment in our study.

Patient	Age (yrs)/sex	Salient features	Outcome
P-1	38/M	Had complaint of a large inflamed patch on left face involving forehead, cheek, chin, left half of the lips, nose and auricle. In addition, he had multiple dull red patches and plaques over neck, trunk and limbs. His left great auricular nerve was enlarged, painful and tender with tingling ear lobe. His left ulnar, radial cutaneous, common peroneal and superficial peroneal nerves were enlarged, painful and tender. He had left little finger abduction weakness, 4+ (full range movement against some resistance) in quick muscle test (QMT). All patches and plaques were anaesthetic to cotton touch. His slit skin smear test from ear lobes and face lesion was negative. He was diagnosed as BT leprosy with reversal reaction. Received MDT (MB) for 12 months and oral prednisolone, tapered in first three months and then continued maintenance dose of 20 mg/day for next eight months with one failed attempt to reduce it.	Neuritis and reaction in skin patches elsewhere responded well with finger power returned back to normal but facial patch remained quiescent as long as oral prednisolone maintained 20 mg/day.
P-2	35/M	Had complaint of a large inflamed plaque on right face involving cheek, chin, right half of the lips, nose, and eye lids with partial sensory loss on the lesion. He also had multiple red swollen plaques over limbs and trunk with anesthesia in multiple patches. His right lids were weak, 4+ in QMT. His slit skin smear test from ear lobes and face lesion was negative. He was diagnosed as BT leprosy with reversal reaction. Received MDT (MB) for 12 months and oral prednisolone, tapered in first four months and then continued maintenance dose of 20 mg/day for next eight months with two failed attempts to reduce it.	Reaction in skin patches elsewhere responded well and lid muscle power returned back to normal but facial patch remained quiescent as long as oral prednisolone maintained 20 mg/day.
P-3	50/M	Had complaint of pink swollen hot large plaque on right half of face involving cheek, right half of the lips, chin, sub-mandibular area, and adjacent neck with partial sensory loss on the plaque. His right great auricular nerve was painful, tender and enlarged with tingling ear lobe. His right lids were weak, 4+ in QMT. His left radial, ulnar and radial cutaneous nerves were painful, tender and enlarged. His slit skin smear test from ear lobes and face lesion was negative. He was diagnosed as BT leprosy with reversal reaction. Received MDT (MB) for 12 months and oral prednisolone, tapered in first four months and then continued maintenance dose of 20 mg/day for next fourteen months with several failed attempts to reduce it.	Patch sensation and lid muscle power returned back to normal but facial patch remained quiescent as long as oral prednisolone maintained 20 mg/day.
P-4	50/M	Had complaint of pink swollen large patch involving whole face and both the auricles extending from frontal hairline to anterior upper neck in front and up to 3 cm behind the auricles in each side with burning and tingling. He had multiple anesthetic pale and red patches over trunk and limbs. He had multiple nerves enlarged painful and tender with right little finger abduction weakness 4+ in QMT. His slit skin smear test from ear lobes was positive, 1+ and face lesion was negative. He was diagnosed as BT leprosy with reversal reaction. Received MDT (MB) for 12 months and oral prednisolone, tapered in first four months and then continued maintenance dose of 20 mg/day for next eight months with one failed attempt to reduce it.	Neuritis and reaction in skin patches elsewhere responded well with returned finger power but facial patch remained quiescent as long as oral prednisolone maintained 20 mg/day.
P-5	28/M	Had complaint of burning/tingling pink swollen hot large plaque on left half of face involving forehead, eye lids, cheek, nose and auricle. Some areas of the plaque were anesthetic (to cotton touch). His forceful eye closure was weak, 4+ in QMT. He had multiple anesthetic pale patches over limbs and trunk and both common peroneal nerves enlarged and tender. His slit skin smear test from ear lobes and face lesion was negative. He was diagnosed as BT leprosy with reversal reaction. Received MDT (MB) for 12 months and oral prednisolone, tapered in first three months and then continued maintenance dose of 20 mg/day for next fifteen months with several failed attempts to reduce it.	Neuritis and reaction in skin patches elsewhere responded well with patch sensation and lid muscle power returned back to normal but facial patch remained quiescent as long as oral prednisolone maintained 20 mg/day.

Five adult patients attended different leprosy clinics in Chittagong (south-eastern part of Bangladesh) in 2010. All had similar history of having borderline tuberculoid (BT) leprosy and reversal reaction in skin and nerves. They had multiple reacting and some non-reacting anesthetic skin lesions over body and all had, in common, one large red/pink, swollen, shiny, burning/tingling plaque on their face. All had multiple nerves enlarged, painful and tender with function loss. All but one had negative slit skin smear from ear lobes and skin lesions. All received World Health Organization recommended multi-bacillary multidrug therapy (MDT-MB) for 12 months and prednisolone for six months (40 mg/day for one month, 30 mg/day for one month, 20 mg/day for one month, 15 mg/day for one month, 10 mg/day for one month and 5 mg/day for one month). All were particular in and compliant with their given treatment. They completed their MDT in due time. Unfortunately all of them noticed recurrence of reversal reaction in their large facial patch at an attempt to reduce their prednisolone dose from 20 mg/day to 15 mg/day at fourth month of their therapy. They had to increase their dose again to 20 mg/day and continue the dose for next 12-15 months with few to several failed attempts to reduce the dose. With this prolonged steroid they got remission of reaction in other skin and nerve lesions and regained nerve function but did not get rid of recurrence of reaction in facial patch. At this stage they all were referred to us for further management (Table-1).



Fig 01. Fifth patient at enrollment. A: Pink swollen hot plaque over left half of the face involving forehead, eye lids, cheek, nose and auricle. B: Normal looking face at the end of twelve months treatment.

With our treatment, heat, swelling and redness took two-four months to go, and tingling and firmness took four-six months to go. Soft supple normal looking skin with normal sensation appeared by twelve months of treatment (Fig-1: A-B). No side effects of whatsoever from topical tacrolimus and lower dose prednisolone was seen in any patient. At the end of twelve months treatment, there was no recurrence of reversal reaction on facial lesion. All of them are fine and enjoying happy life even today (July, 2014).

4. Discussion

Five patients had been suffering from borderline tuberculoid leprosy with recurring reversal reaction on their large facial patch. They were on prednisolone (maintenance dose) for 12-18 months. We treated them with topical tacrolimus and lower dose prednisolone for twelve months. At the end of the course, we achieved complete remission (complete resolution of inflammation together with reappearance of soft supple normal looking healthy skin) of the reaction and successful waning of prednisolone. They remained free from reaction for last 18 months after stoppage of treatment.

Frequency of large facial patch with recurring reversal reaction is 1.36% (in our center, occurrence of reversal reaction in new registered cases is 50.68%. Of them 15.06% occurs only in skin lesions, 23.28% only in nerve, 10.95% both in skin and nerve, and 1.36% occur in large facial patch). Numerically it is insignificant. However, being self-expressive and having potential for affecting the anti-leprosy drive in many ways, it becomes an issue of great concern in the field situation. Prednisolone is the treatment of choice for reversal reaction. Generally BT patients require prednisolone for 4-9 months⁹. However our patients were on it for 12-18 months. With this prolonged prednisolone, they got remission of reversal reaction that occurred in nerves and skin lesions elsewhere but for unknown reason did not get relief of reversal reaction in facial patch. However, reportedly facial patch is one of the risk factors for recurrent reversal reactions¹⁰.

Methotrexate¹¹ has mechanism based action against reversal reaction. It is found fairly safe and effective in managing a severe reversal reaction developed in a BL patient who was intolerant to prednisolone⁵. However, systemic use of methotrexate was not considered to manage a single patch reversal reaction in the said cases.

Cyclosporine⁶ is also found effective in managing severe reversal reaction. However, it is prohibitively expensive and associated with considerable side-effects. Azathioprine⁷ was also found effective in managing reversal reaction with multiple skin and nerve lesions. It is also a steroid-sparing agent. However, its potential for bone-marrow suppression, increase infection risk and gastrointestinal disturbances deterred us to use it in our cases.

Topical tacrolimus⁸ along with oral prednisolone was found effective in managing a very complicated leprosy patient with many reacting skin lesions. Having been given due consideration in its availability in the market and amenability of our patients, its safety and efficacy, we preferred it for our patients having single reacting lesion.

Reversal reaction is a cell mediated immunity directed against *M. leprae* in the skin and nerve lesions. Infection of the skin macrophages and Schwann cells of the nerve by *M. leprae* causes expression of adhesion molecules on their surfaces. This may give rise to antigen presentation which triggers cell mediated immunity that result in localized

inflammation and edema¹². It is a complex immunological mechanism involving release of pro-inflammatory cytokines and mediators, namely, IL-1, IL-2, IL-4, IL-8, IL-10, IL-12, INF- α and TNF- γ ¹³⁻¹⁴. Tacrolimus is a macrolide calcineurin inhibitor agent. It inhibits T-lymphocytes activation by inhibition of transcription and release of pro-inflammatory cytokines and mediators¹⁵. On the other hand, prednisolone suppresses T-lymphocytes during inflammatory process and reduces tissue edema¹⁶. Thus, both the drugs might have worked synergistically to bring complete resolution and permanent remission of the reaction in our cases. But the exact mechanism by which tacrolimus helped in waning prednisolone is yet to be elucidated.

In conclusion, topical tacrolimus together with lower dose prednisolone was found helpful in aborting recurring reversal reaction on large facial patch. Further, formal study is welcomed.

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Conflict of Interest

There is no conflict of interest with this case report.

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