Indian J Lepr 2016, 88 : 29-38

http://www.ijl.org.in

Original Article

Comparative efficacy of four treatment regimens in Type 2 Leprosy Reactions (Prednisolone alone, Thalidomide alone, Prednisolone plus Thalidomide and Prednisolone plus Clofazimine)

HK Kar[1] and L Gupta[2]

Received : 23.06.2015 Revised : 28.12.2015 Accepted : 30.12.2015

This study has been carried out to assess the comparative efficacy of Prednisolone alone or thalidomide alone for the first attack of T2R, and combination of prednisolone plus thalidomide or prednisolone plus clofazimine for chronic and recurrent T2R. Efficacy of all four regimens was assessed on the basis of clinical recovery of T2R measured by reaction severity scores (RSS) ,visual analogue scale (VAS) and other relevant parameters, requirement of extra dose of steroid for clinical recovery, recurrence of T2R and side effects observed in each regimen. The designof study was an open prospective longitudinal single centre investigation. In the first episode T2R group I (prednisolone alone) the efficacy was 58.8% (10/17) compared to 93.75% (15/16) in Group 2 treated with thalidomide alone. This difference was statistically significant $p < 0.05$ when compared using unpaired t test. When clinical outcome was compared in recurrent/relapse of T2R Groups 3 and 4, it was observed to be statistically significant $p<0.05$ when compared using unpaired t test. It was 82.35% (14/17) in Group 3 (prednisolone plus clofazimine) and 10/16 (62.5%) in Group 4 (prednislone plus clofazimine). To conclude, for the management of recurrent/chronic ENL, both the combinations-prednisolone with thalidomide or clofazimine appear to be efficacious. While prednisolone with thalidomide appears to be better than prednisolone and clofazimine, however, by 20 weeks difference narrows down. As of now these findings may be considered indicative and larger experience on more number of cases using robust statistical design is required for marching towards making recommendations for clinical application.

Key words : comparative efficacy, regimens type 2 reactions, thalidomide, clofazimine, prednisolone

Introduction

Reactional states are acute inflammatory events that commonly occur in leprosy during the course of the disease. Reactions are classified as type I (T1R) or reversal reaction, and type 2 (T2R), or erythema nodosum leprosum (ENL). (Jolliffe 1977). Both types have been found to cause nerve inflammation (neuritis), which is the primary cause of disability, irreversible deformities and morbidity in leprosy patients. Known to occur in

[1] HK Kar, MD, Former Director & Medical Superintendent, PGIMER and RML Hospital, New Delhi
[2] L Gupta, Former Consultant, Dermatology and Venerology, PGIMER and RML Hospital, New Delhi
Correspondence to: HK Kar Email: hkkar_2000@yahoomail.com

borderline-lepromatous (BL) and lepromatous-leprosy (LL) patients, the frequency of ENL may vary. In a previous study, it was demonstrated that 57% of patients undergoing multibacillary multidrug therapy (MDT) presented reaction, with 55% having ENL (Nerry et al 1998). Their early detection and prompt optimal treatment can reduce the complications associated with these conditions significantly (Sehgal 1987). Along with timely detection, precise and adequate therapy with appropriate drug regimens also plays an important role in reducing morbidity.

Type 2 reaction, characterized by the appearance of tender, erythematous, subcutaneous nodules located on apparently normal looking skin. It is frequently accompanied by systemic symptoms such as fever, malaise, enlarged lymph nodes, anorexia, weight loss, arthralgia, and edema(Sehgal 1987, Rea and Levan 1975). Other organs like peripheral nerves, testes, joints, eyes, and kidneys may also be affected. Furthermore, a patient may present significant leukocytosis that typically recedes after the reactional state has subsided (Parida et al 1992). Some reports have confirmed the presence of high levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6, and IL-1 in the sera of ENL patients, suggesting that these pleiotropic inflammatory cytokines may be at least partly responsible for the clinical manifestations of T2R (Sampaio et al 1991, Pannikar 2003).

Steroids are the principal agents used for treatment of reactions and neuritis (Lockwood 2000, Naaf et al 1979, Naaf 1996). Many steroid regimens have been tested and practiced for the same (Meyerson 1996, Naafs 2003, Richardus et al 2003 a, b, Smith et al 2004, Rao et al 2006, van Brakel et al 2003, WHO 1998). Steroids being inherently associated with side effects, particularly in T2R. Therefore the dosage and duration of these regimen and the cumulative amount of steroid dose assumes significance.

Many studies conducted during the last 10 years have shown that thalidomide not only is a potent immune response modulator but also has a substantial beneficial effect in blocking the effects of TNF-α, most probably a critical factor in the control of ENL.Though thalidomide is very effective but due to its teratogenic potential and cost factor, it has its own limitations. However, other recognized side effects of thalidomide like peripheral neuropathy and sedation do not represent a serious threat.

WHO has recommended the anti-inflammatory clofazimine for chronic and severe T2R that does not respond satisfactorily to corticosteroid or for those the risk of steroid toxicity is high (Naafs 1996). For recurrent or chronic T2R, there is no evidence based standard drug combination regimen, when the individual anti-reactional drug fails to control the T2R.

Chronic type 2 reactions are defined as those reactional episodes which persist for more than 6 months or shows relapse of reaction within 3 months of stopping anti-reactional treatment. Recurrent T2R was defined as the type which relapsed after 3 months of stopping anti-reactional treatment.

The present study was conducted to assess the comparative efficacy of

- Prednisolone alone or thalidomide alone for the first attack of T2R
- Combination of prednisolone plus thalidomide or prednisolone plus clofazimine for chronic and recurrent T2R.

The efficacy of all four regimens were evaluated on the basis of clinical recovery of T2R, requirement of extra dose of steroid for clinical recovery,

recurrence of T2R and side effects observed in each regimen.

Materials and Methods

In this open prospective longitudinal single centre study at the Department of Dermatology, STD and Leprosy at Dr. RML Hospital all eligible LL/BL patients with T2R who gave informed consent for the trial were enrolled in this study during 2008-2012. Patients of either sex ranging in age 18 years and above were included. Pregnant and lactating women or women planning conception and not using/ready to use effective contraceptive measures were excluded. Patients with contraindications for steroid use (namely diabetes, tuberculosis, gastritis etc.) were also excluded.

All patients were either already under multi drug therapy (MDT-MB) or started MDT-MB at the time of diagnosis if not started earlier. The diagnosis of leprosy was done based on the clinical and slit skin smear (SSS) examination supported by histopathological examination of the involved skin. The diagnosis of T2R was also confirmed by histopathology. Clinical assessment in terms of Severity Index of T2R, the Reaction Severity Score (RSS) as described by Smith et al (2004) was estimated before and after treatment in all the patients. Nerve function impairment (NFI) and various grading disability were also assessed.

All the enrolled patients were randomized into four treatment groups. The two single drug regimens (either prednisolone in Group 1 or thalidomide in Group 2) were used for those patients who had episodes of T2R for the first time. The other two groups of patients having chronic/recurrent T2R were allotted combination regimens, either prednisolone plus thalidomide (Group 3) or prednisolone plus clofazimine (Group 4).

For the first episode of T2R

Group 1

Prednisolone was administered at 1 mg/kg/day for 2 weeks, tapering 10 mg at every 2 weeks interval upto 20 mg, and then tapering every 5 mg every 2 weekly to zero over a period of 20 weeks.

Group 2

Thalidomide was started at dose of 400 mg/day (200mg BD) for the first week, then 300 mg/day (100mg in the morning and 200mg in the evening) for next 4 weeks, then 200 mg OD at bed time for the next 4 weeks. It was further reduced to 100 mg OD at bed time for next 4 weeks. Finally the dose was tapered to 50 mg OD at bed time for 7 weeks over a period of 20 weeks.

For recurrent and chronic T2R

Group 3

Prednisolone was given in the same dose as in Group 1. Along with prednisolone, thalidomide was given at dose of 400 mg/day for the first week and subsequently tapered as in Group 2 over a same period of 20 weeks.

Group 4

Prednisolone was given in the same dose as in Group 1. Along with prednisolone clofazimine was started at 300 mg/day for first 12 weeks. Then it was tapered to 200 mg/day for next 4 weeks and then reduced to 100 mg/day for next 4 weeks for a period of 20 weeks.

Additional doses of prednisolone were added for all groups of patients in case of relapse/ reactivation of signs and symptoms of T2R or increase in severity of T2R while undergoing respective group anti-reactional treatment in a tapering dose schedule. All change of dosage schedule were recorded in the charts. This extra dose of prednisolone to control reaction was used as the basic parameter for judgment of the efficacy of the group regimen. For fresh

appearance of the any two or more of the following signs and symptoms of T2R rescheduling of prednisolone dose was made by adding 20 to 40 mg higher than the present dose and 100 to 200 mg of thalidomide in case of Group 2 and then gradually tapered. The signs and symptoms of T2R (any two) considered as relapse/ reactivation of T2R are as below : Fresh episode of high fever (100^0F and above) with malaise, fresh new multiple ENL lesions with/without pustular/ ulcerative lesions, fresh development of acute neuritis (tenderness/pain in peripheral nerve/s), orchitis, arthritis and iridocyclitis.

All the patients were admitted in the Dermatology wards as indoor patients for monitoring for a minimal period of initial three months, then discharged with adequate counseling and instruction to follow the treatment regimen and to attend follow up clinic monthly once for assessment or anytime with fresh appearance of signs and symptoms of T2R while under treatment. Evaluation of response, number of recurrences, clinical outcome, additional steroid requirement, and side effects of treatment were evaluated during the course of treatment on daily basis while admitted in the hospital and after discharge on their visit to OPD clinic. Patients were followed up for a minimum of 6 months after 20 weeks course of treatment to note signs and symptoms of reactions and any further recurrence of T2R. The recovery of reaction was judged as disappearance of the common signs and symptoms of T2R as mentioned above.

Results

Out of 80 patients (20 in each group) 66 patients who completed the study were analyzed (17 patients in Group 1, 16 in Group 2, 17 in Group 3 and 16 in Group 4). The defaulter rate was 17.5%. There was no statistically significant difference in the number of patients who completed in each group ($p<0.05$). There were 61 males and 5 females, M:F ratio was 12.2:1. Out of five females,

Table 1 : Details of patients in four treatment groups

Treatment	Group 1 Prednisolone alone	Group 2 Thalidomide alone	Group 3 Prednisolone + Thalidomide	Group 4 Prednisolone + Clofazamine
Number of enrolled patients	20	20	20	20
Number of patients completed treatment	17	16	17	16
Male/ Female	15/2	16/0	17/0	13/3
Average age (years)	34.11 yr	33.7 yr	31.4 yr	35.82 yr
BL + T2R	7	7	6	6
LL + T2R	10	9	11	10
Average BI	4.08	3.81	3.83	3.51
Clinical outcome (percentage improvement)	10/17 (58.8%)	15/16 (93.75%)	14/17 (82.35%)	10/16 (62.5%)
Average steroid / Thalidomide dose (in g)	4.98 g Prednisolone	22.05 g Thalidomide	4.36 g Prednisolone	4.75 g Prednisolone

2 were in Group 1 and 3 in Group 4. The age range was 18-65 years with a median of 34.73 years. 27/66 belonged to 31-40 yrs followed by 17 in 21-30 and remaining in 18-20 (9), 41-50 (7), 51-60 (4) and two in 61-65 age group.

Among the 66 patients analyzed 40 (60.60%) were of Lepromatous leprosy with T2R and 26 (39.39%) were BL Hansen with T2R at the time of initial presentation. There was no statistically significant difference in the clinical presentation in the four groups when compared with the age, sex distribution, and the clinical presentation (Table 1). The time interval between the noticing of clinical manifestation of leprosy by the patient and starting of MDT ranged from 15 days to 3 years. Only 52% of the patients were diagnosed as leprosy within the first year after noticing the signs/symptoms of leprosy; 25% within the first 6 months. About 13% of patients presented withT2R at the time of diagnosis of leprosy. Out of 66 patients 59 (89.39%) patients developed T2R while on MDT whereas 7 (10.61%) developed T2R after RFT. The average Bacteriological Index (BI) was 3.8 with overall 95.31% positivity. BI positivity was 16/17 (94.11%) in Group 1, 100% in Group 2 and Group 4. 15 out of 17 (88.23%) in Group 3. There was no statistically significant difference noticed p >0.05 in the four groups using ANNOVA test.

All the patients were examined for skin, nerve and systemic involvement thoroughly. Skin was examined for ENL lesions and all peripheral nerves were examined for nerve thickening and tenderness/pain, nerve function impairment (NFI), fever and constitutional symptoms, joint pain, neuritis, edema, uveitis/iridocyclitis, bone pain, lymphadenitis, orchitis and muscle pain on visual analogue scale (VAS). Reaction severity score (RSS) improved significantly in all groups using the regimen prescribed for that group (Table 3). We also recorded the improvement in VAS score at 4 weeks, 8 weeks, 16 weeks and after 20 weeks of starting treatment (Table 4). Based on this scale the improvement in these symptoms was maximum in Group 3 (74%), followed by group 1 (71.56%), Group 2 (65.4%) and in Group 4 (62%) at 20 weeks. The rate of improvement was statistically significantly faster in Group 1 and

Table 2 : Number of recurrences and average Prednisolone/Thalidomide requirements in all groups

	No recurrence		Recurrence (<3)		Recurrence (>3)	
	n	**Average Prednisolone/ Thalidomide (g)**	**n**	**Average Prednisolone/ Thalidomide (g)**	**n**	**Average Prednisolone/ Thalidomide (g)**
Group 1 (n=17)	10	P = 4.12 g	4	P = 5.69 g	3	P = 6.91 g
Group 2 (n=16)	15	T = 22.05 g	1	T = 27.54 g	0	-
Group 3 (n=17)	14	P = 4.12 g T = 22.05 g	2	P= 5.34 g T = 23.14 g	1	P = 5.92 g T = 24.24 g
Group 4 (n=16)	10	P = 4.12 g	3	P = 5.43 g	3	P = 6.21 g

Group 3 at 4 and 8 weeks when compared to Group 2 and 4. This might be due to the faster onset of action of prednisolone as compared to that of thalidomide and clofazimine.

When we compared the clinical improvement for first episode of T2R it was 58.8% in Group 1 (10/17) compared to 93.75% (15/16) in Group 2 (Table 1). This was statistically significant ($p < 0.05$) when compared using unpaired t test. When clinical outcome was compared in recurrent/ chronic T2R Groups 3 and 4 [82.35% improvement (14/17) in Group 3 and 62.5% (10/16) in Group 4. It was observed that improvement in Group 3 regimen was better than that in Group 4 regimen which is statistically significant ($p<0.05$) when compared using unpaired t test.

The total prednisolone requirement per patient as per the protocol was 4.12 g (Table 2). However, to control reaction total steroid requirement was higher in Group1, 3 and 4. It was highest in Group 1 (6.91 g), Majority of the patients required a longer duration of steroid at a dose of 30-40 mg/day rather than tapering at 2 weeks interval as per the protocol, since the patients showed recurrence of lesions when the dose was reduced below 30 mg as per the protocol. The average prednisolone requirement in Group 1 was 4.98 g (additional prednisolone = 0.86 g), 4.36 g in Group 3 (additional prednisolone = 0.25 g) and 4.75 g in Group 4 (additional prednisolone = 0.63 g. The p value was significant when the steroid dose was compared in Groups 3 and 4 ($p>0.05$) in chronic/ recurrent T2R. In Group 2 only in one patient additional thalidomide = 5.49 gover and above total dose of 22.05 g.

The patients in all groups were evaluated for recurrences during the 20weeks treatment period (Table 2). Seven patients in Group 1 and 1 patient in Group 2 developed recurrence. Three patients in Group 3 and 6 patients in Group 4 developed recurrence. Out of three patients in Group 1 who developed more than 3 recurrences, two were moved to Group 3 regimen and one patient was shifted to the Group 4 regimen. Only one patient in Group 2 who developed recurrence was controlled with higher dose of thalidomide as mentioned above (additional 5.49 g of thalidomide.

Table 3 : RSS Score in different treatment groups

	RSS (0 weeks)	RSS (20 weeks)	p	significance
Group 1	13.82+2.04	6.29+1.49	p=0.016	significant
Group 2	14.69+2.6	5.75+1.12	p=0.006	highly significant
Group 3	29.47+6.61	9.35+2.78	p=0.000	highly significant
Group 4	26.13+5.47	16.81+4.27	p=0.000	highly significant

Table 4 : Percentage improvement in the VAS Score at 4 weeks, 8 weeks, 16 weeks and 20 weeks between group1 and group 2 and between gr 3 and group 4

	4 weeks	8 weeks	16 weeks	20 weeks
Group 1	28.4%	52.1%	64.16%	71.56%
Group 2	10.8%	26.4%	42.8%	65.4%
Group 3	26.8%	50.04%	62.4%	74%
Group 4	8.4%	22.8%	45.6%	62%

Most of the side effects in the study were minor and easily manageable. 52.94% (9/17) patients in the Group 1 (prednisolone alone group) developed side effects with iatrogenic Cushing's being the most common (6/9), onset of diabetes (1/9) and cataract (1/9). Five patients (5/16) in Group 2 developed drowsiness and 3 (3/16) developed constipation. No incidence of neuropathy apparent due to thalidomide was reported. In Group 3, 29.41% (5/17) patients developed side effects. One patient developed deep vein thrombosis (DVT) in right lower limb, which was managed with warfarin and withdrawal of thalidomide. There was recanalization of the deep veins in the follow up period. Two patients (2/17) developed hypertension and two (2/17) patients developed diabetes. In Group 4, (13/16) patients developed skin discoloration and xerosis with clofazimine which was managed with emollients. Two out of 16 patients developed diabetes. Oral Metformin was started in the patients who developed iatrogenic diabetes. Patients who developed cataract were referred to Ophthalmology for surgery.

In the follow up period of 6 months, 2 patients (11.76%) in the Group 1, 1 patient (6.25%) in Group 2, 3 patients (17.64%) in Group 3 and 4 patients (25%) in Group 4 developed fresh episode of T2R. All T2R relapsed patients irrespective of groups were managed with combination of prednisolone and thalidomide.

Discussion

Recently there has been a surge of interest in treatment schedule of severe, chronic and recurrent T2R. There has been a lot of variable opinion on the treatment of T2R using WHO standard protocol (WHO 1998). These recommendations are for health care workers at the primary health care level. Steroids have been extensively used for management of reactions including prevention and treatment of nerve function impairment (Smith et al 2004, Sugumaran 1997, vanBrakel and Khawas 1996). However, at times it is difficult to control many cases with T2R with prescribed dose of prednisolone (40 mg /day). In many situations where the steroids are tapered many of these patients develop new ENL lesions. Also these patients are in dire need of effective and safe treatment, since there is a great danger that these patients with chronic recurrent T2R become steroid dependent. It is often not realized that addition of an alternative drug; thalidomide or clofazimine may reduce the need for steroids. Further, due to long term side effects of steroids after a cumulative dose, researchers have been searching for better steroid based regimens. In the present study we compared the therapeutic efficacy of three most commonly prescribed drugs for T2R: prednisolone, thalidomide and clofaziminewhich to the best of our knowledge have not been compared in this manner.

For first episode of T2R, clinical improvement was better when thalidomide alone was administered compared to prednisolone alone. The side effects were also lower when only thalidomide was administered. Combination of prednisolone and thalidomide was more efficacious as compared to prednisolone and clofazimine for chronic/ recurrent T2R. This combination was also associated with lower incidence of recurrence.

In a study conducted by Kaur et al (2009) which compared the efficacy and safety of thalidomide (300mg/d and then tapered gradually) to that of oral prednisolone (40 mg/d for 2 weeks and then tapered by 10 mg every 2 weeks) in the treatment of moderate to severe T2R in 60 patients who were randomly allocated to two groups comprising 30 patients each. Thalidomide induced a faster clinical response (cutaneous as well as systemic) compared with prednisolone. In this study, the patients taking thalidomide had fewer

relapses and a longer period of remission than those receiving prednisolone (Kaur et al 2009).

In another retrospective study involving 76 T2R patients, prednisolone (n=29) alone was compared with combination of prednisolone and thalidomide (n=47). As the differences of treatment outcomes between the groups remain non-significant they concluded that patients with more severe T2R were more likely to receive combination treatment (prednisolone with thalidomide) compared to prednisolone alone. This study had several limitations such as difference in the sex distribution, duration of treatment and severity of T2R, patients were not randomized, additional drugs were used and regimens were not fixed, and treatment has a bias due to the availability of Thalidomide (Feuth el al 2008). This is some agreement with our results where in they had also observed that combination of prednisolone and thalidomide was better for recurrent/chronic T2R.

Clofazimine, an anti-mycobacterial drug is effective in treatment of leprosy and has good anti-reaction/anti-inflammatory properties. Serious side effects like bowel obstruction, splenic infarction, gastrointestinal bleeding and hepatitis are rare. In many countries national guidelines advise the prescription of Clofazimine particularly in cases of recurrent severe T2R, however, this is often not done. Clofazimine will not relieve acute symptoms. It is not very effective T2R drug but is slow acting. It is a common knowledge that in drug regimen with Clofazimine like WHO-MDT fewer reactions are observed. This suggests that Clofazimine could probably be used in successful control of chronic recurrent T2R. Patients with severe bouts of T2R over a short period of time should be given high dose (300 mg) Clofazimine for 2 months together with steroids to relieve symptoms. Clofazimine should be continued at 200-300 mg for a long time if recurrent reactions are there and the steroid should be tapered gradually under the umbrella of Clofazimine. This is not a magical solution as it may take a year or even more before the patient will be steroid free. However, it is better that steroid dependent patient to look after. Hence forth Clofazimine has a role to play in recurrent and chronic T2R to avoid steroid dependency.

However, there are no comparative studies which have assessed Clofazimine in combination with Prednisolone. Treatment with Clofazimine and steroids can be a good combination in chronic and recurrent T2R because of its anti-inflammatory effect and in cases where Thalidomide cannot be given because of availability, in eligibility and logistics of lack of mandatory supervision.

Thalidomide has proven to be a very effective drug but cannot completely replace steroids. Signs and symptoms can resolve even more rapidly but in case of acute nerve damage or iridocyclitis higher steroid doses may be required. Further, there are several newer/ old known alternate drugs such as cyclosporine, pentoxyphylline, methotrexate etc which have been recommended under certain conditions including cases which are non responsive to commonly described reaction agents. These , however, need larger experience (Kar and Gupta 2016).

Early detection of nerve damage in leprosy and its prompt treatment is of paramount importance in reducing deformities and disability. The regimens containing higher dose of prednisolone (60 mg or 1mg/kg) with adequate duration are able to treat reactions as well as early nerve damage in leprosy and minimize recurrence. In view of the reduced recurrence with these regimens, the need for additional steroid requirement or repeat therapy is minimized.

The present study should be followed by prospective study(ies) which should not have limitations of randomization, numbers and

duration of long term follow-up. Reaction severity scales in fresh / cases with first episodes versus recurrent/ chronic cases are different but these are comparable between group 1 and 2, similarly group 3 versus 4 are comparable. We also need to carefully compare the results of RSS and VSS scores in significant number of cases at similar intervals. Nevertheless out study has come out with interesting findings with potential application which needs to be confirmed by study on lager numbers and preferably by multicentric studies. To conclude for the management of first episode of T2R thalidomide appears to be better than prednisolone taking into account the cure rate and adverse reactions. For recurrent/ chronic ENL, prednisolone with thalidomide or clofazimine are both efficacious. However, prednisolone with thalidomide appears to be better than prednisolone and clofazimine. In spite of its slow onset of action, clofazimine has a definite role specially when thalidomide cannot be administered because of non availability, high cost and contraindication of its use in women in child bearing age. In out study the effecticacy gap was observed to be quite narrow at 20 weeks between prednisolone plus thalidomide versus prednisolone plus clofazimine. Twenty weeks anti-reactional treatments may not be adequate to control reaction in all cases. In some patients, prolonged therapy may be required to control T2R. In addition relapse of T2R in few patients is bound to occur irrespective of therapy regimen which may be better controlled with combination therapy (Prednisolone + thalidomide). Alternative newer regimens need to be investigated in multi centric study (ies).

References

1. Feuth M, Brandsma JW, Faber WR et al (2008). Erythema nodosum leprosum in Nepal: a retrospective study of clinical features and response to treatment with prednisolone or thalidomide. *Lepr Rev.* 79: 254-69.
2. Jolliffe DS (1977). Leprosy reactional states and their treatment. *Br J Dermatol.* **97**: 345-352.
3. Kar HK and Gupta R (2016). Management of leprosy reactions. In IAL Text Book of Leprosy, HK Kar and B Kumar (Eds), Jaypee Health Sciences Publisher, New Delhi and other places, 2nd Edition, pp 465-477.
4. Kaur I, Dogra S, Narang T, De D (2009). Comparative efficacy of thalidomide and prednisolone in the treatment of moderate to severe erythema nodosumleprosum: a randomized study. *Austral J Dermatol*. **50**: 181-5.
5. Lockwood DN (2000). Steroids in leprosy type 1 (reversal) reactions: mechanisms of action and effectiveness. *Lepr Rev.* **71** Suppl: S111-114.
6. Meyerson MS (1996). Erythema Nodosum Leprosum. *Int J Dermatol.* **35**: 389-91.
7. Naafs B (1996). Bangkok Workshop on Leprosy Research. Treatment of reactions and nerve damage. *Int J Lepr Other Mycobact Dis*. **64 Suppl**: S21-S28.
8. Naafs B (2003). Treatment duration of reversal reaction: a reappraisal. Back to the past. *Lepr Rev*. **74**: 328-336.
9. Naafs B (2006). Treatment of leprosy: science or politics? *Trop Med Int Health*. **11**: 268-278.
10. Naafs B, Pearson JM, Wheate HW (1979). Reversal reaction: the prevention of permanent nerve damage. Comparison of short and long term steroid treatment. *Int J Lepr Other Mycobact Dis.* **47**: 7-12.
11. Nery JA, Vieira LM, de Matos HJ et al (1998). Reactional states in multibacillary Hansen disease patients during multidrug therapy. *Rev Inst Med Trop São Paulo.* **40**: 363-370.
12. Pannikar V (2003). The return of thalidomide: new uses and renewed concerns. *Lepr Rev.* **74**: 286-288.
13. Parida SK, Grau GE, Zaheer SA et al (1992). Serum tumor necrosis factor and interleukin 1 in leprosy and during lepra reactions. *Clin Immunol Immunopathol.* **63**: 23-27.
14. Rao PS, Sugamaran DS, Richard J etal (2006). Multi-centre, double blind, randomized trial of

three steroid regimens in the treatment of type-1 reactions in leprosy. *Lepr Rev.* **77**: 25-33.

15. Rea TH, Levan NE (1975). Erythema nodosum leprosum in a general hospital. *Arch Dermatol.* **111**: 1575-1580.
16. Richardus JH, Withington SG, Anderson AM et al (2003a). Treatment with corticosteroids of long standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev.* **74**: 311-318.
17. Richardus JH, Withington SG, Anderson AM et al (2003b). Adverse events of standardized regimens of corticosteroids for prophylaxis and treatment of nerve function impairment in leprosy: results from the 'TRIPOD' trials. *Lepr Rev.* **74**: 319-327.
18. Sampaio EP, Sarno EN, Galilly R et al (1991). Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med.* **173**: 699-703.
19. Sehgal VN (1987). Reactions in leprosy. Clinical aspects. *Int J Dermatol.* **26**: 278-285.
20. Smith WCS, Anderson AM, Withington SG et al (2004). Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomized placebo controlled trial (TRIPOD 1). *BMJ* **328**: 1459.
21. Sugumaran DS (1997). Steroid therapy for paralytic deformities in leprosy. *Int J Lepr Other Mycobact Dis.* **65**: 337-344.
22. van Brakel WH and Khawas IB (1996). Nerve function impairment in leprosy: an epidemiological and clinical study - Part 2: Results of steroid treatment. *Lepr Rev.* **67**: 104-118.
23. van Brakel WH, Anderson AM, Withington SG et al (2003). The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev.* **74**: 300-310.
24. van Brakel WH, Nicholls PG, Lockwood DN et al (2007). A scale to assess the severity of leprosy reactions. *Lepr Rev*. **78**: 161-4.
25. World Health Organization (1998). WHO Expert Committee on Leprosy, Seventh Report, WHO, Geneva. *WHO Tech Rep Ser*. **874**: 22.

How to cite this article : Kar HK and Gupta L (2016). Comparative efficacy of four treatment regimens in Type 2 Leprosy Reactions (Prednisolone alone, Thalidomide alone, Prednisolone plus Thalidomide and Prednisolone plus Clofazimine). *Indian J Lepr.* **88** : 29-38.