e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 448-454

Original Research Article

Evaluation of Methotrexate and Sodium Stibogluconate in the Patients of Type Two Lepra Reactions

Pritam Sakhare[1], Ranjit Wagh[2], Rohini Gaikwad[3], PL Waghmare[4], S.P. Rao[5]

[1]Department of Pharmacology ,RCSM GMC, Kolhapur
[2]Department of Pharmacology, MIMER Medical College, Talegaon, Pune
[3]Department of Skin and VD MIMER Medical College, Talegaon, Pune
[4]Medical Officer, Dept of Health Govt of Maharashtra
[5]Departement of PSM, BJ Medical College, Pune

Received: 25-10-2023 / Revised: 23-11-2023 / Accepted: 26-12-2023
Corresponding Author: Dr. Pritam Sakhare
Conflict of interest: Nil

Abstract:

Introduction: Occurrence of Lepra reactions is one of the characteristics of Leprosy. Type 2 lepra Reactions have unpredictable course usually occurs 6 months after starting Multi Drug Therapy; presentation may be intermittent or continuous.

Materials and Method: It was a Prospective, Interventional, Open Label, Systemic Randomized, Parallel Allocation Study carried out on 30 patients with Type 2 Lepra Reactions.

The Anti-Inflammatory and Immunosuppressant are first-choice drugs to control symptoms. Prednisolone + Clofazamine are commonly used regimen, but have limitations. Methotrexate is known immunosuppressant Sodium Stibogluconate had been used for treatment of type 2 lepra reaction since 1940. Recent in vitro studies confirmed the immunosuppressant properties of Sodium Stibogluconate. The effect of Prednisolone + Clofazamine (P+C), Prednisolone + Methotrexate (P+M) and Prednisolone + Sodium Stibogluconate (P+SSG) on arithmetic mean score geometric mean scores were assessed for efficacy analysis.

Results & Conclusions: (1) All three regimens, P + C, P + M, P + SSG reduce the clinical score to minimum after first week of treatment. Thus, these regimens are efficacious in reducing clinical symptoms of type 2 lepra reaction patients. (2) P + SSG provided slightly faster relief in decreasing clinical symptoms than P+C and P + M.

Keywords: Type 2 Lepra Reactions, Sodium Stibogluconate, Methotrexate, Prednisolone, Clofazimine.

Introduction

Leprosy has ability to cause slow, concealed infection with delayed clinical manifestations. Lepra reactions may occur in up to 25% of patients with paucibacillary leprosy and as much as 40% in multibacillary leprosy [1]. Clinical indications of reactions are skin lesions, nerve pain, loss of sensation loss of function with fever and joint pain. The reactions may rapidly cause severe irreversible nerve damage and must always be treated promptly.

Lepra reactions can develop at any time, at onset of the disease, before starting the treatment, during treatment, after completion of the treatment. There are two types of Lepra reactions. Type 1 Reaction: Also called Reversal Reaction can occur in any patient with unstable CMI. Type 2 Reaction: Also called Erythema Nodosum Leprosum (ENL) occurs in patients with Multi Bacillary leprosy having a heavy load of bacilli. Type 2 lepra Reactions are Immune complex mediated phenomenon caused due to reactionary inflammation to Mycobacterium Leprae [1]. Clinical features of ENL are red, painful, tender, subcutaneous (deep) nodules (ENL) appear commonly on face arms and legs, in group and subside within few days. Apart from the nerves, eyes, joints, bones, testes, kidney, lungs may be affected. Treatment with MDT reduces the frequency and severity of lepra reactions [2]. Anti-inflammatory and Immunosuppressant drugs form the mainstay of treatment. WHO and NLEP recommend steroid (Prednisolone) and Clofazamine for the treatment of type 2 reactions, along with Thalidomide for severe type 2 reactions [3].

The course of lepra reaction is highly unpredictable and there are patients of resistant, recurrent and severe type 2 lepra reaction. Methotrexate is an antimetabolite and antifolate drug. Low dose methotrexate is a well-tolerated and generally safe drug in the treatment of certain autoimmune

diseases as an immunosuppressant [4]. Sodium stibogluconate has been used for nearly 70 years for the treatment of type 2 lepra reactions [5]. There are references suggesting usefulness of sodium stibogluconate and methotrexate in treatment of type 2 lepra reaction, but there are no clinical studies to compare these drugs [6]. Experimental studies suggested that pentavalent antimonials potentiated phagocytosis by neutrophils & monocytes, increased superoxide generation by phagocytes. [7] SSG has in-vitro protein tyrosine phosphatase inhibitor action resulting in anti-leukemia activity [8]. Also, in order to avoid adverse effects associated with long term steroid and Clofazamine, this study is undertaken.

Material & Method

This study was planned with the following aims and objectives:

1. To compare efficacy of methotrexate and sodium stibogluconate in patients of type 2 lepra reactions.
2. To study steroid sparing effect of methotrexate and sodium stibogluconate.

Primary end point:

1. To reduce total clinical score in patients of Type 2 Lepra reactions on treatment with standard regimen Prednisolone + Clofazimine and Prednisolone + Methotrexate, Prednisolone + Sodium Stibogluconate.
2. To reduce the dose of steroid to 10mg bd at the end of 4th week of treatment in all three groups.

Secondary endpoint:

To compare safety of Methotrexate and Sodium Stibogluconate in patients of Type 2 Lepra reactions.

The study was duly approved by the Institutional Ethics Committee. 30 Patients were recruited from the Skin out Patient Department (OPD) of the Institution. The study was carried from December 2011 to October 2013.

Selection of Patients

Inclusion Criteria

- Type 2 lepra reaction patients who were willing to participate in the study and comply with its procedures by signing a written informed consent.
- Age group: - 15 – 80 years of either sex.
- Those who understood agreed to adhere to the dosing visit schedules, agree to assess and record their symptom severity scores, medication times, Concomitant Medications, adverse events accurately and consistently in a daily diary.

Exclusion Criteria

- Presence of another serious illness.
- Patient with abnormal haemogram.
- Presence of previous heart disease, history of MI, abnormal ECG changes.
- Presence of liver disease.
- Presence of kidney disease.
- Pregnant patient.

Enrolment of the patient

Written informed consent was obtained from each patient before participating in the study, with explanation of detailed procedure of study in a common language as in patient information sheet. Sufficient time was given to patients for answering their doubts and questions.

Calculation of sample size

The prevalence of type 2 lepra reactions in BL and LL cases has wide geographic variation; varying from 19-26% in Asia[9], so all the patients of type 2 lepra reaction visiting OPD were included into the study. Also the medical records of our institute was studied which suggested that we had treated 10-12 patients of type 2 lepra reaction per year over the last four years. Non-probability, purposive sampling technique was employed.

Study type: Interventional

Study design: Systematic Randomized study

Endpoint Classification: Efficacy**,** Safety of drugs

Intervention Model: Parallel assignment

Masking: Open label

Primary Purpose: Treatment

Drug administration:

Drug	Dose
Prednisolone	40mg BD oral [2]
Clofazimine	100mg TDS oral [2]
methotrexate	7.5 mg per week in three divided doses [4]
Sodium stibogluconate	3 ml intramuscular per day, for 10 days. Each ml contains 100mg. Maximum permissible dose 3 gm over 3 weeks [5]

Study Procedure:

Patients attending Skin OPD were screened by the Physician. The diagnosis of type 2 lepra reaction was made on the basis of patient's chief complaints, past history, clinical examination. The patients fulfilling the inclusion criteria were briefed about the nature of the study, its purpose, study procedures and follow-ups.

Patient information sheet was given to all prospective participants. Written informed consent was obtained from the patients willing to participate in the study. Screening investigations were carried out and the eligible candidates were included in the study.

Parallel systemic allocation

After initial screening, the data regarding age, sex, height, weight, past medical history, family history, physical examination and clinical examination was recorded in the case report form. Laboratory investigations like Hb, CBC (complete blood count), blood urea, serum Creatinine, SGOT, SGPT, serum bilirubin and serum alkaline phosphate were carried out in the Department of Pathology, Department of Biochemistry. ECG was taken and consulted with Department of Medicine. Laboratory investigations were carried out at 0 week for screening and at the end of study for assessment of safety of the investigational drugs.

Concomitant Medications

Patients on MDT were compulsively directed to continue the treatment. Paracetamol was given to all patients for treatment of fever, in doses of 500mg bd permissible up to 500mg four times a day. Patients with concomitant chronic diseases such as diabetes, hypertension, were allowed to continue their medications, but their treatment was adjusted so as to get minimum drug interactions and least additive adverse effects.

All the patients were requested to report in Skin OPD next day for clinical assessment along results of lab investigation. Patients belonging to Prednisolone + Clofazamine group and Prednisolone + Methotrexate group were provided with medications and requested for the follow up every week for clinical assessment. Patients allocated to the Prednisolone and Sodium stibogluconate group were admitted to the skin ward for first ten days of the study and after discharge requested for follow up every week.

The dose of prednisolone was reduced by 10mg every week. Dose of Clofazamine was reduced by 50 mg per week. Methotrexate was given for initial 2 weeks and depending on clinical response repeat dose given in between for recurrences. Full dose of SSG (2.5- 3gms over 3 weeks) was given at the start of treatment, with repeat dose after 15 days in cases of recurrence.

All the patients were informed to report any difficulty related to study and also about any illness, symptom or recurrence.

Clinical Score Scale [10]

Criteria	Severe	Moderate	Mild	Absent
Inflamed Nodules	3(>20, vesiculation and postulation)	2 (>10, all 4 limbs)	1 (<10, one or two limbs)	0
Fever	3 (>102°F)	2(up to 102°F)	1 (100°F)	0
Constitutional symptoms	3 (Severe- Moderate + neuritis)	2 (Moderate- Mild +nausea, vomiting)	1 (Mild- myalgia, arthralgia)	0

Constitutional symptoms-

- Mild- myalgia, arthralgia
- Moderate- Mild +nausea, vomiting
- Severe- Moderate+ neuritis

Mild: Temperature does not rise above 100°F & reacting skin lesions are few confined to one to two extremities, Arthralgia, myalgia.

Moderate: Temperature goes up to 102°F, the skin lesions are more numerous, affecting all the 4limbs, with a few on the trunk and face and perhaps occasional vesiculation or postulation.

Severe: Temperature rises above 102°F, hyperpyrexia may be observed, vesiculation and pustulation are frequent. Temperature in such cases tends to be remitted. Visceral involvement is not uncommon.

Safety assessment

General clinical safety was monitored by vigilant follow up of patients for treatment of emergent adverse events, if any, and recorded in the case report form. Patients with adverse drug reaction were treated appropriately by the physician in Skin OPD.

Statistical analysis

Arithmetic mean and Geometric mean of total scores were compared. Extended Mantel-Haenszel chi square for linear trend among three study groups over the period 12 weeks. This test for trend is applied for dose-response studies and can also be used to test for trends with age, passage of time, or any ordered variable. The Extended Mantel-Haenszel chi square that is calculated reflects the departure of a linear trend from horizontal (i.e., no trend). If the associated p value is less than 0.05, there is 95% probability that a trend exists in

the underlying population. Group difference was ascertained by Analysis of variance (ANOVA). The reason for applying an ANOVA is to see if there is any difference between groups on total clinical score. ANOVA gives the F statistic which is the ratio Between Group Variation to the Within Group Variation. If the Between Group Variation is significantly greater than the Within Group Variation, then it is likely that there is a statistically significant difference between the groups. The significance of F ratio will be assessed by statistical package. P value less than 0.05 was considered as statistically significant. Software for statistical analysis SSPS (Version 22.0) was used.

Flowchart of Study

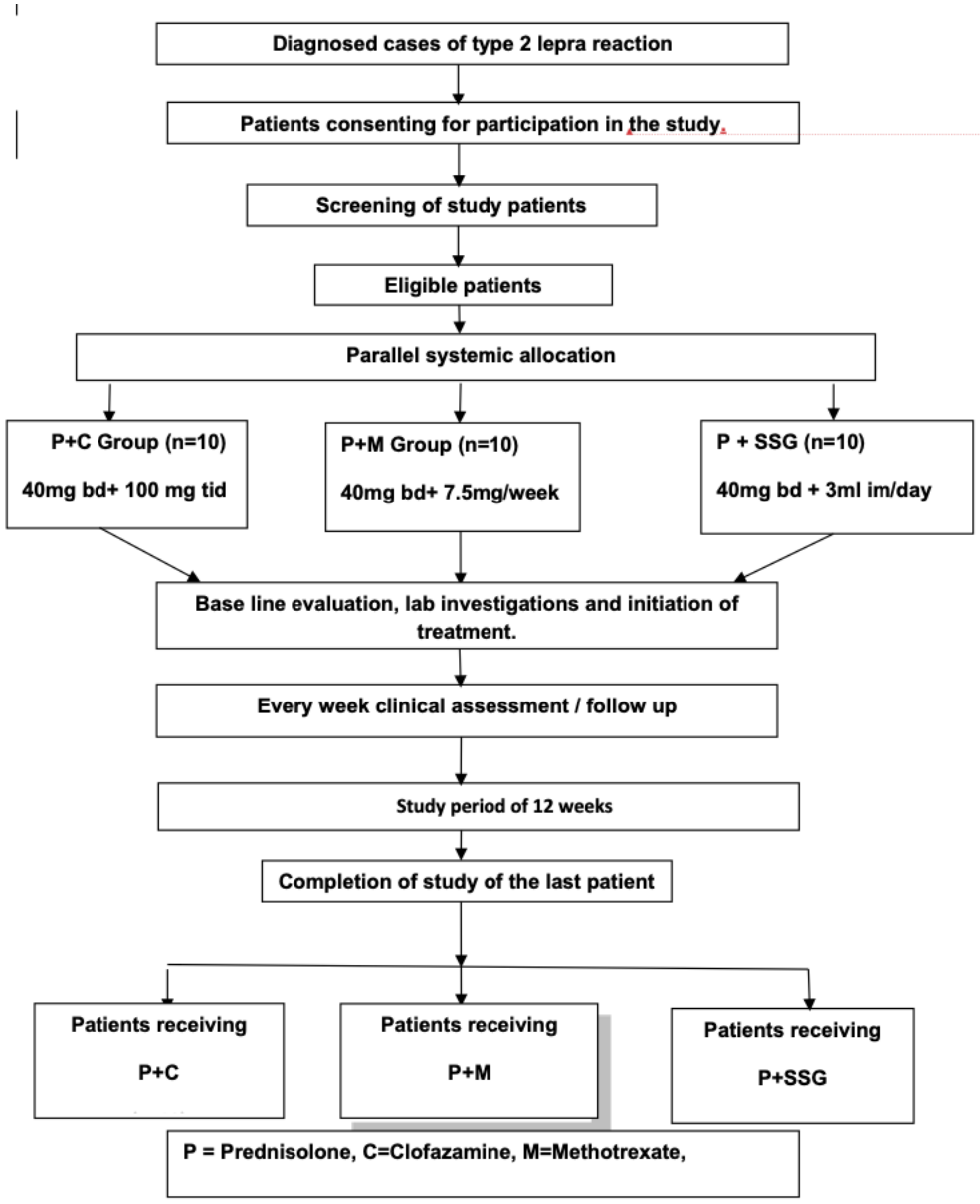
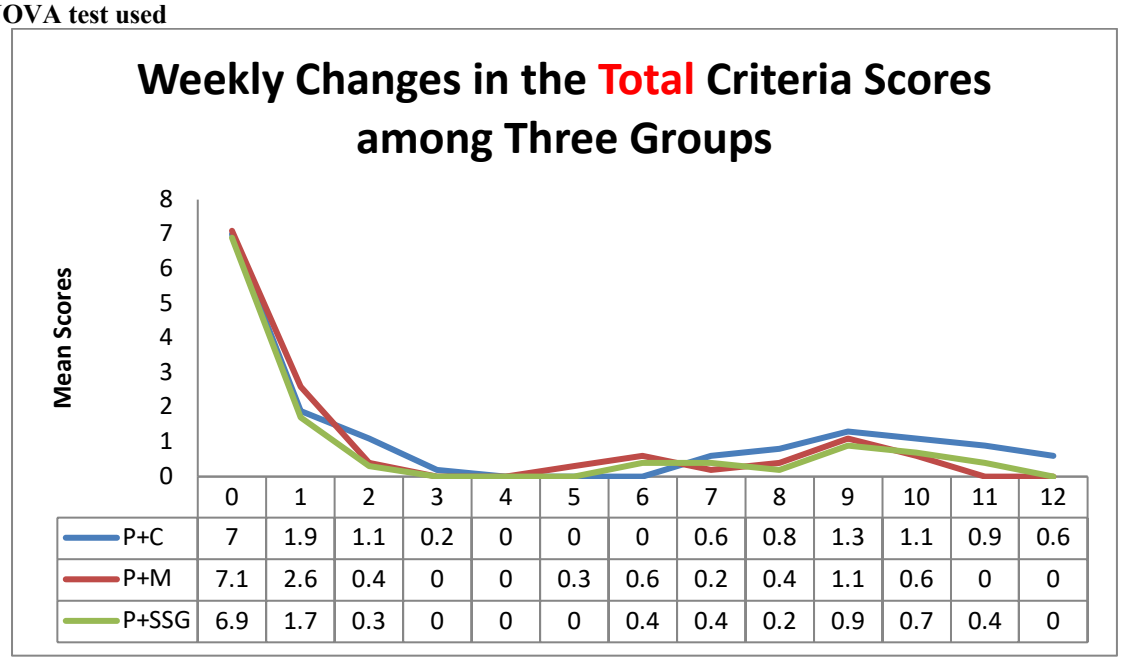


Table 1: Mean and Standard Deviation of Disease Duration in months among the three groups of Patients

SN	Group	Duration of Disease				Significance*
		Mean	SD	Minimum	Maximum	
1	P+C	9.50	4.22	4.0	18.0	F Statistic = 0.21
2	P+M	10.40	2.71	6.0	14.0	P value = 0.812
3	P+SSG	10.30	3.09	5.0	14.0	(Not Significant)

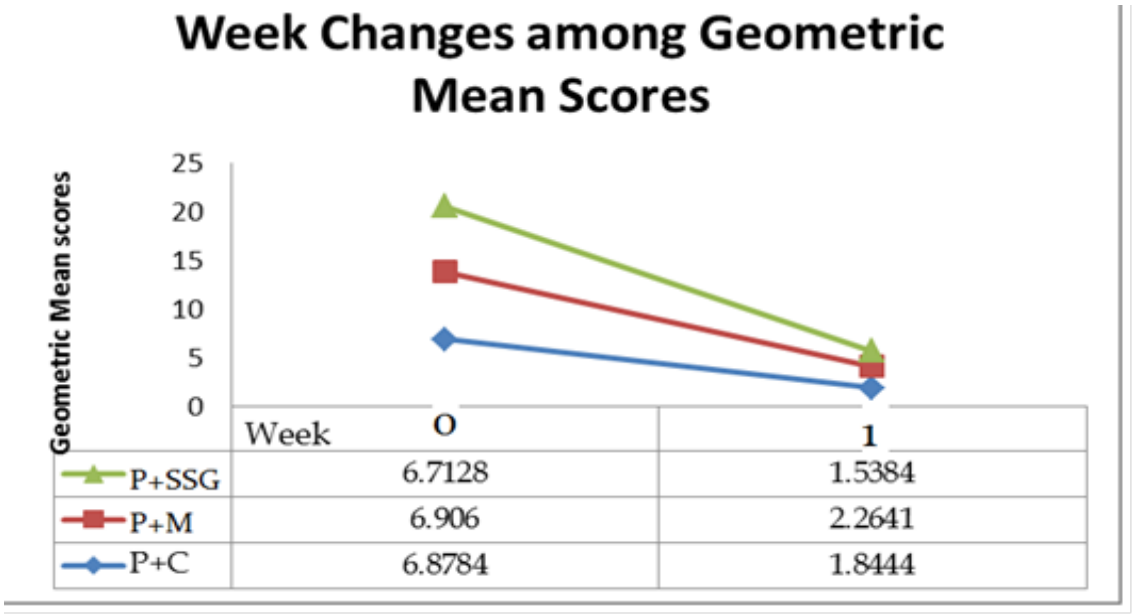
ANOVA test used



	0	1	2	3	4	5	6	7	8	9	10	11	12
P+C	7	1.9	1.1	0.2	0	0	0	0.6	0.8	1.3	1.1	0.9	0.6
P+M	7.1	2.6	0.4	0	0	0.3	0.6	0.2	0.4	1.1	0.6	0	0
P+SSG	6.9	1.7	0.3	0	0	0	0.4	0.4	0.2	0.9	0.7	0.4	0

Figure 1: Weekly Changes in the Total Criteria Scores among Three Groups

As treatment continued patients from P+M and P+SSG had mean scores below one, which has no clinical significance. Also in later weeks all three groups had scores below one which have no clinical significance. So geometric mean of scores is calculated.



Week	0	1
P+SSG	6.7128	1.5384
P+M	6.906	2.2641
P+C	6.8784	1.8444

Figure 2: week changes among Geometric Mean Scores

As the geometric mean scores for all three groups reduced below one which is clinically insignificant, linear trend over the period of 12 weeks were studied.

Table 2: Linear Trend among groups from Baseline week to after 12 weeks

S.N.	Group	Extended Mantel-Haenszel chi square for linear trend	p Value
1	P+C	17.11	0.00003521
2	M+P	43.32	<0.0000001
3	SSG+P	62.12	<0.0000001

As the mean scores and geometric mean scores in all three groups reduced below one over the period of 12 weeks, linear trend among three study groups from baseline that is before starting treatment and at the end of 12 weeks showed p value less than 0.05.

Table 3: INITIAL: Week 0

SN	Group	Week 0	ANOVA	Week1	ANOVA
1	P+C	7.0±1.0	F Statistic= 0.0779	1.95±0.65	F statistic = 3.8087
2	P+M	7.1±1.1972	p value= 0.92 (Not Significant)	2.6±0.8432	P value = 0.034
3	P+SSG	6.9±1.19	Test for equality of variance Chi square =0.35 (Not Significant)	1.7±0.7527	Test for equality of variance Chi square = 0.74

Discussion

Diagnosing a type 2 lepra reaction in a patient of leprosy is not challenging, however treatment is difficult owing to its recurrent nature. There are various precipitating factors for type 2 lepra reaction while the treatment is directed towards the suppression of immunological changes. Type 2 lepra reaction is due to immune complex deposition so Immunosuppressant and Anti-inflammatory drugs are the absolute choices. Therefore, steroids are the most important part of treatment. Treating the symptoms of Type 2 Lepra reactions and ensuring a decent quality of life to the patients is challenging. Currently, used drugs for treatment of lepra reactions have various limitations, so there is need for alternatives.

Taking in to consideration course of the disease, treatment regimen and possibility of follow up, present duration of study is twelve weeks. Increased study duration to six months would have provided better observations over longer period but there were difficulties regarding follow up.

The total clinical score is used for the first time in the study as there are very small numbers of trials conducted on type 2 lepra reactions till date. Also there were scarcities of guidelines regarding clinical trials of type 2 lepra reaction. The total clinical score is mentioned in one of acclaimed and widely referred book in the field of leprosy [10].

We observed significant reduction of total clinical score after the completion of the treatment in P + C, P + M, P + SSG group, with only slight difference between the groups. There was a progressive decrease in the scores within all treatment groups along the course of the study. However there were 13 Cases of recurrences confirming natural course of disease. The recurrence is attributable to various precipitating factors, resistance to various drugs, steroid dependence. Patients belonged to P + SSG group showed slightly faster reduction in the clinical score after the first week, which might be due to professional care at the hospital. Our study shows the efficacy of methotrexate and sodium stibogluconate in treatment of type 2 lepra reaction.

Assessing steroid sparing effects of methotrexate and sodium stibogluconate was another aim which could not be studied due to unpredictable course of illness, differences in properties of drugs used in the study; steroid resistance in some patients. Reducing the dose of prednisolone with subsequent increase in the dose of Clofazamine, Methotrexate and Sodium Stibogluconate substantially increases risk of serious adverse effects, chance of worsening of clinical condition such permanent neuropathy.

There were no serious adverse events in any treatment group. Every patient underwent baseline investigation before enrolling into the study and followed with investigations at the end of study. Due to long term steroid use there were cases of secondary infections, gastritis and steroid induced acne.

Patient belonging to P + M group had common complain of mucositis i.e glossitis, gastritis along with abdominal discomfort. Liver Function Test and Total Leucocyte Counts of patients showed no abnormal variations. But there were cases of reduced hemoglobin. Patients of P+ SSG complained of pain at the site of injection. Liver function test, kidney function test, ECG at the end of study showed no abnormal variations. Patient undergoing treatment with sodium stibogluconate requires admission to the hospital and bedside observation for 2 hours after administration of drug. Such requirements make treatment difficult at primary and secondary centers.

Patients of leprosy belongs very low socioeconomic status and often abandoned by family. These factors affect the outcome as patients cannot bear the cost of treatment, loss of wages, and admission to the hospital. Prolong treatment along with the disabilities and recurrent reactions make life of patient difficult.

References

1. Pandhi D, Chhabra N. New insights in the pathogenesis of type 1 and type 2 lepra reaction. Indian J Dermatol Venereol Leprol [serial online] 2013 [cited 2013 Dec 11]; 79:739-49.
2. Epidemiology. Training manual for medial officers. National leprosy eradication programme (http://nlep.nic.in/guide.html).
3. Leprosy elimination/ leprosy today www.who.int/lep/en/.

4. Tripathi KD, Essential of Medical Pharmacology.In: Tripathi KD, Editor. Anticancer drugs. Eighth edition Delhi Jaypee Brothers Page no 921.
5. Ramanujam K, Dharmendra, Leprosy. In: Dharmendra, Editor. Management of reactions in Leprosy First Edition Mumbai Kothari Medical Publishing House, pages no 513,516.
6. Girdhar BK. Immuno pharmacology of drugs used in leprosy reactions. Indian J Dermatology Venereology Leprology 1990; 56:354-63.
7. Muniz-Junqueira MI, de Paula-Coelho VN. Meglumine antimonate directly increases phagocytosis, superoxide anion and TNF-alpha production, but only via TNF-alpha it indirectly increases nitric oxide production by phagocytes of healthy individuals, in vitro. Int Immunopharmacol. 2008; 8(12):1633-1638.
8. Pathak, M., Hu, X. & Yi, T. Effects of sodium stibogluconate on differentiation and proliferation of human myeloid leukemia cell lines in vitro. Leukemia. 2002; 16: 2285–2291.
9. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 yearexperience from north India. Int J Lepr Other Mycobact Dis, 2004; 72: 125–133.
10. Ramu.G, Dharmendra, Leprosy. In: Dharmendra, Editor. Acute Exacerbations in Leprosy First Edition Mumbai Kothari Medical Publishing House page no 115-122.