Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Assessment of Treatment Outcome in Post-Kala-Azar Dermal Leishmaniasis (PKDL) Patients– A Record-Based Observational study in a Speciality Public Hospital, Kolkata

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Received: May 2019
Accepted: May 2019

ABSTRACT

Background: In the absence of effective vector control measures and vaccines against leishmaniasis, effective chemotherapy remains the mainstay of treatment. Identification of post-kala-azar dermal leishmaniasis (PKDL) is important due to the long and toxic treatment and the fact that PKDL patients may serve as a reservoir for visceral leishmaniasis (VL). This retrospective study was done to assess the outcome of pharmacotherapy in post-kala-azar dermal leishmaniasis (PKDL) patients in a specialty public hospital in Kolkata. **Methods**: The hospital records of all consecutive PKDL patients admitted at Calcutta School of Tropical Medicine (CSTM), Kolkata during the last five years - 2010-2014, were reviewed and the relevant information inputs as documented studied to realize the noted objectives. Clinical presentation on admission including presence of co-infections (particularly HIV), trends and patterns of treatment regimens and rationale thereof, if available; treatment (anti-leishmaniasis) outcomes in reference to efficacy, safety and tolerability, fatality like serious complications and mortality and adverse drug reactions (for anti-leishmaninal drugs primarily), if any was noted. **Results**: PKDL cases presented with insidious onset skin lesions of different types without much systemic illness. 2 out of 19 cases presented with fever and 2 other cases had mild anemia. PKDL cases presented with 4 types of skin lesions. Multiple macular or hyppigmented macular lesions were commonest, 8 out of 19 cases (42.10%). In PKDL cases treatment outcome was difficult to say unless parasitologically declared negative, though clinically regression of the lesions were visible in all cases. Tolerability was least with AmB followed by SSG and best with miltefosine. **Conclusion**: So, it can be concluded from this study that in this institute PKDL were treated with conventional and liposomal AmB as well as with SSG, miltefosine and combination therapy. Among the regimens short course L-AmB was found to be the most efficacious and tolerable in respect to ADRs and hospital stay.

Keywords: Kala-azar, Post-kala-azar dermal leishmaniasis (PKDL), Anti-leishmaninal drugs, Liposomal AmB, Sodium Stibogluconate, Miltefosine, ADRs.

INTRODUCTION

PKDL manifests first as small, measle-like skin lesions on the face, which gradually increase in size and spread over the body. Eventually the lesions may coalesce to form disfiguring, swollen structures resembling leprosy. The gold standard for diagnosis is visualization of the amastigote in splenic aspirate or bone marrow aspirate. Serological testing is much more frequently used in areas where leishmaniasis is endemic particularly different rapid diagnostic tests.[1,2] One of them (the rK39 immunochromatographic test) gave correct, positive results in 92% of the people with visceral leishmaniasis and it gave correct, negative results in 92% of the people who did not have the disease.[3,4]

In India 48 districts in eastern states namely Bihar, Jharkhand, Uttar Pradesh, West Bengal are endemic,

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sporadic cases are also reported from few other districts. Estimated 165.4 million populations mostly of poor socio-economic groups primarily living in rural areas of 4 states are at risk.[5] Miltefosine the first oral drug for this disease has received approval by the Indian regulatory authorities in 2002. Calcutta School of Tropical Medicine is a pioneer institute for treatment of VL and PKDL and it caters the people living in nearby endemic areas for years together since the period of Dr. U N Brahmachari. VL and PKDL patients are treated here after admission on diagnosis in the inpatient department of this hospital. So critical review of the hospital records of admitted PKDL patients of last five years from 2010 to 2014 may give us interesting knowledge of the treatment followed here under different clinical settings, their outcome and ADRs encountered. Also this hospital has been declared as a centre of excellence (COE) for the treatment of HIV patients. As the co-infection of HIV and VL is not uncommon, it may be worthy to see the presence of HIV among the admitted VL and PKDL patients, and if response to treatment in such subgroups differ from those without it.

Aim:

To assess the outcome of pharmacotherapy in post-kala-azar dermal leishmaniasis (PKDL) patients in a specialty public hospital in Kolkata

Objectives:

Primary Objectives

1) To explore the choice of treatment regimens in PKDL patients over the period under study
2) To assess the response to the different treatment regimens in PKDL patients
3) To study the safety and tolerability of anti-leishmanial drugs in such patients
4) To study the adverse drug reactions (for anti-leishmanial drugs primarily), if any, and how they were managed

Secondary Objectives

1) To examine the association, if any, between occurrence of PKDL and the use of any specific anti-leishmanial regime
2) To explore the possibility of re-admission of PKDL within the period under study and probe for its reason, as far as practicable

MATERIAL AND METHODS

The Retrospective, record-based, observational study was conducted in the department of clinical and experimental pharmacology at Calcutta School of Tropical Medicine, Kolkata. The hospital records of all consecutive PKDL patients admitted at Calcutta School of Tropical Medicine (CSTM), Kolkata during the last five years - 2010-2014, were reviewed and the relevant information inputs as documented studied to realize the above-noted objectives. All in-patients of VL and PKDL admitted during 2010-2014 at CSTM were considered. The total number of patients studied was 115.

Inclusion criteria

Case records or Bed Head Tickets (BHTs) of all consecutive VL and PKDL patients admitted at Calcutta School of Tropical Medicine, Kolkata (CSTM), during the five years - 2010-20142, as available in the Hospital Records Section. No case was excluded.

Study technique

With due permission of the hospital administration, the relevant hospital records were accessed and critically reviewed to look for

- clinical presentation on admission including presence of co-infections (particularly HIV)
- trends and patterns of treatment regimens and rationale thereof, if available
- treatment (antileishmaniasis) outcomes in reference to efficacy, safety and tolerability, fatality like serious complications and mortality
- adverse drug reactions (for antileishml drugs primarily), if any, and how they were managed
- duration of hospital stay and advice on discharge if available.
- any other information, if considered important

The Data Collection Form was designed based on the above critical review elements.

While conducting the study it was found that the required information was incompletely available from the BHTs. So, it became necessary to consult with respective treating physicians to fill the gaps of information which may be regarded as source documents. Moreover, whenever possible patients were contacted by telephone which were available on BHTs, gave important information. Data collected were compiled and analyzed using appropriate descriptive statistical methods. The study was undertaken only after the Institutional Ethics Committee approved the study protocol.

RESULTS

In the present study, the total number of BHTs accessed was 115. Among them 96 had VL as the primary diagnosis and 19 had PKDL. Total number of VL cases without HIV was 78. Among them 71 were admitted as new cases, 3 as relapse. In PKDL group there were 19 cases admitted for treatment, 16 cases were new, 2 FU cases where 1 patient was admitted as FU case without prior history of PKDL in the study period and 1 patient was readmitted. Another patient was admitted as Relapse of PKDL. So, altogether 18 patients were considered in PKDL group [Fig. 1]. Number of patients was not the same as the number of cases / BHTs, as the patient might

have been admitted more than once with a diagnosis of relapse and follow up.

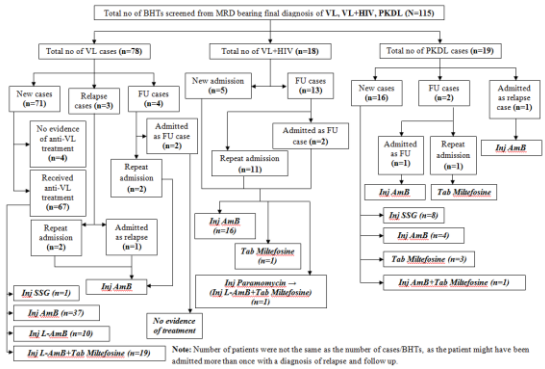

Figure 1: Flowchart of the study

The mean age of PKDL cases under study was 29.31 ± 13.23 years; range was from 14 to 60 years. Only 1 case was from the paediatric age group (0 to 17 years) and 2 cases from the age group of 46 to 60 years. But the maximum no of cases (16, 84%) belonged to 18 to 45 years [Table 1]. In PKDL cases sex distribution was, 78.94% (15 out of 19) of male and 21.04% (4 out of 19) of female ratio being 3.75:1 [Table 2]. West Bengal was the residential address of 15 PKDL patients and 4 cases were from Bihar. Kolkata again having highest numbers (7) of PKDL cases, followed by 2 each from Maldah, Howrah and Burdwan, 1each from North 24 Parganas and Alipurduar districts [Table 3].

PKDL cases presented with insidious onset skin lesions of different types without much systemic illness. 2 out of 19 cases presented with fever and 2 other cases had mild anemia. PKDL cases presented with 4 types of skin lesions. Multiple macular or hyppigmented macular lesions were commonest, 8 out of 19 cases (42.10%). Next group of cases were macula-nodular with 5 (26.31%) cases out of total 19 PKDL cases. Nodular variety was present in 4 cases (21.05%). Nodular cases resemble lepromatous leprosy and they are equally disfiguring, their skin biopsy shows plenty of LD bodies and so are rich reservoirs of infection. Erythematous plaque lesions were least frequent with only 2(10.52%) cases [Table 4].

Over the five years the most preferred regimen was AmB (60%), followed by combination regimen of L-AmB and miltefosine (21%), L-AmB (10%), no treatment in 6% cases and 1% each of SSG, miltefosine and paramomycin followed by combination therapy of L-AmB and miltefosine [Table 10].

Trends and patterns of treatment regimens in PKDL patients

Eight out of 19 PKDL cases admitted received Injection SSG 10 mg/kg body weight 120 injections. In the admitted period the drug was given on IV route, but further doses were given on daily basis deep IM through OPD. Half of the cases encountered the commonest ADR arthralgia, myalgia treated with analgesic. One case encountered thrombophlebitis which was treated with antibiotic and analgesic.

Six out of 19 cases of PKDL received Injection AmB in the dose of 1mg/kg body weight for 20 doses followed by 20 days gap next again repetition of AmB, 4 cycles were given. ADR encountered in all cases in the form of fever with chill and rigor which were treated with antihistaminic and paracetamol, but two cases encountered increased creatinine for which infusion was withheld for the values to come down to normal. Hypokalemia occured in 2 cases which were treated with Injection KCL.

Four out of 19 admitted cases were given tablet Miltefosine as monotherapy 50 mg twice daily for 28 days with one case encountered vertigo which might not be related with miltefosine. One case was treated with Injection AmB infusion for 20 doses followed by Tablet Miltefosine 50 mg twice daily for 28 days. This patient encountered hypokalemia for which orally KCL syrup was given during the therapy of AmB [Table 8].

Year-wise preference of treatment regimen was variable:

In 2010 maximum (67.67%) cases got SSG followed by 33.33% Miltefosine.

In 2011 SSG was used in 2 cases (66.67%), followed by Miltefosine in 1 case (33.33%).

In 2012, 2 (50%) cases received SSG and 25% (n=1) each got AmB and Miltefosine.

In 2013, 1(50%) out of 2 cases received AmB and 1 (50%) received combination of AmB with Miltefosine.

In 2014, all 4 (100%) cases received AmB [Table 9].

Duration of hospital stay: In PKDL cases average hospital stay with SSG was14.62 ± 4.69 days, with AmB 23.17± 15.31 days and with Miltefosine it was 12 ± 8.41 days; so minimal hospital stay was with miltefosine therapy.

Treatment outcomes

In PKDL cases treatment outcome was difficult to say unless parasitologically declared negative, though clinically regression of the lesions were visible in all cases. Tolerability was least with AmB followed by SSG and best with miltefosine [Table 10].

Table 1: Age distribution of PKDL cases

Age group (years)	No of cases	Percentage
0-17	1	5
18-45	16	84
46-60	2	11

Commonest age group was from 18 to 45 years. Mean age was 29.31 ± 13.23 years [Table 1].

Table 2: Sex distribution of admitted PKDL cases during study period

Sex	No of cases	Percentage
Male	15	79
Female	4	21

Male female ratio in admitted PKDL cases were 3.75:1 [Table 2].

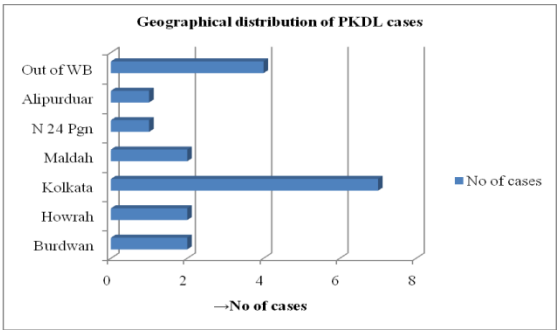

Figure 2: Geographical distribution of PKDL cases

Table 3: Geographical distribution of PKDL cases

Geography	No of cases	Percentage
Burdwan	2	10
Howrah	2	11
Kolkata	7	37
Maldah	2	11
N 24 Pgn	1	5
Alipurduar	1	5
Bihar	4	21

Maximum number of PKDL cases was from Kolkata, West Bengal 21% cases were from Bihar [Table 3].

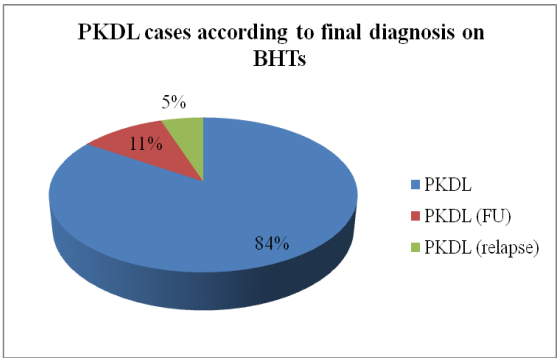

Figure 3: PKDL cases according to final diagnosis on BHTs

Table 4: Skin lesions at presentation of PKDL cases

Type of skin lesion	No of cases	Percentage (%)
Macular	8	40
Maculo-nodular	5	30
Nodular	4	20
Erythematus	2	10

Table 5: PKDL cases according to final diagnosis on BHTs

Types of PKDL	No of cases	Percentage (%)
PKDL	16	84
PKDL (FU)	2	11
PKDL (relapse)	1	5
Total	19	100

Out of 19 admitted PKDL cases one case was readmitted as relapse. So, altogether there were 18 patients [Table 5].

Table 6: Year wise PKDL cases admitted

Year	No of cases	Percentage
2010	6	32
2011	3	16
2012	4	21
2013	2	10
2014	4	21

Maximun numbers of PKDL cases were admitted in the year 2010 followed by 2011 [Table 6].

Table 7: PKDL cases treated in different regimens

Treatment regimens	No of cases	Percentage (%)
SSG	8	42
AmB	6	32
Miltefosine	4	21
AmB+ Miltefosine	1	5
Total in 5 years	19	100

Commonest drug prescribed was SSG followed by AmB and miltefosine [Table 7].

Table 8: ADRs encountered in treatment of PKDL cases

ADRs	No of cases	Percentage (%)
Arthralgia/Myalgia	4	19
Chill & Rigor	4	19
Hypokalemia	4	19
Increase creatinine	2	9
Vertigo	1	5
No ADR	6	29

Maximum number of ADRs was chill and rigor, arthralgia/myalgia, and hypokalemia all 19% but there were no ADRs in 6 cases (29%) [Table 8].

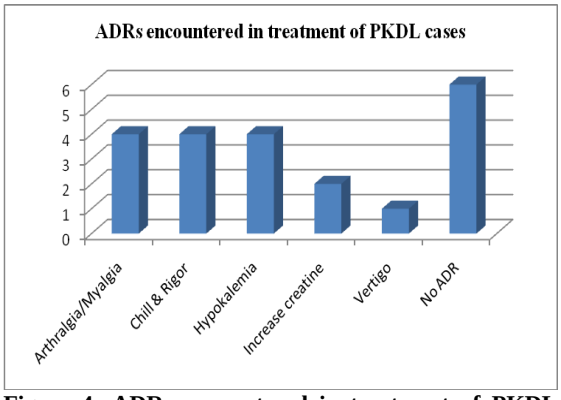

Figure 4: ADRs encountered in treatment of PKDL cases

Table 9: Treatment regimen for PKDL cases followed in different years

Years	SSG	AmB	Miltefosine	AmB+Miltefosine
2010	4	0	2	0
2011	2	0	1	0
2012	2	1	1	0
2013	0	1	0	1
2014	0	4	0	0
Total in 5 years	8	6	4	1

The most preferred regimen across the study years was SSG followed by AmB and Miltefosine [Table 9].

Table 10: Treatment outcome in different regimens for PKDL cases

Drug regimen (n=no cases received)	Efficacy/ clinical cure rate (%)	ADRs encountered	Average days of hospital stay	Tolerability
SSG (n=8)	Indeterminate	5(62.5%)	14.62 ± 4.69	Moderate
AmB (n=6)	Indeterminate	6 (100%)	23.17 ± 15.31	Least
Miltefosine (n=4)	Indeterminate	1(25%)	12 ± 8.41	Well
AmB+ Miltefosine (n=1)	Indeterminate	1 (100%)	29	Moderate

Clinical cure was indeterminate in all admitted cases of PKDL at the end of treatment. All regimens showed equivalent efficacy but safety and tolerability were different [Table 10]. On further review of PKDL cases it was found that out of 19 cases 17 (89.47%) had the past history of either VL, PKDL or both but in 2 (10.53%) cases there was no such history. 12 cases gave the past history of VL, 3 cases PKDL. 2 cases had the history of both VL and PKDL, VL occurring earlier than PKDL. On enquiry of the past drug history it was found that out of 18 cases 13 (76.47%) got SSG, 2 (11.76%) cases AmB and 2 (11.76%) cases miltefosine.

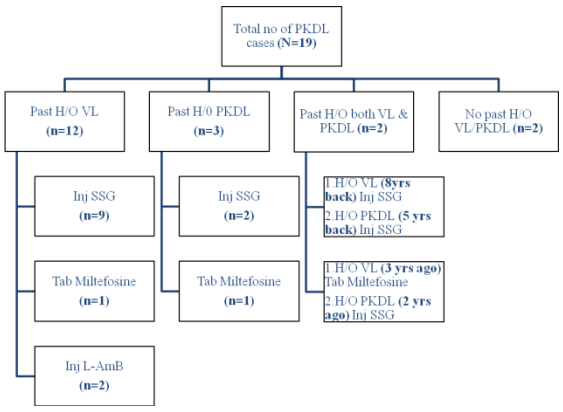

Figure 5: Past treatment history of PKDL cases studied

DISCUSSION

This retrospective record based study was conducted to assess the outcome of pharmacotherapy in post-kala-azar dermal leishmaniasis (PKDL) patients admitted in the period of 2010 to 2014 in Calcutta School of Tropical Medicine, Kolkata. This hospital caters a vast population from all over West Bengal as well as the adjoining states, so, demographic profiles of the cases admitted here may differ from what are obtained in field study. In Operational Guidelines in Kala-Azar (Visceral Leishmaniasis) Elimination in India - 2015, by NVBDCP, the commonly affected age group was in children of 5 to 9 years with male female ratio of 2:1, whereas in present study the commonest age group was 18 to 45 years both in VL and PKDL cases, with male female ratio of 1.46:1 in VL and 3.75:1 in PKDL.

Government of India, as a part of the global initiative, have launched through NVBDCP the enthusiastic plan for elimination of Kal-azar initially targetting year 2010, then 2015 and finally 2017. Active measures taken in these programmes in endemic areas have brought down the number of both Kala-azar and PKDL cases considerably. This is reflected by the number of cases admitted in the five years of study, which was much higher in earlier decades.[6]

AmB or conventional preparation was the most preferred drug as 58 (60%) cases out of 96 VL cases got this medicine including 16 out of 19 VL with HIV co-infected cases. This drug was also preferred for monthly prophylaxis in HIV with VL coinfected cases. This was administered in the dose of 1mg/kg body weight dissolving in 5% Dextrose solution to be infused slowly taking 4 to 6 hours. Total 15 to 20 doses either daily or on alternate day basis were transfused. Before starting the full daily dose a test dose was initially administered on routine basis. This was to safeguard for any feature of hypersensitivity or other untoward reactions which might arise. Some of the treating physicians have given the gradual escalating doses on daily dosing to reach the target dose, however those test doses were considered while calculating the total dose to be administered. Both these procedures were followed in previous study.[7]

Adverse effects associated with AmB require close monitoring with increased hospital stays, which increase the cost of therapy. All cases have experienced the adverse drug reaction as chill and rigor with or without fever. To combat this ADR antihistamine tablets or injection along with paracetamol tablets had to be given. In some instances these were started even before starting the infusion as prophylaxis. Other measures taken were slowing of the drip rate, temporarily stopping the drip for few hours, totally stopping the infusion for that day and advising further to infuse on alternate day basis according to severity of the reaction. Shyam Sunder,H. Mehta et al have shown in their study similar findings.[7]

Another important ADR was hypokalemia. It increases the risk of an abnormal cardiac rhythm such as bradycardia and cardiac arrest. Though it is an important finding only in 8.33% of cases showed mild to moderate hypokalemia. Mild hypokalemia was treated with oral potassium chloride syrup, where as in other cases they were managed by intravenous administration of potassium chloride in doses as required. One of the treating physicians

administered routinely Inj.potassium chloride with the IV infusion bottle prophylactically thereby avoiding this complication to a large extent.[8]

In literature search it was found that AmB cause renal impairment in the form of increased serum creatinine level. But in present study 58 cases serum creatinine reports were avilable out of them only 2 cases of increased level obtained, one of them got L-AmB other one conventional preparation. This important finding may indicate that renal toxicity is less common than those obtained in African or Latin American cases.8 The drug has high efficacy; however, prolonged hospitalization, adverse reactions like high fever with rigor and chills, and the need to close monitoring of renal functions and electrolyte levels are well-recognized drawbacks of AmB treatment.[9]

Miltefosine as monotherapy was given in one patient who was suffering from VL with HIV and had the history of previous treatment with conventional AmB. This particular patient was given Tab miltefosine in the dose of 50 mg tablet twice daily for 28 days as per the recommendation and there was no reported adverse reaction. A large phase IV study showed CR of 95%.[10] Its efficacy, ease of use and applicability in the control program made this drug the backbone of the elimination program in India, Nepal and Bangladesh. However, relapse rate doubled and efficacy reduced after a decade of use of the drug in the Indian subcontinent.[11] Injection Sodium Stibogluconate (SSG) which was the most frequently prescribed drug in the past, had only been used in single case of VL. The dose of SSG was 20 mg/kg as a single daily dose intravenously (over 5 minutes) for 30 days. This patient did not encounter any ADR. During hospital stay the patient was given the drug by I/V route but on discharge he was advised to take rest of the injections by I/M route from outpatient department.

In Bihar (India) and to some extent in adjoining Nepal there has been increasing resistance to SSG and this has led to implementation of alternative treatment regimens for these regions. However its efficacy remains high in other parts of world.12, 13 Arthralgia, myalgia, elevated hepatic and pancreatic enzymes are other common associated toxicities. Response to SSG in patients with HIV–VL coinfection, however, has shown less efficacy and been associated with increased mortality as compared to HIV-negative VL cases. Some adverse effects especially chemical pancreatitis is more common in HIV coinfected patients.[14,15]

Combination chemotherapy of L-AmB followed by miltefosine was the second in frequency of regimens used; approximately 20% cases received this therapy. One interesting fact came out on scrutiny of the year wise distribution of such cases. In the year 2010, 14 cases, in 2011, 4 cases, and in 2012 only one got this therapy. But, in 2013 and 2014 no case was given this regimen. It was known that L-AmB is better tolerated drug but it was out of favor because of the cost. This costly drug might have been provided for part of a research work where this combination therapy was tested for the safety efficacy and acceptability profile.In this regimen single dose of L-AmB at 7.5 mg/kg body weight was infused slowly followed by 14 days of oral miltefosine in the dose of 50 mg tablet twice daily for those patients over 25 kg weight and once daily for body weight less than 25 kg. All cases suffered from mild to moderate nausea and vomiting which started with miltefosine therapy which supports similar ADR reporting in previous studies. A number of patients needed ondansetron to combat such situations. A few cases also complained of chill, rigor, and fever following infusion of L-AmB which was taken care of by administering chlorpheniramine maleate and paracetamol.

Combination therapy with L-AmB and miltefosine was studied in a multidrug therapy randomized, non-comparative, group-sequential, triangular design study where 181 subjects were assigned to treatment with 5 mg/kg of L-AmB alone, 5 mg/kg of L-AmB followed by miltefosine for 10 days, or 14 days of 3.75 mg/kg of L-AmB followed by miltefosine for 14 days. When it became apparent that all regimens were effective, 45 additional, nonrandomized patients were assigned to receive 5 mg/kg of L-AmB followed by miltefosine for 7 days. Final CRs was similar in all groups (>95%).[16]

In a subsequent large phase III study in the Indian subcontinent, three drug combinations (single injection of 5 mg/kg L-AmB and 7-day 50 mg oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM) showed an excellent CR (>97%) in treatment of VL. Another combination trial in India where single dose of L-AmB 5 mg/kg and miltefosine 2.5 mg/kg/day for 14 days, showed a CR of 91.9% by intention to treat and 97.6% by per protocol analysis.[17,18]

The situation was different in the treatment of PKDL cases. Eight out of 19 PKDL cases admitted received Injection SSG 10 mg/kg body weight 120 injections. In the admitted period the drug was given on IV route, but further doses were given on daily basis deep IM through OPD. Half of the cases encountered the commonest ADR arthralgia, myalgia treated with analgesic. One case encountered thrombophlebitis which was treated with antibiotic and analgesic.

Six out of 19 cases of PKDL received Injection AmB in the dose of 1mg/kg body weight for 20 doses followed by 20 days gap next again repetition of AmB, 4 cycles were given. ADR encountered in all cases in the form of fever with chill and rigor which were treated with antihistaminic and paracetamol, but two cases encountered increased creatinine for which infusion was withheld for the values to come down to normal. Hypokalemia had

occurred in 2 cases which were treated with potassium chloride.

Guidelines for the treatment of Post-kala-azar dermal leishmaniasis (based on WHO Technical Report Series 949) B and introduced by NVBDCP oral Miltefosine was the preferred first-line drug for the treatment of PKDL cases.6 The second line drug AmB was recommended in the patients not responding to the first-line of drug or the drug was discontinued due to toxic effect, women during pregnancy, in the dose of 1 mg per kg body weight per day through intravenous infusion in 5 per cent dextrose after mixing the drug in water for injection, very slowly in 6 to 8 hours for upto 60-80 doses over 4 months.6 As this was a retrospective record based study, it was not possible in most of the cases to judge the treatment outcomes because of incomplete documentation. By interviewing the treating physicians and communicating with some of the patients whose contact numbers were available and working, the idea of outcomes has been deduced.

In PKDL cases treatment outcome was difficult to say unless parasitologically declared negative.19 Generally patients with nodular lesion showed response in the form of disappearance of nodules, but the macular lesions remain as such for a long time after completion of treatment, making it really difficult to declare cure at the end of treatment. So to comment on efficacy it is difficult to predict in PKDL cases. Tolerability was least with AmB followed by SSG and best with miltefosine.

In a recent study conducted by Ramesh et al., 79.8 % (n = 225) of PKDL patients reported history of VL. There was no association between type of clinical presentation and history of VL. Overall, the median time of manifestation of PKDL after VL treatment was 36 months (range = 1–384 months). PKDL lesions developed within 1 year in 13.3 % (n = 30), within 2–5 years in 56 % (n = 126) and after 5 years or more in 30.7 % (n = 69) cases, after apparent cure from VL. Majority of cases with history of VL (93.3 %, n = 210) had been treated for VL with SSG while the remaining were treated with amphotericin B (5.3 %, n = 12) or miltefosine (1.3 %, n = 3). The median time lapse after VL treatment with SAG was 36 months (range, 1–384 months) which was less compared with amphotericin B (48 months, 3.6 – 84 months) but more compared to miltefosine treatment (21 months, range 12–36 months).[20]

The present study gave emphasis on the history of past chemotherapy for VL in PKDL cases to find out whether PKDL is a drug related phenomenon. Among 19 cases of PKDL screened, 17 gave past history of VL and / PKDL treatment. And in 2 cases there was either no history of VL and/or PKDL or treatment thereof. Among the 17 patients, 12 had past history of VL treatment with SSG, 3 with miltefosine and 2 with L-AmB. So, PKDL occurred in VL cases that were treated with all sorts of anti-VL chemotherapy except AmB.

Major limitations of the study were small sample size and it's retrospective and record based nature. In most of the cases documentations were incomplete in terms of history, investigations, ADRs and outcomes. So, information had to be collected from the patients and treating physicians that might have a lot of recall bias. Computerized documentation in future will be helpful for this kind of studies.

CONCLUSION

The mean age of PKDL patients in the study was 29.31 ± 13.23 years. Male: female ratio was 4:1 approximately. About half (42%) of the PKDL patients received SSG, about 1/3 (32%) received AmB infusion; about 1/5th (21%) received miltefosine and a single patient received AmB followed by miltefosine. In PKDL group, ADRs were encountered in 70% of cases. Artharlgia and myalgia were noted in ½ of the cases treated with SSG. Chill, rigor and hypokalemia were recorded in about 1/2 and rising creatinine levels in about 1/4th of the cases treated with AmB.

Efficacy of the regimens for treating PKDL was ill defined as it was based on treating physicians' assumption of reduction of skin lesions (size and number). In no case parasitological or nucleic acid assessment was done. However, as per records, patients were discharged with positive outcome. AmB was least tolerable in respect to ADRs (100%) and prolonged hospital stay (60 to 90 days), SSG was moderately tolerable as ADRs were 60 % and in most of the cases, treatment continued on outdoor basis after discharge. Miltefosine was found to be best tolerable as it was least toxic (Nausea and vomiting in 1 patient) and all 4 patients received treatment on outdoor basis after discharge.

The study gave emphasis on the history of past chemotherapy for VL in PKDL cases to find out whether PKDL is a drug related phenomenon. Among 19 cases of PKDL screened, 17 gave past history of VL and / PKDL treatment. And in 2 cases there were either no history of VL and / PKDL or treatment thereof. Among the 17 patients, 12 had past history of VL treatment with SSG, 3 with Miltefosine and 2 with L-AmB . So, PKDL occurred in VL cases that were treated with all sorts of anti-VL chemotherapy except AmB.

So, it can be concluded from this study that in this institute PKDL were treated with conventional and liposomal AmB as well as with SSG, Miltefosine and combination therapy. Among the regimens short course L-AmB was found to be the most efficacious and tolerable in respect to ADRs and hospital stay. ADRs were common with SSG, AmB, Miltefosine and almost absent with L-AmB. HIV co-infection was found to be the common cause for relapse and readmission of VL cases. PKDL might develop after most of the antileishmanial chemotherapy except after full course of conventional AmB.

REFERENCES

1. Das VN, Pandey K, Verma N, Lal CS, Bimal S, Topno RK, et al. Short report: Development of post-kala-azar dermal leishmaniasis (PKDL) in miltefosine-treated visceral leishmaniasis. Am J Trop Med Hyg. 2009;80:336–8.
2. Kumar D, Ramesh V, Verma S, Ramam M, Salotra P. Post-kala-azar dermal leishmaniasis (PKDL) developing after treatment of visceral leishmaniasis with amphotericin B and miltefosine. Ann Trop Med Parasitol. 2009;103:727–30.
3. Boelaert M, El-Safi S, Hailu A, Mukhtar M, Rijal S, Sundar S, et al. Diagnostic tests for kala-azar: a multi-centre study of the freeze-dried DAT, rK39 strip test and KAtex in East Africa and the Indian subcontinent. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2008;102((1)):32–40.
4. Boelaert M, Verdonck K, Menten J, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. Cochrane Database Syst Rev. 2014;(6):CD009135.
5. Sinha PK, Das VNR, Pandey K, Ranjan A, Bimal S, Singh V, et al. Evaluation of clinico-pathological features in Indian kala-azar patients with HIV co-infection in relation to amphotericin-B treatment. Proc: WHO workshop on strategies for control of kala-azar and malaria, Balaji Uthan Sansthan, Patna, 27-28 December, 2001; 123-7.
6. Operational guidelines on kala-azar (visceral leishmaniasis) elimination in india - 2015 national vector borne disease control programme ministry of health & family welfare directorate general of health services.
7. Sundar S, Mehta H, Suresh A V, et al. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. Clin Infect Dis. 2004;38(3):377–383.
8. Burza S, Nabi E, Mahajan R, Mitra G, Lima M. One-year follow-up of immunocompetent male patients treated with miltefosine for primary visceral leishmaniasis in Bihar, India. Clin Infect Dis. 2013; 57: 1363–1364.
9. Olliaro PL, Guerin PJ, Gerstl S, Haaskjold AA, Rottingen JA, Sundar S. Treatment options for visceral leishmaniasis: a systematic review of clinical studies done in India, 1980–2004. Lancet Infect Dis. 2005;5(12):763–74.
10. Bhattacharya S, Sinha P, Sundar S, Thakur C, Jha T, Pandey K, et al. Phase 4 trial of miltefosine for the treatment of indian visceral leishmaniasis. J Infect Dis.2007; 196: 591–598.
11. Sundar S, Singh A, Rai M, Prajapati V, Singh A, Ostyn B, et al. Efficacy of miltefosine in the treatment of visceral leishmaniasis in India after a decade of use. Clin Infect Dis. 2012; 55: 543–550.
12. Sundar S, Chakravarty J. An update on pharmacotherapy for leishmaniasis. Expert Opin Pharmacother.2015; 16: 237–252.
13. Sundar S, More D, Singh M, Singh V, Sharma S, Makharia A, et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 2000;31: 1104–1107.
14. Sundar S, Chakravarty J. Investigational drugs for visceral leishmaniasis. Expert Opin Investig Drugs. 2015; 24: 43–59.
15. Ritmeijer K, Dejenie A, Assefa Y, Hundie T, Mesure J, Boots G, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis. 2006; 43: 357–364.
16. Sundar S, More D, Singh M, Singh V, Sharma S, Makharia A, et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 2000; 31: 1104–1107.
17. Sundar S, Sinha P, Rai M, Verma D, Nawin K, Alam S, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet.2011; 377: 477–486.
18. Sundar S, Sinha P, Verma D, Kumar N, Alam S, Pandey K, et al. AmBisome plus miltefosine for Indian patients with kala-azar. Trans R Soc Trop Med Hyg.2011; 105: 115–117.
19. Adams ER, Versteeg I, Leeflang MM. Systematic Review into Diagnostics for Post-Kala-Azar Dermal Leishmaniasis (PKDL). J Trop Med. 2013;2013:150746.
20. Ramesh, et al. Clinico-epidemiological analysis of Post kala-azar dermal eishmaniasis (PKDL) cases in India over last two decades: a hospital based retrospective study BMC Public Health .2015; 15:1092-100.

How to cite this article: Naser SM, Banu P, Goswami RP, Tripathi SK, Sen S. Assessment of Treatment Outcome in Post-Kala-Azar Dermal Leishmaniasis (PKDL) Patients– A Record-Based Observational study in a Speciality Public Hospital, Kolkata. Ann. Int. Med. Den. Res. 2019; 5(4):PC01-PC08.

Source of Support: Nil, **Conflict of Interest:** None declared