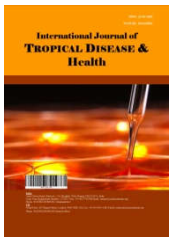

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Post Kala-Azar Dermal Leishmaniasis Following Treatment with 10 mg/kg of Single Dose AmBisome for Visceral Leishmaniasis in Bihar, India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In view of the significant role of Post kala-azar dermal Leishmaniasis (PKDL) patients in the transmission/recurrence of visceral leishmaniasis (VL) outbreaks, control of PKDL is among the priorities. As the Single Dose AmBisome 10 mg/kg (SDA) became the obvious choice for the treatment of VL, therefore, in this study, 896 patients were included to explore the probability of developing PKDL. Among the treated patients, 30 (3.35%) of them found confirmed as PKDL with clinical symptoms. Out of the 30 patients, 53.33% male and 46.67% female patients had macular lesions respectively, with a median time (Interquartile range [IQR]) to development of 13.5 (9–23.5) and 23 (9-17) months following treatment. No, significant associations were established concerning any patient's demographics and clinical characteristics. However, with the patients presenting with confirmed PKDL, females were significantly younger than males. This study suggests the rate of PKDL appearance is directly associated with 10 mg/kg of SDA and therefore there is a need for more concerns regarding doses during treatment.

Keywords: Single dose AmBisome; visceral leishmaniasis; PKDL; SDA.

1. INTRODUCTION

In the past few years, due to the high cure rate (95.7%) with 10 mg/kg of AmBisome, patients are regularly treated with a single infusion of 10 mg/kg at different referral centers [1]. It has earlier reported the rate of conversion of VL to PKDL in patients (8311) administered with 20 mg/kg AmBisome was relatively low (0.3%) with an average development period of 1.2 years (0.8–2.2) of following treatment [2-4]. But, risk factors for Single Dose AmBisome (10 mg/kg/body wt) associated with the conversion of VL to PKDL still remains to be elucidated [5]. Here, a field-based cohort study was performed and those patients who received Single Dose AmBisome (i.e. 10mg/kg/body wt) during 2012-2018 were selected. Depending upon the records available at State/District health offices or at RMRIMS about the treatment VL, from endemic regions of Vaishali, Saran, and Muzaffarpur districts were chosen. Spleen or bone marrow test of cure biopsy was adopted only when treatment failure was suspected within the six months after the initial cure from VL.

2. MATERIALS AND METHODS

Among 896 VL SDA treated individuals, 300 individuals were follow-up with both door to door screening method quarterly between 2012-2014 and, rest 596 were selected from indoor patients who came RMRIMS treatment of VL and were received SDA treatment. From these indoor patients, 20 cases were converted to PKDL between 2015 and 2018. After obtaining written and verbal consent from the head of the family and also from each individual, the rK39 test was performed for the detection of anti-leishmanial antibody [6].

3. RESULTS AND DISCUSSION

During follow up, 17 VL treated cases were lost as they moved to other places. The focus was given to the patients who were suspected of lesions. They were examined with a proper record including morphology onset of lesions and history of VL occurrence, and age group. All suspected PKDL cases were referred to RMRIMS for further slit/skin smear examination. The skin biopsies/smears were aseptically collected from the largest and most prominent lesions as per the protocol described earlier [7-10]. Skin smear slides were immediately fixed with methyl alcohol and allowed to dry at room temperature. Slides were stained with diluted (1:9) Giemsa stain for 25 minutes. Smears are examined under the oil immersion objective of the microscope for the demonstration of *Leishmania donovani* parasites [11,12]. During 36 months follow-up, a sign of PKDL was observed in 30 cases (3.35%) which were further confirmed by demonstration of amastigotes in skin scrapping smear (n=30) (Fig. 1).

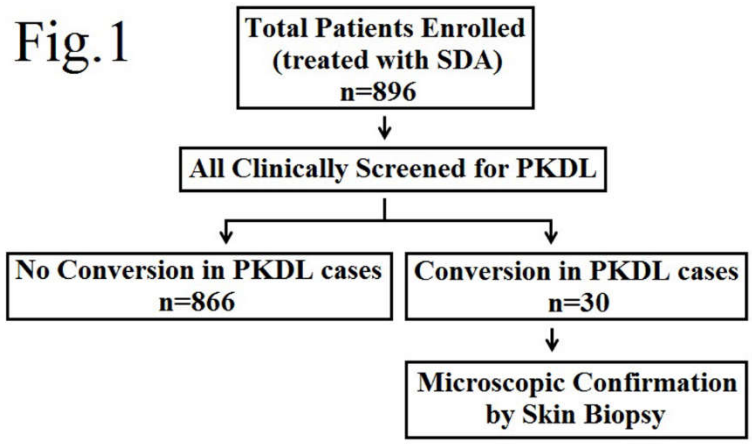

Fig. 1. Flowchart of patients who develop post Kala-azar dermal leishmaniasis (PKDL) after treatment with 10 mg/kg SDA

The conversion period of VL to PKDL varies from 6 to 29 months. Among 896 VL patients, 577 individuals were male and the rest 319 were females, and only 3.35% of VL cases were converted to PKDL cases. There were no significant associations found regarding any patient demographics (sex, age group, caste, the season of treatment) and clinical characteristics (nutritional status, duration of illness before treatment, admission spleen size, and change in spleen size by the time of discharge) at time of preliminary treatment and the risk of developing confirmed PKDL2. The mean ± standard deviation of time to the onset of lesions of confirmed PKDL as reported by the patients was 14.47±4.08 months [13]. A median (IQR) was used to establish the onset of the lesion, formal diagnosis, and different age groups of PKDL patients, separately for males and females (Table1). The median to the onset of lesion of PKDL (IQR) for males and females is 13.5(9-23.5) and 23(9-17) respectively [2,14]. However, the meantime to confirmation of the diagnosis of PKDL was longer at 6.93 months and correspondingly median (IQR) for males and females is 6.5(4-11) and 5(3-8). The time to onset of PKDL lesions is shown in the Kaplan–Meier graph (Fig. 2) survival distributions showed no significant difference between the sexes. Of the patients presenting with confirmed PKDL, females were significantly younger than males (median age 7 vs 60 years, respectively; p=2) [2,15]. The mean age of males and females in confirmed PKDL is 26.94 vs 25.35 respectively. It is worthemphasizing that the present study

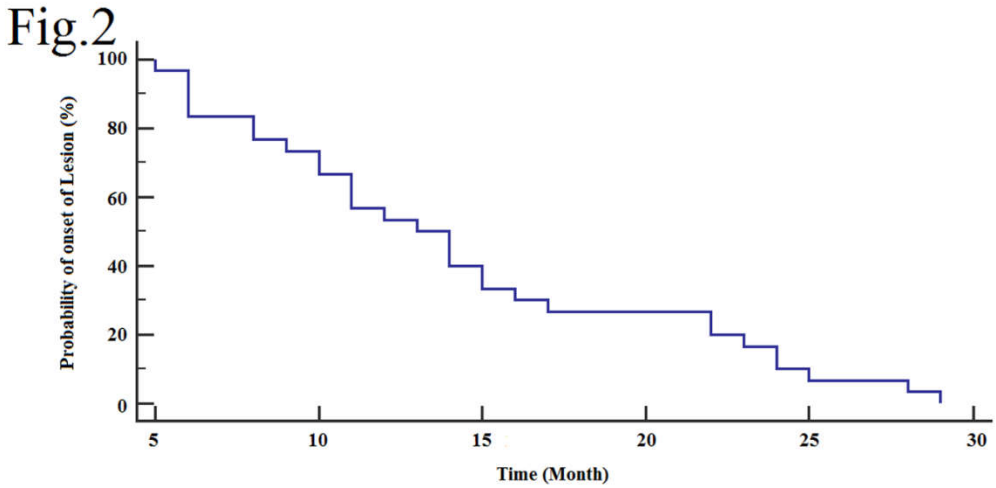

Fig. 2. Uncensored Kaplan–Meier graph of time to developing post kala-azar dermal leishmaniasis (PKDL) lesions following treatment of visceral leishmaniasis (VL) with 10 mg/kg SDA

Table1. Characteristics of patients with confirmed post-AmBisome PKDL stratified by sex (n =30)

Characteristic		Male (%) n=16	Female (%) n=14	P Mann-Whitney
Time to onset of lesions, months	<12	7(43.75%)	6(42.86%)	
	12<16	3(18.75%)	4(28.57%)	
	16<20	1(6.25%)	1(7.14%)	
	20<24	1(6.25%)	2(14.29%)	
	≥24	4(25%)	1(7.14%)	
	Median (IQR)	13.5(9-23.5)	23(9-17)	64
Time to formal diagnosis, months	<12	12(75%)	13(92.86%)	
	12<16	2(12.5%)	1(7.14%)	
	16<20	1(6.25%)	0	
	20<24	1(6.25%)	0	
	≥24	0	0	
	Median (IQR)	6.5(4-11)	5(3-8)	64
Age group, Years	<15	5(31.45%)	4(28.57%)	
	15<25	4(25%)	3(21.43%)	
	25<35	2(12.5%)	2(14.29%)	
	35<45	0	4(28.57%)	
	≥45	5(31.45%)	1(7.14%)	
	Median (IQR)	19(13.5-45)	23.5(11-37)	64
Type of lesion	Macular	11(68.75%)	10(71.43%)	
	Macular-papular	5(31.25%)	4(28.57%)	
	Nodular-papular	0	0	

reflects a higher rate of incidence of confirmed PKDL cases following treatment with 10 mg/kg SDA as compared to 20 mg/kg AmBisome. As PKDL possibly serve as potential reservoirs for transmission and remain as a major challenge to the current control and elimination programs [16-19].

4. CONCLUSION

It is concluded that a detailed investigation is urgently required about the higher incidence conversion rate associated with 10 mg/kg Single Dose AmBisome.

CONSENT

After obtaining written and verbal consent from the head of the family and also from each individual, the rK39 test was performed for the detection of anti-leishmanial antibody.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Goswami RP, Goswami RP, Das S, Satpati A, Rahman M, Short-course treatment regimen of Indian visceral leishmaniasis with an Indian liposomal amphotericin B preparation (Fungisome™). The American Journal of Tropical Medicine and Hygiene. 2016;94(1):93-98.
2. Burza S, Sinha PK, Mahajan R, Sanz MG, Lima MA, Mitra G, Verma N, Das P. Post Kala-Azar dermal leishmaniasis following treatment with 20 mg/kg liposomal amphotericin B (Ambisome) for primary visceral leishmaniasis in Bihar, India. PLos Neglected Tropical Diseases. 2014;8(1): e2611.
3. Azhari AA. Identification of novel hits against Leishmania Donovani. University of South Florida; 2018.

4. Topno RK, Rabi Das VN, Kumar M, Madhukar M, Pandey K, Verma N, Agrawal K, Lal CS, Siddiqui NA, Bimal S, Das P. Advanced case of PKDL due to delayed treatment: A rare case report.
5. Ghosh P, Mondal D, Chowdhury R, Halleux C, Ruiz-Postigo JA, Alim A, Hossain F, Khan MA, Nath R, Duthie MS, Kroeger A. Relationship of serum antileishmanial antibody with development of visceral leishmaniasis, post-kala-azar dermal leishmaniasis and visceral leishmaniasis relapse. Frontiers in microbiology. 2019;10:2268.
6. Das VN, Siddiqui NA, Verma RB, Topno RK, Singh D, Das S, Ranjan A, Pandey K, Kumar N, Das P. Asymptomatic infection of visceral leishmaniasis in hyperendemi areas of Vaishali district, Bihar, India: A challenge to kala-azar elimination programmes. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2011;105(11):661-666.
7. Verma N, Singh D, Pandey K, Das VN, Lal CS, Verma RB, Sinha PK, Das P. Comparative evaluation of PCR and imprint smear microscopy analyses of skin biopsy specimens in diagnosis of macular, Papular, and mixed Papulo- nodularlesions of post-Kala-Azar dermal Leishmaniasis. Journal of ClinicalMicrobiology. 2013;51(12):4217-4219.
8. Verma N, Bimal S, Das VN, Pandey K, Singh D, Lal CS, Singh AK, Sinha PK, Das P. Clinicopathological and immunological changes in Indian post kala-azar dermal leishmaniasis (PKDL) cases in relation to treatment: A retrospective study. BioMed Research International; 2015.
9. Amit A, Dikhit MR, Pandey RK, Singh K, Mishra R, Das VR, Das P, Bimal S. Elevated serum ADA activity as a marker for diagnosis and prognosis of visceral leishmaniasis and post kala-azar dermal leishmaniasis in indian patients. PloSone, 2016;11(5):e0154117.
10. Topno RK, Madhukar M, Pandey K, Kumar R, Rabidas VN, Kumar M, Agrawal K, Verma N, Yadav DP, Bimal S, Siddiqui NA. False positivity of rK39 test in five chronic myeloid leukemia cases from bihar, india: a possible challenge to leishmaniasis diagnosis. The American Journal of Tropical Medicine and Hygiene. 2020; tpmd200301.
11. Verma NK, CS Dey. Possible mechanism of miltefosine-mediated death of *Leishmania donovani*. Antimicrobial Agents and Chemotherapy. 2004;48(8):3010-3015.
12. Allahverdiyev AM, Koc RC, Bagirova M, Elcicek S, Baydar SY, Oztel ON, Abamor ES, Ates SC, Topuzogullari M, Dincer SI, Akdeste Z. A new approach for development of vaccine against visceral leishmaniasis: Lipophosphoglycan and polyacrylic acid conjugates. Asian Pacific journal of Tropical Medicine. 2017;10(9): 877-886.
13. Das AK, Harries AD, Hinderaker SG, Zachariah R, Ahmed B, Shah GN, Khogali MA, Das GI, Ahmed EM, Ritmeijer K, Active and passive case detection strategies for the control of leishmaniasis in Bangladesh. Public Health Action. 2014; 4(1):15.
14. Ganguly S, Saha P, Chatterjee M, Roy S, Ghosh TK, Guha SK, Kundu PK, Bera DK, Basu N, Maji AK. PKDL—A silent parasite pool for transmission of leishmaniasis in kala-azar endemic areas of Malda District, West Bengal, India. PLoSNeglected Tropical Diseases. 2015;9(10):e0004138.
15. Burza S, Sinha PK, Mahajan R, Lima MA, Mitra G, Verma N, Balasegarem M, Das P. Five-year field results and long-term effectiveness of 20 mg/kg liposomal amphotericin B (Ambisome) for visceral leishmaniasis in Bihar, India. PLos Neglected Tropical Diseases. 2014;8(1): e2603.
16. Das VN, Pandey RN, Siddiqui NA, Chapman LA, Kumar V, Pandey K, Matlashewski G, Das P, Longitudinal study of transmission in households with visceral leishmaniasis, asymptomatic infections and PKDL in highly endemic villages in Bihar, India. PLoSNeglected Tropical Diseases. 2016;10(12):e0005196.
17. Olliaro PL, Shamsuzzaman TA, Marasini B, Dhariwal AC, Be-Nazir A, Mondal D, Banjara MR, Das P, Sundar S, Rijal S, Arana B. Investments in research and surveillance are needed to go beyond elimination and stop transmission of *Leishmania* in the Indian subcontinent. PLoSNeglected Tropical Diseases. 2017; 11(1):e0005190.
18. Rana S, Mahat JP, Kumar M, Sarsaiya S. Modeling and docking of cysteine protease-A (CPA) of *Leishmania donovani*. J. Appl. Pharm. Sci. 2017;7(9):179-84.

19. Topno RK, Shankar V, Dikhit MR, Madhukar M, Pandey K, Das VN, Kumar M, Kumar B, Agrawal K, Siddiqui NA, Sahoo GC. Noninvasive sweat-based diagnosis of visceral leishmaniasis and post kala-azar dermal leishmaniasis. The American journal of Tropical Medicine and Hygiene. 2018;99(5):1162-4.

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