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# Pharmacovigilance of Miltefosine in Treatment of Visceral Leishmaniasis in Endemic Areas of Bihar, India

Krishna Pandey,[1] Vidyanand Ravidas,[1] Niyamat A. Siddiqui,[1] Sanjay K. Sinha,[1] Rakesh B. Verma,[1] Tripurari P. Singh,[2] A. C. Dhariwal,[3] R. K. Das Gupta,[3] and Pradeep Das[1]*

[1]*Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Patna, India;* [2]*Sadar Hospital, East Champaran, Bihar, India;* [3]*Directorate of National Vector Borne Disease Control Programme (NVBDCP), Delhi, India*

*Abstract.* Miltefosine, the only oral drug for visceral leishmaniasis (VL), is being used as the first-line drug under the VL elimination program in the Indian subcontinent. Miltefosine is an oral drug which was used as a topical application for skin metastasis of breast cancer. It was found to be effective against *Leishmania donovani*. The main adverse events (AE) reported previously with miltefosine use includes diarrhea, vomiting, and dehydration. Other AEs include, raised serum alanine transaminase/aspartate aminotransferase and renal parameters such as creatinine. In this study, we report AEs in a large patient cohort of VL treated with miltefosine. The purpose of this pharmacovigilance study was to assess adverse drug reactions (ADRs)/AE of miltefosine treatment under unrestricted condition in the field setup. Patients were followed up to 6 months for therapeutic effectiveness. Outcomes of a larger data set of patients treated with this regimen from April 2012 to March 2015 were recorded. In the present study, 646 patients of VL were given miltefosine. Majority of the study subjects (58%) were male. Relapse occurred in 7% during follow-up period. Main causes of death were VL–pulmonary tuberculosis coinfection, extreme diarrhea, and acute pancreatitis which were reported in 1.7% subjects. Of 553 (85.6%) patients completing full course of treatment, 463 (83.7%) showed ADR with miltefosine during the study period. About 2.3% were suffering severe ADR, 51% from moderate, and the rest had mild ADR. The initial and final cure rate was 97.4% and 85.6%, respectively.

## INTRODUCTION

Visceral leishmaniasis (VL), commonly known as kala-azar, is a disease of utmost public health importance in the Indian subcontinent. The global incidence and prevalence of kala-azar cases per year is 0.5 million and 2.5 million, respectively (World Health Organization [WHO] Report, 1998), whereas 350 million people are at risk.[1] Four states in India namely Bihar, Jharkhand, West Bengal, and Uttar Pradesh are highly affected.[2] Bihar alone accounts for more than 70% of the total Indian VL cases. The main drugs for treatment include sodium antimony gluconate (SAG), amphotericin B, liposomal amphotericin B, miltefosine, and paromomycin. SAG has been phased out due its cardiotoxicity and decreasing efficacy.[3]

Pharmacovigilance is the process for monitoring and evaluating safety of the drug through assessment of adverse drug reactions (ADRs)/adverse events (AEs). It is a key component of effective drug regulation system, clinical practice, and public health programs. The number of ADRs reported helps to understand the pharmacovigilance of the drug involving high-level expertise to rapidly detect drug risks and acts as a decision-making tool to either defend the product against its inappropriate removal or negate its use in treatment. The current global network of pharmacovigilance centers, coordinated by the Uppsala Monitoring Center (UMC), is supposed to be strengthened by an independent system of review.[4,5] Recently, pharmacovigilance has been confined, mainly to detect adverse drug events that were previously either unknown or poorly understood. Pharmacovigilance is an important and integral part of clinical research, and these days it is growing in many countries. Miltefosine is the only oral drug available for treatment of Indian VL cases with efficacy of about 94% in phase III and phase IV trials in the Indian subcontinent.[6] Its unrestricted use has raised concern about its continued effectiveness.

The pharmacovigilance is an important issue under kala-azar elimination program as currently there is no pharmacovigilance system available for evaluating the AEs and effectiveness of miltefosine in real-life situations. Earlier studies provide documented information on both major and minor side effects among a cohort of patients treated with miltefosine.

This study also establishes standard protocol for registration and treatment of women patients in reproductive age with miltefosine. Study has a large data bank on ADR and will guide the program for better drugs used as well as compliance. The key lessons learned from the findings of this study will guide the Directorate of National Vector Borne Disease Control Program (NVBDCP) to incorporate in the kala-azar elimination program at a wider scale.[7]

**Drug-related side effects and laboratory test.** Miltefosine caused several side effects such as vomiting, diarrhea, abdominal pain, dehydration, edema, decreased urine output, jaundice, and fatal nephro-/hepatotoxicity in about 1% cases. As per phase IV trial of miltefosine, serious side effects were reported in the range of 3–5% of the subjects.

The main focus of these studies in the endemic regions of kala-azar in Bihar were to support better informed policy making for kala-azar case management by 1) undertaking a pharmacovigilance study to systematically document and compile both major and minor side effects among a cohort of patients treated with miltefosine, 2) establishing and piloting standard protocol for registering and treating women in reproductive age with miltefosine, 3) contributing to the assessment of rational and more effective use of miltefosine for improving patient care and safety, 4) making appropriate recommendations in national policy on kala-azar elimination program for administration of miltefosine as first line

*Address correspondence to Pradeep Das, Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Agam Kuan, Gulzarbagh, Patna 800007, India. E-mail: drpradeep.das@gmail.com

of medicine for the treatment of kala-azar, and 5) documenting human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) comorbidity among kala-azar cases included for the pharmacovigilance study.

## MATERIALS AND METHODS

An open-label, single-arm trial was designed to investigate the safety and efficacy of miltefosine in the treatment of VL patients under unrestricted condition in the field setup. A total of four sentinel sites in the highly endemic districts of Bihar were selected as per the readiness criteria like availability of recombinant kinesin-39 (rk-39) for VL diagnosis, use of miltefosine for VL treatment, availability of health personnel and other infrastructure needed for proper health delivery, etc. The identified sites included two district hospitals—East Champaran and Samastipur Districts and two primary health centers—Paroo of Muzaffarpur and Baniyapur of Saran District of Bihar.

**Inclusion and exclusion criteria.** Females and males between 6–70 years of age having signs and symptoms suggestive of VL (fever of 2 weeks with splenomegaly, not responding to antimalarials and antibiotics) and diagnosed for VL infection as per the prevailing guidelines of VL diagnosis in national kala-azar elimination program were included in this study.

Criteria for exclusion were pregnant/breast-feeding women, women of child-bearing age not consenting to avoid pregnancy during and after 6 months of treatment, seropositive for HIV, presence of a serious illness, concurrent diseases, such as tuberculosis or bacterial pneumonia, hemoglobin level < 5.0 g/dL, granulocyte count < 1,000 granulocytes/$mm^3$, platelet count < 40,000 platelets/$mm^3$, hepatic transaminase levels > 5 times of the normal limit, total bilirubin level > 2.0 mg/dL, serum creatinine level above the upper normal limit (> 1.5 mg/dL), prothrombin time > 5 seconds above control, and/or inability of the subject or guardian to provide written informed consent.

**Diagnosis of VL and post-kala-azar dermal leishmaniasis.** All patients with a history of 2 weeks of fever and splenomegaly were considered suspects for VL. Diagnosis was confirmed with rK-39 rapid diagnostic kit test. Patients having a history suggestive of relapse or with atypical clinical signs or negative diagnostic tests but a high index of suspicion of VL were referred for parasitological diagnosis through splenic or bone marrow biopsy. Patients having macular/papular/nodular/mixed lesions on face, back, abdomen, and/or limbs were defined as post-kala-azar dermal leishmaniasis (PKDL), and were confirmed by skin snip examination and demonstration of *Leishmania donovani* (LD) bodies under microscope.

**Treatment and follow-up.** The study subjects ($N$ = 646) were given 28-day miltefosine treatment regimen orally for VL as per the standard protocol, that is, 100 mg in two divided doses for patients > 12 years of age or body weight ≥ 25 kg ($N$ = 513), and 50 mg or 2.5 mg per kg body weight for patients ≤ 12 years or body weight < 25 kg, ($N$ = 133). Under domiciliary mode of treatment, patients were provided calculated number of miltefosine capsules for 1 week and asked to visit at the end of the week for 4 weeks to complete the 28-day treatment regimen. Patients were considered "initially cured" once they completed a full course of VL treatment and showed clinical improvement, cessation of fever and reduction of spleen size at the time of discharge following WHO descriptions of treatment response.

After end of treatment (EoT), two follow-ups were made to assess side effects and disease relapse—one after 2 months and then after 6 months of EoT. Patients without any signs and symptoms suggestive of kala-azar at 6-month follow-up were considered as finally cured (Figure 1).

Of 646 patients enrolled in the study, 553 (85.6%) completed 6-month follow-up. During the study period, 11 deaths were reported, of which three were due to ADR [one due to diarrhea (probably drug related), other one due to VL–pulmonary tuberculosis (PTB) infection (probably unrelated), and the third one due to acute pancreatitis (probably drug related)].

**Monitoring of side effects.** The measures performed to recognize occurrence of side effects included 1) clinical monitoring of the patients for signs and symptoms indicative of both major and minor side effects of drugs, 2) monitoring laboratory parameters, and 3) documentation of the side effects. Periodic meetings were organized with program personnel to review the reported side effects and take appropriate measures.

**Data collection.** A standard protocol for diagnosis, treatment, and reporting of AEs was followed at all the sites to minimize the information bias. The study-specific data (Pre-, during, and posttreatment) were captured on specially designed information sheets. On the basis of miltefosine phase IV trial observations, side effects were categorized as major and minor. Major side effects considered were gastrointestinal complaints such as nausea and abdominal pain with swelling, persistent vomiting, dehydration, and increased level of creatinine, alanine transaminase (ALT)/aspartate aminotransferase (AST) with majority in common toxicity criteria (CTC) grade I and II. Pneumonia with acute renal failure, anasarca, edema, decreased urine output, and jaundice were the other major side effects. Minor side effects recorded were vomiting, diarrhea, abdominal pain, flu-like symptoms, skin rash, epistaxis, and hemoptysis.[8]

Data collected for all patients diagnosed with VL/PKDL included general demographic information, clinical history, height, weight, and rapid diagnostic test result. Laboratory tests included complete blood counts, liver function test, that is, tests for AST, ALT, and bilirubin, and kidney function test (creatinine) on 0 day, 14th day, 29th day and 2nd and 6th month follow-up. Electrolyte tests (serum sodium and potassium) were also performed whenever patient complained of diarrhea, dehydration, vomiting, etc.

**Data entry.** All data captured in the source documents were thoroughly checked for consistency and entered into database using Microsoft Office Excel 2007. Regular update and database cleaning were performed to ensure data accuracy.

**Data analysis.** Statistical analysis was conducted using SPSS 21 version (IBM Corp., Armonk, NY). Patient-time at risk for ADR/ AE was calculated for each patient, right from the start date of VL treatment to 6-month follow-up. The cumulative incidence of relapse was estimated using Kaplan–Meier method. The data were also evaluated on Naranjo ADR probability scale and Uppsala monitoring scale.[9,10]

**Ethics statement.** The study was approved by the Ethical Committee of Rajendra Memorial Research Institute of Medical Sciences, Patna, India. A written informed consent

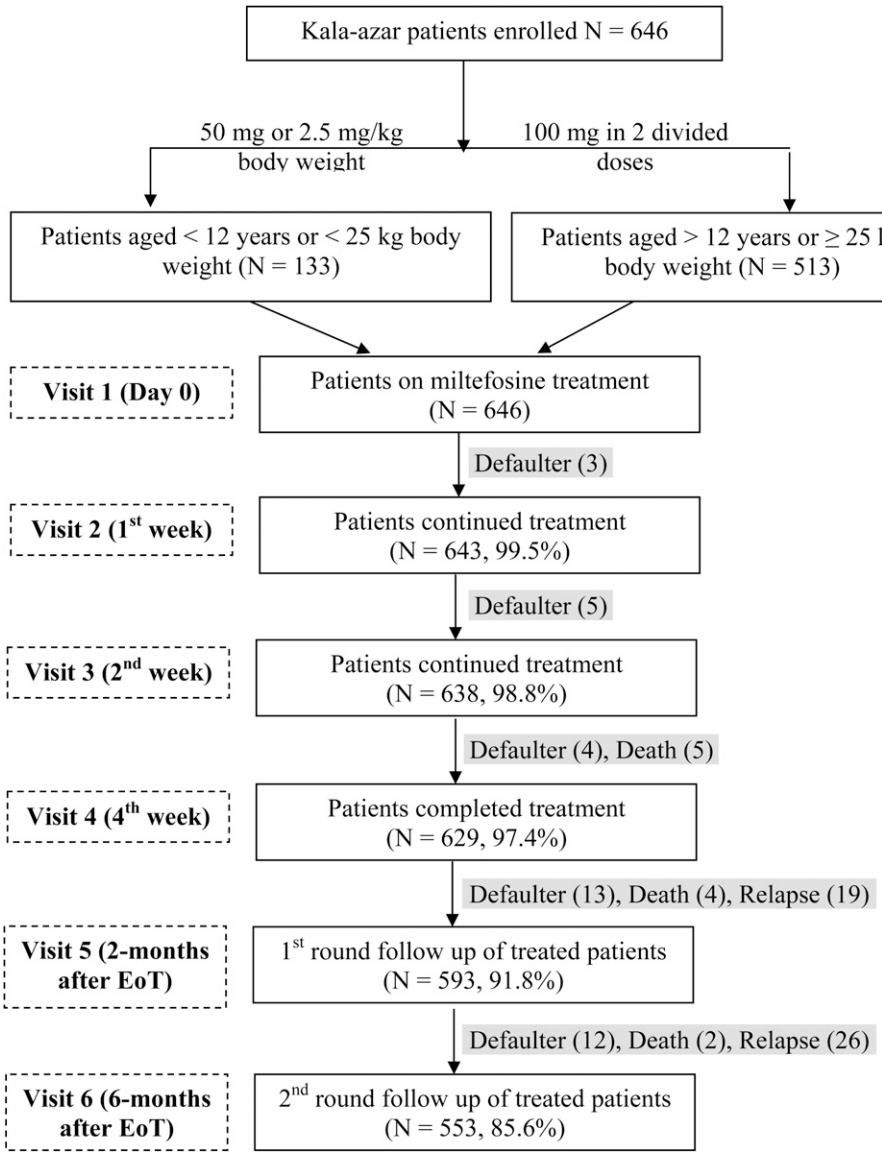


FIGURE 1. Treatment compliance chart.

was obtained from the patients/legal guardians (if applicable) prior to inclusion in the study.

## RESULTS

**Patient characteristics.** Altogether, 646 VL patients treated with miltefosine at all the four sentinel sites were included in the study; of them, 58% were male and 42% were female. Higher proportion of the study subjects (31%) were < 14 years of age, followed by age group of 14–25 years (21%) (Table 1).

**Treatment compliance and outcome.** Of 646 study subjects, 629 (98.8%) complied full course of miltefosine treatment in domiciliary mode and 553 (85.6%) completed 6-month follow-up after EoT. All the patients had defervescence of fever at the EoT. Mean spleen size of 5.3 cm and 4.4 cm in male and female before treatment reduced significantly to 2.1 cm ($P \leq 0.0001$) and 1.7 cm ($P \leq 0.001$), respectively, after treatment. Similarly, mean liver size also reduced significantly in both sexes at EoT (2.7–1.2 cm in male, $P \leq 0.0001$; 2.3–1.0 cm in female, $P \leq 0.0001$) (Table 2).

Taking into account the study participation period of about 9 months duration for each study subject, 37 (5.7%) subjects did not turn up on the scheduled visit (marked as

TABLE 1
Demographic characteristics of study subjects ($N = 646$)

| Variables | *N* | % |
|---|---|---|
| Sex | | |
| Male | 375 | 58 |
| Female | 271 | 42 |
| Age group (years) | | |
| < 14 | 199 | 31 |
| 14–25 | 137 | 21 |
| 25–35 | 98 | 15 |
| 35–45 | 88 | 14 |
| 45–55 | 73 | 11 |
| ≥ 55 | 51 | 8 |

TABLE 2
Sex-wise status of spleen and liver size (mean value in cm) before and after treatment

| Sex | Before treatment | After treatment (29th day) | *P* value |
|---|---|---|---|
| **Spleen (mean value)** | | | |
| Male | 5.3 | 2.1 | < 0001 |
| Female | 4.4 | 1.7 | < 001 |
| **Liver (mean value)** | | | |
| Male | 2.7 | 1.2 | < 0001 |
| Female | 2.3 | 1.0 | < 0001 |

defaulter), 11 died, and 45 initially cured (of 629, i.e., 7.1%) patients relapsed during follow-up (Figure 1).

**Adverse/serious AEs.** Besides baseline clinical examination (0 day), the study subjects were clinically examined on each visit to assess clinical improvement as well as AE, if any. Altogether, 401 AEs were reported in the study subjects, of which gastrointestinal side effects, such as nausea (26.4%), diarrhea (22.2%), abdominal pain (12.7%), and dehydration (9.7%), were the most common recorded complaints. All patients were graded under CTC; 256 (64%) were in grade I, 75 (19%), 52 (13%), seven (1.5%), and 11 (2.5%) were in grades II, III, IV, and V, respectively (Table 3). Four patients developed PKDL during follow-up. Hypopigmented macular lesions were seen on face and chin in the fourth month after the treatment. One subject showed nodular lesions after seven months of treatment. Further confirmatory tests were done by skin smear and demonstration of *Leishmania* parasites. These patients were treated with 12 weeks of miltefosine therapy as per NVBDCP guidelines. These patients had CTC grade I and II ADRs such as diarrhea, nausea, and vomiting. None of them had severe ADRs.

Of 11 deaths reported as serious AE (SAE), the explored cause of deaths were extreme diarrhea ($N = 7$), kala-azar–pulmonary tuberculosis coinfection ($N = 2$), HIV/AIDS coinfection ($N = 1$), and acute pancreatitis ($N = 1$). A total of 33 patients required hospitalization during domiciliary mode of treatment with miltefosine to manage the AEs and reported as SAE (Table 4).

In those patients having ADR/AE, 6% were suffering from severe ADRs, 58% were suffering from moderate ADR, whereas the rest were suffering from mild ADRs.

**Body mass index.** Body mass index (BMI) was assessed to quantify the amount of tissue mass (muscle, fat, and bone) in an individual, and categorized as underweight, normal weight, overweight, or obese based on BMI value. Furthermore, BMI appears to be as strongly correlated with various metabolic and disease outcomes as these are more direct measures of body fatness. Initially at day 0, 41.7% male and 46.3% female were found underweight. After using miltefosine, at the end of follow-up, underweight reduced significantly and normal weight increased from 56% in male and 53% in female to 71% and 69%, respectively (Table 5).

## DISCUSSION

Miltefosine is the only oral drug available for the treatment of VL. Several advantages of miltefosine treatment include easy to administer, treatment at home, does not require hospitalization, can be given easily even in very sick patients, feasible at the peripheral level, does not require sodium/potassium estimation as in case with amphotericin B,

TABLE 3
Distribution of adverse events reported in study subjects treated with miltefosine ($N = 401$)

| Severity/adverse events | *N* | % | CTC Grade | | | | |
|---|---|---|---|---|---|---|---|
| | | | Grade I | Grade II | Grade III | Grade IV | Grade V |
| Gastrointestinal | | | | | | | |
| Diarrhea | 89 | 22.2 | 46 | 11 | 21 | 4 | 7 |
| Abdominal pain* | 51 | 12.7 | 39 | 5 | 6 | | 1 |
| Nausea | 106 | 26.4 | 85 | 19 | 2 | | |
| Increased hepatic enzyme | 32 | 8.0 | 19 | 9 | 4 | | |
| Persistent vomiting | 6 | 1.5 | | 5 | 1 | | |
| Dehydration | 39 | 9.7 | 24 | 6 | 7 | 2 | |
| Urogenital | | | | | | | |
| Pneumonia with acute renal failure | 0 | 0.0 | | | | | |
| Increased serum creatinine | 5 | 1.2 | 3 | 2 | | | |
| Musculoskeletal | | | | | | | |
| Arthalgia | 4 | 1.0 | 2 | 1 | 1 | | |
| Myalgia | 2 | 0.5 | 1 | | 1 | | |
| Respiratory | | | | | | | |
| Pneumonia | 3 | 0.7 | 2 | | 1 | | |
| Pulmonary tuberculosis | 4 | 1.0 | | 1 | 1 | | 2 |
| Skin | | | | | | | |
| Angioedema | 3 | 0.7 | | | 2 | 1 | |
| Peripheral edema | 11 | 2.7 | 7 | 3 | 1 | | |
| Skin rash | 2 | 0.5 | 1 | 1 | | | |
| Epistaxis and hemoptysis | 2 | 0.5 | | 1 | 1 | | |
| Other | | | | | | | |
| Drug ineffective | 0 | 0.0 | | | | | |
| Flu-like symptoms | 27 | 6.7 | 19 | 6 | 2 | | |
| Mouth bleeding | 0 | 0.0 | | | | | |
| Anasarca | 14 | 3.5 | 8 | 5 | 1 | | |
| HIV/AIDS | 1 | 0.2 | | | | | 1 |

AIDS = acquired immune deficiency syndrome; CTC = common toxicity criteria; HIV = human immunodeficiency virus.
*Acute pancreatitis.

TABLE 4
Distribution of serious adverse events reported in study subjects treated with miltefosine

| Severity | *N* | % |
|---|---|---|
| Death (*N* = 11) | | |
| Extreme diarrhea leading to acute renal failure | 7 | 63.6 |
| Acute pancreatitis | 1 | 9.1 |
| Coinfection with other diseases (PTB-2/HIV-1) | 3 | 27.3 |
| Hospitalization (*N* = 35) | | |
| Fluctuation in blood pressure | 3 | 9.1 |
| Edema | 9 | 27.3 |
| Increased serum creatinine | 4 | 12.1 |
| Acute renal failure | 2 | 6.1 |
| Abdominal pain | 7 | 21.2 |
| Abdominal discomfort | 2 | 6.1 |
| Diarrhea | 6 | 18.2 |

HIV = human immunodeficiency virus; PTB = pulmonary tuberculosis.

high rate of final cure (94% reported in outpatient setting), and very mild side effects in about 3–5%. However, being an antineoplastic agent, its possible teratogenic effect prohibits its use in breast feeding/lactating/pregnant women, and women of child-bearing age not willing to avoid pregnancy till 6 months after EoT. It is also not advisable in children below 2 years of age due to its possible deposition in bones.

The common side effects/ADRs observed in the present study were almost similar to those reported in its phase III and phase IV clinical trials. However, we observed a very uncommon side effect, that is, acute pancreatitis.[11] In this study, the AEs/SAEs/ADRs with miltefosine were evaluated as per Naranjo and WHO UMC scales. All the AEs have been compared with relation to Naranjo and WHO-UMC scale (Table 6).

Although there is no standard treatment protocol for HIV–VL coinfection, amphotericin B or combination therapy with liposomal amphotericin B with paromomycin injection or miltefosine is being tried. All the female patients were suggested not to become pregnant within 6 months of treatment. However, 15 patients became pregnant within 6 months of follow-up (after 2 months of treatment completion). All these patients became pregnant 2 months after EoT. All of them were followed up till 1 year and all had full-term normal pregnancy with no congenital anomalies. None of the patients had any ophthalmological problem, as was reported in the dose-finding study of miltefosine in PKDL treatment.[12] Unlike other antineoplastic agents, miltefosine may paradoxically act as a bone marrow stimulant thereby increasing the total leukocyte count, platelet, and hemoglobin. Similarly, the increase in weight leads to an increased BMI.

TABLE 6
Comparison of ADRs with relation to Naranjo and WHO-UMC Scale

| Severity/adverse events | *N* | Naranjo | WHO-UMC |
|---|---|---|---|
| Gastrointestinal | | | |
| Diarrhea | 249 | 5 | Probable |
| Abdominal pain | 71 | 5 | Probable |
| Nausea | 156 | 5 | Probable |
| Increased hepatic enzyme | 46 | 5 | Probable |
| Persistent vomiting | 13 | 5 | Probable |
| Dehydration | 53 | 5 | Probable |
| Urogenital | | | |
| Increased serum creatinine | 7 | 5 | Probable |
| Musculoskeletal | | | |
| Arthalgia | 6 | 2 | Possible |
| Myalgia | 4 | 1 | Possible |
| Respiratory | | | |
| Pneumonia | 5 | 2 | Possible |
| Pulmonary tuberculosis | 4 | 1 | Possible |
| Skin | | | |
| Angioedema | 7 | 1 | Possible |
| Peripheral edema | 15 | 2 | Possible |
| Skin rash | 5 | 2 | Possible |
| Epistaxis and hemoptysis | 4 | 0 | Unlikely |
| Other | | | |
| Flu-like symptoms | 37 | 4 | Possible |
| Anasarca | 24 | 1 | Possible |
| HIV/AIDS | 1 | 0 | Unlikely |

ADR = adverse drug reaction; AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency virus; UMC = Uppsala Monitoring Center; WHO = World Health Organization.

The initial and final cure rates were consistent with the other studies.[13] Previously, miltefosine was being used in the VL elimination program as per NVBDCP guidelines. However, now it has been changed to single-dose ambisome (10 mg/kg IV). Miltefosine is also being used in combination with paromomycin with a high efficacy of 98.7% as a short-course therapy.[14]

As regards the treatment of pregnant/lactating women and children below 2 years, we have at present safer drugs such as amphotericin B and liposomal amphotericin B. Similarly, for the treatment of HIV–VL coinfection, various other combination therapies as well as monotherapy are being tried. The drug treatment of HIV–VL coinfection is quite difficult because of 1) nonauthentification of drug, 2) drug–drug interaction, and 3) frequent relapses. In a collaborative study with MSF, liposomal amphotericin B in the dose of 5 mg/kg for 4 days was given with very good response.[15] Similarly, conventional amphotericin B is being given as a monotherapy for a longer duration such as 22 days. Splenectomy has also been tried in such cases with variable results. Combination studies using liposomal amphotericin B + miltefosine or paromomycin are underway in these cases.

TABLE 5
Percentage distribution of category-wise BMI of study subjects at different time points (day 0 to 6 months follow-up)

| | 0 day | | 29th day | | 2 months | | 6 months | |
|---|---|---|---|---|---|---|---|---|
| BMI category | Male | Female | Male | Female | Male | Female | Male | Female |
| Underweight | 41.74 | 46.36 | 41.74 | 46.36 | 38.14 | 42.73 | 25.23 | 28.18 |
| Normal weight | 56.46 | 52.73 | 56.46 | 52.73 | 59.16 | 55.91 | 71.17 | 69.09 |
| Overweight | 1.20 | 0.91 | 1.20 | 0.91 | 2.10 | 1.36 | 3.30 | 2.73 |
| Obesity | 0.60 | 0.00 | 0.60 | 0.00 | 0.60 | 0.00 | 0.30 | 0.00 |
| Total | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 |

BMI = body mass index.

## CONCLUSIONS

VL is under elimination mode in India, and miltefosine is one of the treatment options under the road map for treatment. This pharmacovigilance study will guide the policy makers and implementation authorities including NVBDCP in finalizing continued use of miltefosine or improving the treatment options with its combination. Miltefosine has been found to be very effective and extremely safe for use in adults. However, because of long half-life, it can be a candidate for development of resistance. It is the number one drug for treatment of PKDL as per NVBDCP guidelines as well. No side effects of miltefosine in pregnant women reported in this study attracts a comprehensive study to establish its use in pregnant women or women of child-bearing age without use of contraceptive measures. Pharmacovigilance of other anti-VL drugs being used in national program will be helpful in establishing its sustained use as safe treatment options for VL in the Indian subcontinent.

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Authors' addresses: Krishna Pandey, Vidyanand Ravidas, Niyamat A. Siddiqui, Sanjay K. Sinha, Rakesh B. Verma, and Pradeep Das, Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Patna, India, E-mails: drkrishnapndey@yahoo.com, drvnrdas@yahoo.com, niyamatalisiddiqui@yahoo.com, sinhask70@yahoo.com, rbihariverma@yahoo.com, and drpradeep.das@gmail.com. Tripurari P. Singh, Sadar Hospital, East Champaran, Bihar, India, E-mail: drtpsinghmd@gmail.com. A. C. Dhariwal and R. K. Das Gupta, Directorate of National Vector Borne Disease Control Programme (NVBDCP), Delhi, India, E-mails: dracdhariwal@gmail.com and rkdasgupta2003@yahoo.com.

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