NEWSLETTER

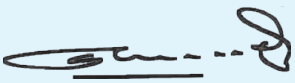
Focused Pharmacovigilance for Kala-azar in Nepal

Vol: 01 Issue: May, 2016

Forewords

Nepal government is implementing activities with an aim to eliminate Kala-azar by the end of the year 2017. I am pleased to share with you the opening issue of Pharmacovigilance newsletter in the field of Kala-azar in Nepal. Epidemiology & Disease Control Division, Department Health Service, Government of Nepal in collaboration with BPKIHS Dharan and PATH India is implementing VL focused Pharmacovigilance activities to strengthen the patients' safety. I hope this newsletter will provide the basic information, process and results of the pharmacovigilance activities.

Thank you.



Dr. Babu Ram Marasini

Director, Epidemiology & Disease Control Division

Department of Health Services, Ministry of Health

It gives me an immense pleasure to share with you the first issue of Pharmacovigilance newsletter in Nepal. B.P. Koirala Institute of Health Sciences, Dharan in collaboration with Epidemiology & Disease Control Division and PATH India is implementing VL focused Pharmacovigilance activities in Nepal. This activity will ensure the safety of Kala-azar patients against anti-leshmanial drug. I hope after reading this newsletter you will gain information regarding pharmacovigilance and anti-leshmanial drug safety.

Thank you.

Prof. Dr. Prahlad Karki

Professor & Head, Department of Internal Medicine

Lead, VL focused Pharmacovigilance Program, BPKIHS Dharan

BACKGROUND

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. In Nepal, pharmacovigilance programme is a recent development and is still in infancy stage. Epidemiology & Disease Control Division, Government of Nepal in collaboration with B.P. Koirala Institute of Health Sciences, Dharan and PATH India is implementing VL focused Pharmacovigilance program in Nepal. . The objective(s) of program are to enhance patient care, patient safety and outcomes associated with the use of VL drugs; and to support control programme by providing reliable, balanced information for the effective assessment of the risk-benefit profile of drugs.

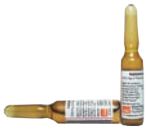
CURRENT STATUS OF KALA-AZAR IN NEPAL

Kala-azar, also known as visceral leishmaniasis is a disease characterized by high fever, enlargement of the spleen and liver, substantial weight loss, and anaemia l. Kala-azar is endemic in 12 districts in the South-Eastern plains, known as the Terai bordering North Bihar (India); however, in recent years cases have been reported from other parts of the country including hilly districts.The number of VL cases have declined significantly from 575 in 2012 to 206 in 2015 with all the 12 endemic districts have shown to have reached the elimination target (less than 1:10 000) based on the data recorded in the programme, which is remarkable success in the Indian Sub-continent

TREATMENT FOR KALA-AZAR IN NEPAL

The National Strategic Guideline on Kala-azar Elimination programme has recommended the following drug regimens for the treatment of Kala-azar and data on the safety of anti-VL drugs should be systematically collected and monitored.

Table 1: Drugs are in use for treatment of Kala-azar in Nepal

	**First line therapy:** **Liposomal Amphotericin B (L-AmB):** Currently, this is the drug of choice as a single dose (10mg/kg body weight per day) OR in 3 doses (15mg/kg body weight per day Also recommended as combination regimen: L-AmB (5mg/kg bwt on D1) + Inj. Paromomycin (D2-D11)
	**Paromomycin (15mg/kg body weight per day):** Recommended for treatment of KA only in combination regimen either with L-AmB OR Miltefosine • Miltefosine (D1-D10) + Paromomycin (D1-D10) & L-AmB (5mg/kg bwt. on D1) + Paromomycin (D2-D11)
	**Second line therapy:** **Miltefosine:** The first and only approved oral drug for KA treatment for 28 days. • Miltefosine 50mg twice daily for adults (≥11 years & ≥25 kg body weight); 50mg daily for (≥11 years and <25 kg body weight); Children (2-11 years age): 2.5mg/kg body weight 10mg formulation.
	**Non-Liposomal Amphotericin B (0.75 -1mg/kg daily for 14 days):** Still, the most effective drug in the Indian sub-continent and kept as second line therapy.

Source: National Strategic Guideline on Kala-azar Elimination Program in Nepal, 2014

Table 2: Commonly reported adverse events of anti-Kala-azar drugs.

Liposomal amphotericin B (IV)	• Chills/rigor, fever, nausea, vomiting, backache, renal toxicity
Paromomycin (Intramuscular injection)	• Injection site pain, fever, nausea, vomiting, ototoxicity, nephrotoxicity, increased AST/ALT
Miltefosine (Oral tablet)	• Nausea, vomiting, diarrhoea, abdominal pain, renal toxicity
Amphotericin B (IV)	• Fever with chills and rigor, nausea, vomiting, renal toxicity

Source: National Strategic Guideline on Kala-azar Elimination Programme in Nepal, 2014

NEED FOR PV FOR KALA-AZAR TREATMENT

The parasite Leishmania donovani is capable of developing resistance to any of the existing anti-Leishmania drug. Further, knowledge about adverse drug reaction (ADRs) of anti-leishmanial derived from clinical trials only and due to this, it has certain limitation. So, the pharmacovigilance of the drugs/treatments used for Kala-azar paves the way to explore the unseen and unknown ADRs and therefore, improve the safety of Kala-azar patients.

The WHO Regional Technical Advisory Group (RTAG) emphasis in the introduction of focused PV for Kala-azar in the members' countries of the elimination programme. As a result of this, Kala-azar elimination programme has introduced VL focused pharmacovigilance programme in Nepal with the joint effort of Epidemiology & Disease Control Division, Department of Health Services, Ministry of Health & Population and B.P. Koirala Institute of Health Sciences, Dharan, Nepal with support from PATH India have initiated VL focused pharmacovigilance programme in Nepal.

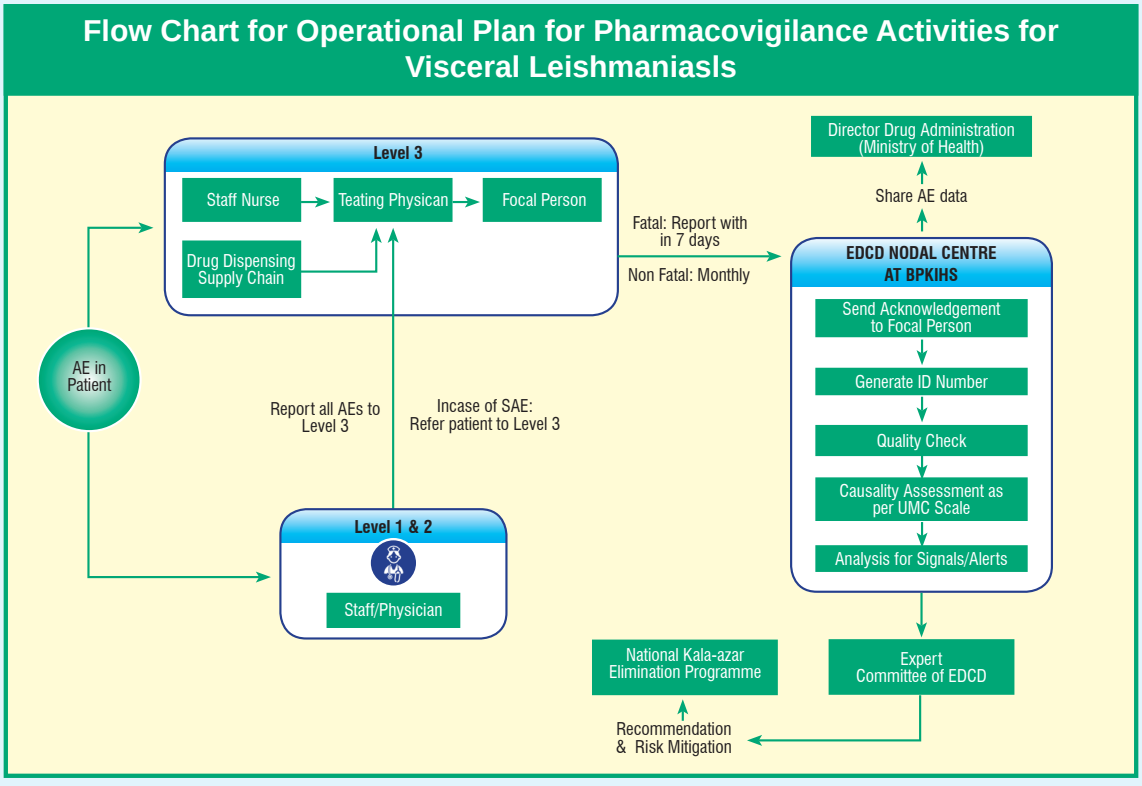


Figure 1: Flow chart for operational plan for pharmacovigilance activities for KA in Nepal.

PROCESS OF REPORTING ADVERSE EVENTS FOR KA DRUGS IN EPAL

Detection and documentation of adverse drug reaction: at PV monitoring sites nurses, paramedics and doctors who play the major role in detection and documentation of possible ADRs because these are the persons who coming to notice the potential ADRs and fills an adverse events reporting form. These person handover the completed ADR reporting form to the nodal contact person of the respective monitoring sites. The treating physician should sign on the form at the end, before sending to EDCD nodal centre at BPKIHS Dharan.

Reporting mechanism: The nodal contact person at BPKIHS Dharan using Microsoft Excel and email it to responsible person at EDCD and PATH India.Examination of the report and dissemination: At EDCD Nodal center BPKIHS, reporting form is reviewed; ID number is generated; a quality check is completed; the data is generated in an excel spreadsheet and VigiFlow; and it is analyzed for signals/alerts. Finally, results of PV activities are being shared with National pharmacovigilance expert committee to make recommendation & risk mitigation to the programme. The process of reporting is given in figure 1.

VigiFlow is a web-based Individual Case Safety Report (ICSR) management system that is specially designed for use by national centers in the WHO Programme for International Drug Monitoring.

CAUSALITY ASSESSMENT

Although across the world, there are several procedures for assessment of ADR. In general the WHO-UMC (World Health Organization- Uppsala Monitoring Centre) proposed procedure is highly accepted and widely used.

Table 3: WHO-UMC CAUSALITY ASSESSMENT CRITERIA (www.who-umc.org)

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake. • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically). • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). • Re-challenge satisfactory, if necessary.
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Unlikely to be attributed to disease or other drugs. • Response to withdrawal clinically reasonable. • Re-challenge not required.
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). • Disease or other drugs provide plausible explanations.
Conditional / Unclassified	• Event or laboratory test abnormality. • More data for proper assessment needed, or • Additional data under examination.

Un-assessable/ Unclassifiable	• Report suggesting an adverse reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified.

ADR MONITORING SITES FOR KA IN NEPAL

In Nepal, there are 20 VL focused pharmacovigilance ADR monitoring sites (figure 2).. Out of them, 14 centers (district and zonal hospitals) were located in the VL endemic districts and 6 centers (tertiary care) were located in the capital, Kathmandu (table 4). Figure 2 shows the VL focused PV monitoring sites in Nepal.

Table 4: Status of ADR monitoring sites for Kala-azar in Nepal

SN	Name of ADRs monitoring centres	Total cases admitted and treated (01 September 2014 – 31 Dec 2015)	Total cases reported AEs (01 September 2014 – 31 Dec 2015)
1	Mechi Zonal Hospital, Bhadrapur	0	0
2	Koshi Zonal Hospital, Biratngar	9	8
3	B.P. Koirala Institute of Health Sciences, Dharan	65	45
4	Sunsari District Hospital, Inaruwa	0	0
5	Sagarmatha Zonal Hospital, Rajbiraj	4	1
6	Lahan Hospital, Lahan	8	6
7	Siraha District Hospital, Siraha	2	0
8	Udayapur District Hospital, Gaighaat	0	0
9	Janakpur Zonal Hospital, Janakpur	38	22
10	Mahottari District Hospital, Jaleshwor	36	11
11	Sarlahi District Hospital, Malangwa	4	0
12	Rautahat District Hospital, Gaur	0	0

13	Bara district Hospital, Kalaiya	0	0
14	Narayani Sub-regional Hospital, Birgunj	0	0
15	Sukraraj Tropical Hospital, Kathmandu	4	1
16	TU Teaching Hospital, Kathmandu	0	0
17	Bir Hospital, Kathmandu	0	0
18	Civil Service Hospital, Kathmandu	0	0
19	Nepal Police Hospital, Kathmandu	0	0
20	Kanti Children Hospital, Kathmandu	1	1
	TOTAL	**171**	**95**

Table 5: Descriptive analysis of the reported adverse events information (N=95), September 2014 – December 2015

SN	Name of drugs used for KA treatment (N)	# of patients reported AEs (%)	Types of AEs reported (n)
1	Liposomal Amphotericin B (n= 8)	4 (50.0%)	• Chills/rigor/fever = 3 and backache = 1 Note: 2 patients reported ≥1 AEs: backache (1) & pain in left thigh (1)
2	Amphotericin B (n=98)	65 (66.33%)	• Chills/rigor/fever = 61 • Nausea & vomiting = 3 & renal toxicity: 1 Note : AEs reported in 26 patients ≥1 AEs: nausea & vomiting (20), nausea, vomiting and diarrhoea (3), abdominal pain (1), diarrhoea (1), renal toxicity (1)
3	Miltefosine + Paromomycin (n =7)	6 (85.71%)	• Injection site pain = 4 ; nausea & vomiting • Renal toxicity = 1 (increase sr. urea & creatinine)
4	Miltefosine (n=58)	20 (34.48%)	• Nausea & Vomiting = 14 • Abdominal pain = 4 , increase billirubin? = 1 • Increase billirubin? = 1 Note : 6 patients reported ≥1 AEs: abdominal pain (3), diarrhoea (3)
	TOTAL (N=171)	**95 (55.56%)**	

Healthcare professionals who reported the most AEs reporting forms to EDCD Nodal centre, BPKIHS Dharan

Laxmi Rai
Nursing Officer, Tropical Ward
B.P. Koirala Institute of Health Sciences, Dharan

Ashok Yadav
Kala-azar Treatment Assistant
Janakpur Zonal Hospital

Rita Chamling
Sister In-charge
Mahottari District Hospital

ACTIVITIES UNDERTAKEN

Pharmacovigilance activities kick-off meeting and training to healthcare providers, BPKIHS Dharan

Training to healthcare providers before the initiation of Pharmacovigilance programme was organized on August 20, 2014 at BPKIHS Dharan to orient the revised National guideline for VL treatment, and operational plan of VL focused pharmacovigilance. The programme was focused to make them acquainted with the basic and essentials of pharmacovigilance terminologies, standards and processes for adverse drug reaction (ADR) reporting and causality assessment.

Participants on training before initiation at BPKIHS ▲

Refresher training to healthcare providers (already reporting centers) at BPKIHS Dharan

One day refresher training to healthcare providers was organized at BPKIHS Dharan on March 12, 2015 for healthcare providers due to staff change. The objective was to review the implementation of PV activities, collect the feedback on PV reporting forms and discuss the ways of improvement way forward.

Participants on refresher training at BPKIHS ▲

Pharmacovigilance Training to healthcare providers working at hospitals located in Kathmandu.

One day orientation to healthcare providers working at tertiary care center, Kathmandu on "operational plan to Pharmacovigilance implementation" was organized in collaboration with Epidemiology & Disease Control Division, Government of Nepal on September 03, 2014. Medical doctors and nursing personnel working at six hospitals participated in the training programme.

Participants on training at Kathmandu ▲

National Pharmacovigilance Expert Committee Meeting, Kathmandu, Nepal

National pharmacovigilance expert committee meeting was organized in collaboration with Epidemiology & Disease Control Division, MOH and support from PATH India at Kathmandu on December 19, 2014.

The operational plan of VL focused PV activities implementation was shared, reviewed and also shared the AEs collected data and developed the future activities for implementation.

ACHIEVEMENTS

Currently there are twenty adverse drug reactions monitoring centres; only three centres namely BPKIHS Dharan, Janakpur zonal hospital and Mahottari district hospital are actively reporting PV form to Nodal centres at BPKIHS,Dharan regularly. The KA cases admitted and treated to the rest of the fourteen monitoring centres were almost negligible. The cumulative numbers of PV form filled and cumulative numbers of patients reported with adverse events is given in figure 3. Altogether 84 healthcare providers (medical doctor: 31, nurses: 36, paramedical staff: 12 and medical recorder: 5) were trained/oriented on PV programme.

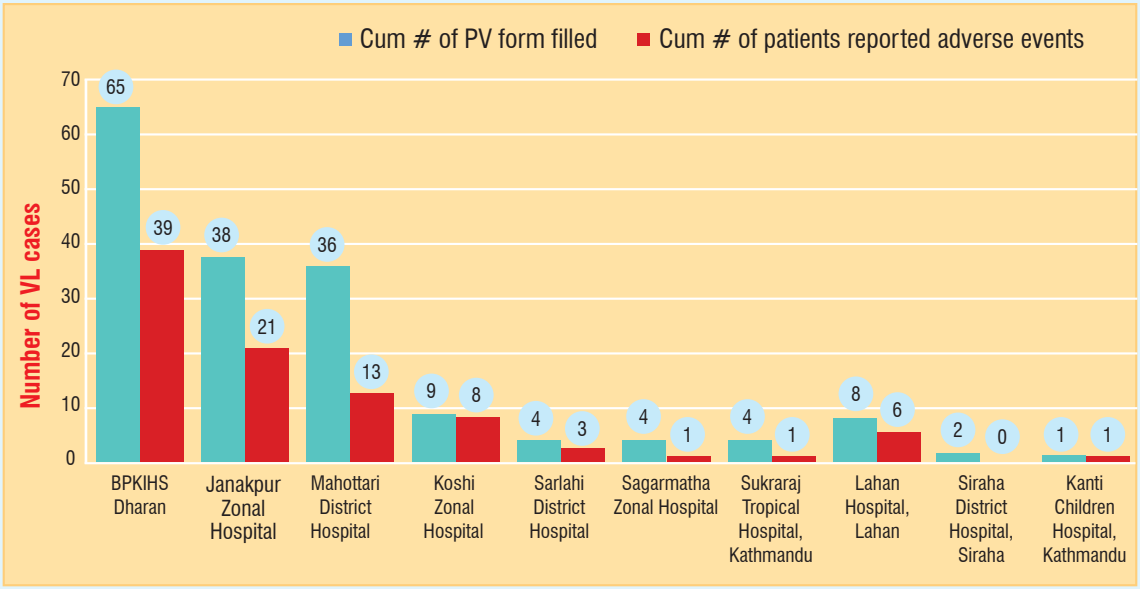


Figure 3: Cumulative number of PV form filled and patients reported adverse events (September 2014 – Dec2015)

PLAN FOR THE FUTURE

Observed challenges:

- Political instability and agitation in the country: especially in the Terai districts
- Considered as additional burden /time consuming to complete and report the PV form

Measures being taken to encourage reporting in future.

- Continue regular telephonic calls (weekly) to nodal contact persons at monitoring sites
- Follow-up meeting with sentinel sites for PV activities implementation & encourage PV reporting with main emphasis to Kathmandu centers
- Onsite monitoring and supervision visits to follow up PV activities implementation
- Involvement of government representatives during follow-up meeting and monitoring & supervision visits

So far there were only 95 patients reported with ADR which is not sufficient to come up with concrete conclusion and decision. In addition, it is also noticed that the quality of ADR report needs further improvement. Therefore, the activity must be continued.

ACKNOWLEDGMENTS

Epidemiology & Disease Control Division
Department of Health Services, Teku
Ministry of Health, Government of Nepal

PATH