GLOBAL JOURNAL OF BIOLOGY, AGRICULTURE & HEALTH SCIENCES
(*Published By*: Global Institute for Research & Education)
www.gifre.org

Treatment Of Kala-Azar Cases With Miltefosine In West Bengal, India

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Abstract
***Background & objectives*:** Visceral leishmaniasis (VL), also known as Kala-azar in the Indian sub-continent, is endemic in Brazil, Sudan, India, Bangladesh, Nepal and Bhutan. Ninety percent of all cases in these countries occur in India, Nepal and Bangladesh. Based on the unique epidemiology and technological development, India, Bangladesh and Nepal embarked on elimination of kala-azar from the three countries. Miltefosine was recommended as the *first-line drug* for the treatment of VL in the programme. Concerns have been expressed of non-compliance due to long (4 weeks) treatment and possible appearance of resistance due to its long half-life. The Regional Technical Advisory Committee (RTAG) has recommended phasing out of Miltefosine use and introduce single dose lipid amphotericin B in the programme.
Methods: Retrospective and published data regarding Miltefosine treatment was collected from the records of the District hospital, South 24 Parganas of West Bengal, India, "Health on the March" published by Government of West Bengal and analysed for compliance to 4-week treatment of Miltefosine and its efficacy.
Results: A total of 52 (Male=31, Female=21) VL cases occurred during 2011-2013. cure rate was ~ 98% and compliance was 100%.
***Interpretation & conclusions*:** Miltefosine was found to be safe and effective drug for the treatment of VL cases, while 100% compliance to full treatment was achieved by treating the patients after hospitalization. Advantages and disadvantages of this recommendation have been discussed citing the relatively small experience in the Noth 24 Parganas district in West Bengal State, India.
Key words: Kala-azar, Visceral leishmaniasis, rK39, Miltefosine, SAG, West Bengal

Introduction
Visceral leishmaniasis (VL), popularly known as Kala-azar in the Indian sub-continent, is a protozoan parasitic disease, endemic in Brazil, Sudan, India, Bangladesh, Nepal and Bhutan. Ninety percent of all cases in these countries occur in India, Nepal and Bangladesh. Sixty six percent of them occur in North Bihar, India, alone. Fifty-two districts in India, 45 districts in Bangladesh, 12 districts in Nepal and 4 districts in Bhutan are endemic for Kala-azar (VL). The disease is caused by *Leishmania donovani* and is transmitted by the bite of an infected sand fly. Man is the only reservoir of infection. There is no extra-human (canine) reservoir. Early diagnosis with rK39 and effective treatment with oral Miltefosine are available as well as suitable vector control methods. The disease is confined to limited areas in these countries. Based on this unique epidemiology and technological development, India, Nepal and Bangladesh embarked on elimination of kala-azar from the three countries in 2005.

Memorandum of Understanding (MoU):
For the purpose of Kala-azar Elimination, a Memorandum of Understanding (MoU) was signed by the Health Ministers of India, Bangladesh and Nepal in 2005 in Geneva to jointly embark on to eliminate the disease from the three countries pledging cooperation with each other and effective collaboration. This had tremendous implications because 40%-50% KA cases are seen in the adjoining areas of the international borders between the three countries. It was envisaged to eliminate the disease by 2015 with a target of less than 1 case per 10,000 populations in Kala-azar endemic districts/sub-districts/upazila levels in India, Nepal and Bangladesh. Miltefosine was recommended as the *first-line drug* for the treatment of VL in the programme[1]. Since it is unlikely that the goal will be achieved by 2015, a fresh MoU has been signed by India, Nepal, and Bangladesh; Bhutan also joined. The MoU is valid up to 2020.

Material & Methods
Endemic districts in West Bengal: Besides the States of Bihar, Jharkhand and Uttar Pradesh**,** Kala-azar is also endemic in 11 districts of West Bengal State of India. These 11 districts are: Darjiling, Uttar Dinajpur, Dakshin Dinajpur, Malda, Murshidabad, Nadia, North 24-Parganas, and South 24-Parganas, Hugli, Bardhaman and Birbhum. Table 1 shows the distribution of VL cases according to year (2006-2014) and districts in West Bengal.
***Miltefosine*:** It was initially developed as an anti-cancer drug, particularly for skin metastasis from breast cancer. Later on, it was shown to have activity against *Leishmania Donovani*. Subsequently, the drug had undergone Toxicological studies followed by Clinical trials[2-4] (Phase I, II and III) followed by Phase 4 trial[5] in Bihar amongst VL patients. It was found to be effective in ~ 95% VL cases. The PKDL trial of 4 weeks and 12 weeks of treatment with Miltefosine showed that it had an efficacy of ~95%[6]. Side-effects included nausea, vomiting, diarrhea and abdominal pain mostly in the first week of treatment and may be abated by rehydration before and during the treatment. The drug

was registered in Germany, India, Bangladesh and Nepal. Following the Phase 4 trial, it was concluded that the drug can safely be used in outpatients' real-life situation and was taken up as the *first-line drug* for the Kala-azar elimination programme in India, Bangladesh, India and Nepal. It was seen that in Miltefosine Phase 4 trial < 2% of cases treated with drug may have severe side-effects involving the liver and kidneys. During the implementation of the elimination programme, concern was expressed of possible non-compliance due to long (4 weeks) treatment and possible appearance of resistance due to its long half-life.

Subjects: Patients having fever>= 14 days, splenomegaly, anemia, and loss of weight were captured by the surveillance system set-up by the District Health Services. They were subjected to rK39 testing and if positive, were admitted to the hospital and the diagnosis was confirmed by demonstration of the parasite in the bone marrow. Splenic aspiration was not attempted. Since the district was participating in the elimination programme, all the cases were treated with Miltefosine in standard doses for 28 days. Any adverse reaction was recorded by the attending nurses and physicians.

Ethical clearance: Since this was a central/ state government sponsored programme, all ethical issues were addressed while formulating the programme and were cleared by the central and state governments for implementation. This report only describes certain policy issues by referring to published data (appropriate reference given). Therefore it was felt that no separate ethical clearance is required.

Results and Discussion

***Experience in South 24 Parganas (West Bengal)*:** According to the 2011 Census, there were 8,16,1,961 people (Male= 4,17,3,778, Female= 3,98,8,183) in South 24 Parganas, one of the 11 VL endemic districts in West Bengal. From the records available with the District Hospital in South 24 Parganas for 2011-2013, it was seen that a total of 52 (Male=31, Female=21) VL cases were admitted, whereas in 2011, 33 (Male=19, Female=14) VL cases, in 2012, 9(Male=6, Female=3) VL cases and in 2013, 10 (Male=6, Female=4).

Of the total of 42 (Male=21; Female=21) cases treated during 2011-13, cure rate was ~ 98%. Side effects included nausea, some vomiting, diarrhea, and abdominal cramps, particularly in the first week of treatment. It was possible to treat them with Oral Rehydration Salt Solution and feeding before giving the drug as was recommended in the guidelines developed by the programme. None of the patients left the hospital before completing 28-day course and they tolerated the mild side effects observed, particularly in the initial stages of treatment. In this fashion, it was possible to ensure almost cent percent compliance by the VL patients to treatment, except in 2013 it was about 92%.

Since 2005, when the VL elimination programme was initiated in the 3 countries, the total number of cases was huge (e.g., about 33598 cases in India and 1256 cases in West Bengal in 2008). So treatment by hospitalization of the patient was not recommended because of various logistics and cost considerations. However, since at present the number of VL cases has declined significantly, it may be wise to initiate active case search to mop up the remaining VL cases and treat them as described above by admitting the VL patient into the hospital, particularly in situations where hospital facility is available and number of cases are not so huge. This will eliminate non-compliance and thus it is expected to prevent/delay emergence drug resistance[7, 8.] . Noteworthy, Miltefosine is the only drug that can be given orally.

It is recommended to undertake a study in a few representative districts to really ascertain the magnitude of non-compliance to Miltefosine and occurrence of drug resistance. A study[9] conducted in South 24 Parganas in West Bengal recruited 71 patients between December 2007 and July 2009 from amongst those attending the Canning Sub divisional Hospital. At the end of treatment, the initial cure rate was 97.5% (intention to treat), and 6 months after the end of treatment, the same (final cure) was 90.3%. The overall death rate was 0.9% (5 of 567), and 2 deaths were related to drug toxicity. Gastrointestinal intolerance was frequent (64.5%). The drug was interrupted in 9 patients (1.5%) because of drug-associated adverse events.

However, we should not loose sight of the advantages of using single dose lipid amphotericin B in the programme since it is safe and ensures full compliance[10]. The programmes in the 3 countries were geared up for Oral Miltefosine treatment. It is imperative to reorganize the patient care delivery system for introduction of single dose therapy of lipid amphotericin B. Both the drugs are costly. WHO/TDR initiated training of doctors in Bangladesh on administration of single dose lipid amphotericin B. Although the Regional Technical Advisory Committee (RTAG) recommended the new drug as *first line drug* and Miltefosine should be phased out in the elimination programme, it is up to the Progamme Managers of the countries to take a position and if required the policy should be modified. Such decision must address health care delivery infrastructure, development of guidelines, training components, cold chain, generator, and the cost of treatment and easy availability of the drug. Drugs if centrally purchased by the WHO will be very useful for the countries.

Acknowledgement

The authors acknowledge using the published data from "*Health on the March*", published by West Bengal State Bureau of Health Intelligence, Directorate of Health Services, Government of west Bengal. The project was supported by National Academy of Sciences, India, by awarding a Senior Scientist Platinum Jubilee Fellowship to Dr. Sujit Kumar Bhattacharya.

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Annexure

Table 1: Distribution of VL cases according to year and district

Districts	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Darjiling	126	182	126	100	220	384	211	104	197
Uttar Dinajpur	60	56	62	35	58	180	79	21	52
Dakshin Dinajpur	333	285	197	124	120	129	92	89	91
Malda	429	535	497	268	630	827	400	179	227
Murshidabad	575	630	265	149	279	288	135	87	47
Nadia	13	3	0	6	17	13	0	2	0
North 24-Parganas	64	39	24	12	21	14	15	1	2
South 24-Parganas	140	36	41	42	66	33	9	5	13
Hugli	6	3	4	0	12	3	3	8	2
Bardhaman	58	22	14	6	10	39	8	10	6
Birbhum	39	26	26	14	42	52	43	18	32
Total	**1843**	**1817**	**1256**	**756**	**1475**	**1962**	**995**	**595**	669