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Adherence to miltefosine treatment for visceral leishmaniasis under routine conditions in Nepal

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Abstract

OBJECTIVE To assess patient adherence to unsupervised single-drug miltefosine treatment for visceral leishmaniasis and to identify the factors influencing adherence.

METHODS This is a prospective cohort study of 171 patients with Visceral leishmaniasis (VL) in three healthcare settings in Nepal. Adherence was assessed through pill count, checking of treatment cards and adherence questionnaires, as well as miltefosine concentration measurements at the end of treatment. Poor adherence was defined as less than 90% of required capsules taken.

RESULTS Patient adherence to miltefosine was 83%. Predictors of adherence were being the male sex (OR = 2.60, 95% CI 1.02–6.67) and knowing the duration of treatment (OR = 3.05, 95% CI 1.16–8.04). Adherence was also better for patients who were literate and knew the side effects of treatment. Gastrointestinal side effects and negligence after the resolution of clinical symptoms of VL were the main reasons for poor adherence. Poor adherence was associated (though not statistically significant) with future relapse.

CONCLUSION Effective counselling during the treatment, a short take-home message on VL and on side effects and action of miltefosine, and follow-up visits are the best way to prevent poor adherence. Single end-of-treatment measurements of miltefosine concentrations as objective assessment of adherence would only be useful in addition to the subjective assessments when substantial doses of miltefosine have been missed.

keywords visceral leishmaniasis, treatment, miltefosine, adherence, Nepal

Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is a major public health concern in large parts of India, Bangladesh and Nepal. These countries, along with Sudan and Brazil, hold about 90% of the 200 000–400 000 estimated annual VL cases worldwide (Alvar *et al.* 2012). On the Indian subcontinent, VL is mainly caused by *Leishmania donovani*, a protozoan parasite transmitted by a sand fly, *Phlebotomus argentipes*.

Early diagnosis and treatment is one of the major pillars of the ongoing elimination programme. Miltefosine (MIL) has replaced sodium stibogluconate (SSG) as 1st line therapy for VL [WHO SEARO 2005; Epidemiology & Disease Control Division (EDCD) 2009], as increasing treatment failure of SSG was reported from India and Nepal (Sundar *et al.* 2000; Rijal *et al.* 2003). Miltefosine is the first oral drug for VL and requires 28 days of treatment at a conventional dose of 2.5 mg/kg body weight per day (max of 100 mg/day). It can be taken on ambulatory basis, and hospitalisation is not required (Sundar *et al.* 2002). Miltefosine treatment has been available at district hospitals in Nepal since 2007. The drug is delivered free of charge through the public health system and is not available in private pharmacies.

Although MIL showed excellent efficacy in phase three clinical trials (Sundar *et al.* 2002), recent data indicate increased failure rates after a decade of use in Bihar, India (Sundar *et al.* 2012) and 5 years of use in Nepal (Rijal *et al.* 2012). A similar result was reported from Bangladesh (Rahman *et al.* 2011). Although emergence

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of parasite resistance to MIL was anticipated in the context of its elimination, due to its long half-life (Bryceson 2001; Dorlo *et al.* 2008) and the fact that resistance to MIL can easily be induced *in vitro* (Seifert *et al.* 2003), there may be several other causes for its falling efficacy. These include more severe cases being included in routine cohorts compared to trials, immuno-genetic host factors, low quality of drug (Dorlo *et al.* 2012a,b) and poor patient adherence (Sundar & Murray 2005).

Given the high prevalence of gastrointestinal side effects of MIL (>60%, Sundar *et al.* 2012) on one hand and the relatively fast resolution of clinical VL symptoms on the other, patients may lose the motivation to complete the 28 days of treatment. Therefore, adherence to treatment is a key factor worth monitoring. So far, no formal evaluation of adherence to MIL has been reported from Nepal or from any other region.

This study was conducted to assess patient adherence in a prospective cohort of patients with VL treated with MIL under routine conditions in Nepal. We also explored reasons for non-adherence. The results from this study will be important in designing appropriate implementation strategies for MIL treatment at primary and secondary healthcare level.

Materials and methods

Study settings and population

The study was conducted in different health structure settings: (i) one referral hospital, BP Koirala Institute of Health Sciences (BPKIHS), where MIL has been used for longer and (ii) two district hospitals where ambulatory treatment with MIL has only recently been implemented. The study was conducted within the framework of the Kaladrug-R project (www.leishrisk.net/kaladrug). The health facilities were selected on the basis of their VL caseload in 2008/2009. Patients with VL recruited and treated in the Kaladrug-R study from March 2010 to August 2011 were automatically eligible and included for study.

Treatment and follow-up

Patients with VL were treated with MIL (Paladin Labs Inc., Montreal, Canada) as per national guidelines: $\geq$12 years weighing >25 kg: 100 mg daily (50-mg capsule twice a day); <25 kg: 50 mg daily (50-mg capsule once a day). Children (2–11 years): 2.5 mg/kg body weight in divided doses daily for 28 days (EDCD 2009). The 10- and 50-mg MIL capsules were dispensed in a packaged blister strip. When the daily dosing comprised more than one capsule, patients were advised to divide the number of capsules over two intakes, to reduce gastrointestinal upset.

All patients were hospitalised during the initial 2–3 days of treatment for observation of possible side effects. At discharge, the patients were provided with a limited drug supply till the next follow-up visit at day 14, and a treatment card indicating the date for follow-up. Clinical and laboratory follow-up was conducted on the 14th and 28th day of therapy, at the hospital. At the 28-day visit, initial outcome was assessed using the standard definitions: clinical cure, death, treatment switch for serious adverse events (SAE), defaulter and non-response. Supplementary data collected in the Kaladrug-R study were used to verify and cross-check the data (e.g. late treatment outcomes, laboratory and parasitological assessments of cure, as well as MIL concentration at the end of treatment for patients treated at BPKIHS only).

Sample size and sampling procedure

This is an observational study to estimate the proportion of adherent patients. Assuming a true proportion of non-adherence of 10%, with a precision of $\pm$5%, an α-error of 5% and loss to follow-up or withdrawal of 20%, the total sample size required was 144 patients. There was no 'sampling' or 'random selection' of patients, nor any control group treated with other drugs.

Data collection

Data were collected on three visits: at discharge, on the day of refill after 2 weeks and on the day of post-treatment outcome evaluation (D28). Basic characteristics of patients and their caretakers (age, sex, educational level, country of residence, caretaker's relationship to the patient) as well as knowledge on VL and treatment prescribed were recorded on the day before leaving the hospital. Then and at each follow-up visit, detailed information on capsule intake, side effects and their effects on capsule intake and events such as capsules missed/vomited was collected. Patients and caretakers were asked to bring the used blister packs at each visit, to count remaining capsules. The capsule intake was also determined by reviewing the VL treatment card provided by the health facility. Reasons for non-adherence to MIL treatment were recorded. Punctuality to the follow-up visits was assessed, as well as reason for delay. Interviews were conducted by trained interviewers in a separate place in the hospital using a standardised semi-structured questionnaire.

Data analysis

All data sets were first checked to see whether MIL treatment prescriptions were correct according to age and weight. Data entry errors were cross-checked by performing cross-tabulation of data and verifying against the source documents.

Adherence to MIL treatment was assessed on the basis of two criteria: (i) capsule adherence (self-report in combination with capsule count, side effect reporting and treatment interruption) and (ii) timeliness of follow-up visits.

Poor adherence was defined empirically as a total, capsule intake of less than 90% of the total daily dose of MIL prescribed (i.e. <50 capsules of the 56 required in BID or <25 of 28 in OD) assessed through capsule count, observed treatment interruptions or self-reporting of missed tablets. Perfect adherence was defined as absence of reported problems, that is, no delay for the refill (D14), no left-over capsules, no self-reported side effects affecting capsule intake, no forgetting or losing capsules and no skipping days for whatever reason. Delay for the end-of-treatment visit (D28) was not considered as non-adherence, but failure to attend this visit (default) was. Treatment interruption was defined when treatment was not taken ≥ 2 consecutive days [1 day of missing treatment was not considered as treatment interruption, only as missed capsule(s)].

Adherence results were compared with final treatment outcomes assessed 6 and 12 months after treatment completion, obtained through treatment outcome monitoring as piloted in the Kaladrug-R project.

For a subsample of MIL-treated patients at BPKIHS ($n = 31$), we disposed of the results of MIL concentration measurement in blood at the end of treatment, allowing us to compare the results and to see whether poor adherence correlated with lower MIL concentration at the end of treatment. In brief, all available blood samples taken at the end of treatment (± 6 days) were stored and transported in appropriate conditions (temperature of maximum -20 °C) for analysis at the Slotervaart Hospital, Amsterdam, using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), based on the method described previously by Dorlo *et al.* (2008).

Statistical analysis

Data were entered in Microsoft Access database by a data entry clerk and analysed in Stata/IC V10.1 (Stata Corp., College Station, TX, USA) for frequency and proportions of adherence. Determinants of patient adherence assessed included patient characteristics, doses and prescribing and dispensing practice and knowledge on VL. Observed associations were assessed through logistic regression. Variables with a P-value ≤ 0.10 in univariate analysis were included in the multivariate logistic regression model. Variables for the final model were selected using the backward elimination strategy. The probability of removal was set at $P = 0.05$. We tested all interactions that are biologically plausible in the multivariate model.

Ethical considerations

The ethical committee of BPKIHS Dharan, Nepal, and the University Antwerp (UZA), Antwerp, Belgium, approved the study protocol. District hospital staff and staff at the tropical ward of BPKIHS were informed about the study. Informed written consent was obtained from patients or caretakers (for children) prior to the interview. Participation was completely voluntary.

Results

A total of 171 patients receiving MIL treatment were interviewed at three hospitals: 57 (33.3%) in BPKIHS, 33 (19.3%) in Lahan and 81 (47.4%) in Mahottari District Hospital (Figure 1). Nobody refused participation. Of the 171 patients, six were switched to second-line therapy for severe adverse events (two with hepatotoxicity, four for grade III/IV gastrointestinal side effects) and seven did not attend the last follow-up visit. All patients came with a caretaker; in 54 (32%), the caretaker was interviewed because the patient was <13 years of age. Median age of patients was 22 years, and interquartile range was 10–40 years. Male/female ratio was 2:1. General characteristics of the study population are shown in Table 1. All patients had received correct dosing in line with the treatment guidelines.

Knowledge

Almost all interviewed (99.4%, 170/171) reported being informed on the diagnosis of VL before starting treatment. More than 90% of the patients knew that the capsules they received were to treat VL. Only 39.8% (68/171) of the patients had known about VL before their diagnosis. 165 (96.5%) reported they knew the number of capsules to take per day but only 80.0% (123/171) were aware of the exact duration of the treatment. All patients had received the first dosage of MIL at hospital. Only 35.0% (60/171) patients could cite possible side

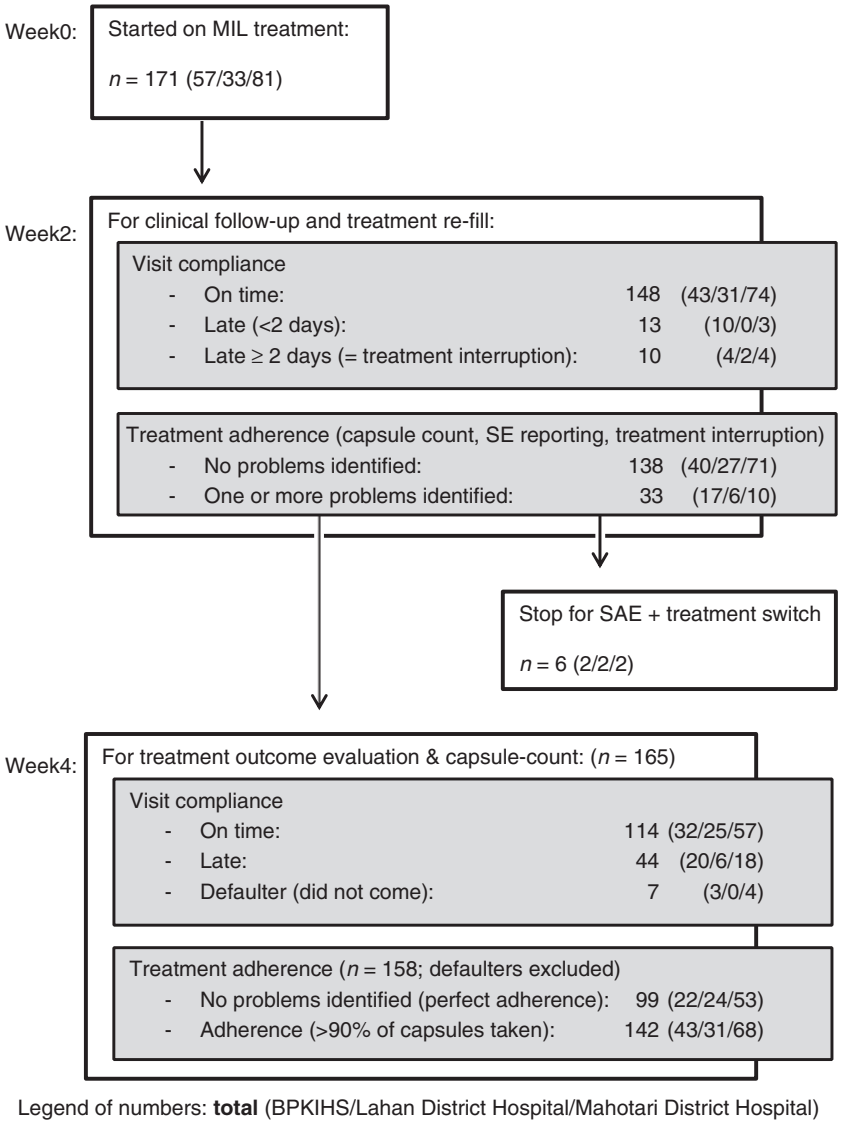

Figure 1 Flowchart of main study outcomes.

effects of treatment such as diarrhoea (25/60), nausea and vomiting (21/60) and nausea, vomiting and diarrhoea (14/60).

Timeliness of follow-up visits

One hundred and forty-eight patients of the 171 (86%) visited the hospital on time for clinical follow-up and treatment refill at day 14. Thirteen patients were 1 day late, and 10 had ≥ 2 days delay (defined as treatment interruption). The reported reasons for delay were forgetting the exact follow-up date given (9/23), busy at work (4/23), bus strike on the day of visit (4/23) and worsening after intake of capsules and financial problem to visit hospital.

For the end-of-treatment visit at week 4, 114 of the 165 patients still under MIL treatment attended on time (69%), 44 came late and seven did not come at all. Treatment outcome evaluation was performed later through defaulter tracing in four of these patients, but data on adherence were not collected because of assumed recall bias.

Among the 44 latecomers, 61% (27/44) mentioned the completed treatment and feeling well as reason for their delay. Other reported reasons were improvement of fever (12/44), work at home (3/44) and no cap-

Table 1 Characteristics of study patients and caretakers interviewed for the study, south eastern, Nepal, March 2010–August 2011

Variables	Patients (n = 117) Number (%)	Caretakers (n = 54) Number (%)
Age		
<13 years	54 (31.58)	–
13–30 years	57 (33.33)	–
≥31 years	60 (35.09)	–
Median (Interquartile range) (years)	22 (10–40)	–
Sex		
Male	74 (63.25)	46 (85.19)
Female	43 (36.75)	8 (14.81)
Level of education		
Illiterate	87 (74.36)	42 (77.78)
Primary school completed	18 (15.38)	2 (3.70)
Secondary school completed	11 (9.40)	8 (14.81)
Diploma completed	1 (0.86)	2 (3.70)
Country of residence		
Nepal	82 (70.69)	37 (68.52)
India	34 (29.31)	17 (31.48)
Caretaker's relationship to the patients		
Father	–	5 (9.2)
Mother	–	30 (55.6)
Other family members	–	19 (35.2)

sules to take (2/44). Among the seven defaulted patients, four were traced via telephone call and found well. Unfortunately, we could not trace the remaining three patients by telephone or home visit.

Treatment adherence

Of the 171 patient assessed at week two, 138 had completed the prescribed MIL treatment regimen correctly. In the other 33 patients, one or more problems were recorded: 10 interrupted their treatment for 2 or more days by not attending on time, five stopped their treatment because of side effects that later led to treatment switch (a sixth one was stopped on doctor's initiative because of hepatotoxicity identified through laboratory analysis only), in four, the capsule count did not match reported intake, 24 self-reported that they had not taken their treatment correctly for 1 or more days (various reasons), and 13 had refused to take the medicine because of side effects. Thus, in 28 of 33 cases, the patient (or his attendant) self-reported non-optimal intake.

Assessment of adherence at the end of treatment (D28) was complicated by latecomers and defaulters. Of the seven who did not come for end-of-treatment evaluation, four claimed they had completed treatment up to day 28 without any problem when contacted later. The other three received their refill at week 2, but treatment completion could not be taken for granted. From the 158 interviewed on adherence over the previous week, four had capsules remaining (ranging from 2 to 8 caps) and 19 self-reported that they skipped 1 or more days of treatment for various reasons: forgetting (9), feeling better (9) and/or not feeling well (2).

Overall adherence over the full treatment period was assessed as described above. Perfect adherence was recorded in 57.9% (99/171). There was significant difference between the settings: 39% at BPKIHS, against 73% at Lahan and 65% at Mahottari District Hospital.

Poor adherence was identified in 29 patients (17%). These include the five patients who had treatment switch for SAE; the patient who was stopped on doctors' advice for hepatotoxicity did take his treatment correctly up to the day of switch. For those who completed treatment and reported poor adherence, median % of capsule intake was 87.5% with IQR (Q1;Q3) 85.71–89.29% and with 71% as the minimum.

Side effects

The number of side effects reported varied over time: 20% (36/171) at discharge, 9% (14/171) at the 2nd week follow-up visit and none in the 4th week visit. Nausea and vomiting were the most common side effects reported. Of all those who reported vomiting within 30 min after intake (n = 30), only one had taken a second capsule. Thirteen patients reported that these side effects affected their capsule intake.

Relation between measured adherence and end-of-treatment MIL concentration

End-of-treatment MIL concentrations were available for 31 patients at BPKIHS. In Figure 2, we plotted out measured MIL concentration against assessed capsule intake for adults and children separately, because linear dosage (2.5 mg/kg of body weight) results in relatively lower drug exposure compared to adults (Dorlo *et al.* 2012a,b). As shown, patients with capsule count between 80% and 90% of the prescribed amount did not have significantly lower end-of-treatment concentrations.

Factors influencing adherence

To measure possible associations between adherence and other variables, odds ratios (ORs) were calculated.

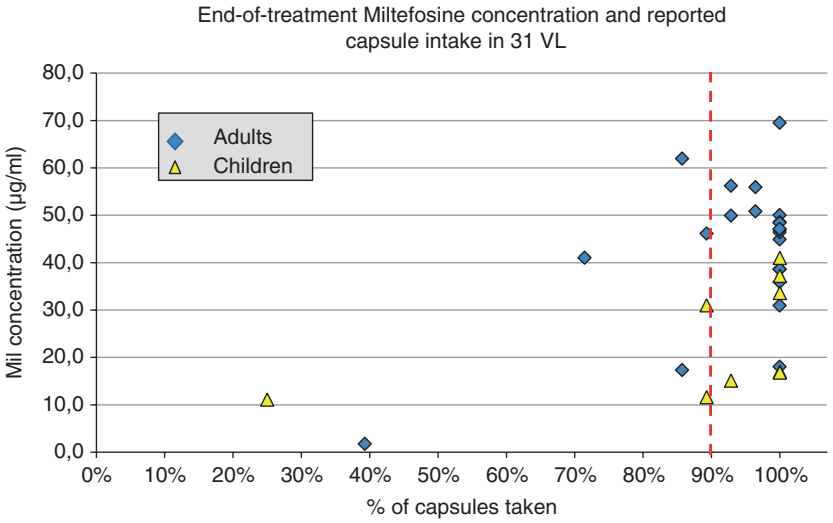

Figure 2 Capsule intake *vs.* Miltefosine (MIL) concentration at end of treatment period.

Table 2 Potential factors influencing adherence to miltefosine among 165 patients with Visceral leishmaniasis (VL) in univariate (crude) and multivariate model (adjusted)

Variable	Total *n* = 165*	Adherent *n* = 142 (86.1%)	Crude OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Patient characteristics						
Age <13 years	52	45 (86.5)	1			
Age 13–30 years	55	47 (85.5)	0.88 (0.29–2.69)	0.82		
Age ≥31 years	58	50 (86.2)	0.91 (0.30–2.77)	0.86		
Male	107	97 (90.7)	2.87 (1.15–7.20)	0.02	2.60 (1.02–6.67)	0.047
Female	58	45 (77.6)	1			
Literate	36	34 (94.4)	4.04 (0.88–18.49)	0.07		
Illiterate	129	108 (83.7)	1			
Doses, prescribing and dispensing						
Once a day (OD)	50	44 (88.0)	1.33 (0.48–3.68)	0.58		
Twice a day (BD)	115	98 (85.2)	1			
Adult dosage	159	138 (86.8)	2.24 (0.34–14.59)	0.40		
Paediatric dosage	6	4 (66.7)	1			
Knowledge on VL						
Knew the drug is for VL	65	55 (84.6)	0.82 (0.27–2.44)	0.72		
Did not know the drug is for VL	100	87 (87.0)	1			
Treatment instruction given when alone	51	46 (90.2)	1.59 (0.53–4.78)	0.41		
Treatment instruction given with caretaker	114	96 (84.2)	1			
Knew the no. of capsule to take per day	160	138 (86.3)	1.76 (0.18–17.70)	0.63		
Not know the no. of capsule to take per day	5	4 (80.0)	1			
Knew the duration of treatment	118	106 (89.8)	3.39 (1.31–8.79)	0.01	3.05 (1.16–8.04)	0.023
Did not know the duration of treatment	47	36 (76.6)	1			
Knew the side effects of treatment	54	50 (92.6)	2.73 (0.86–8.64)	0.08		
Did not know the side effects of treatment	111	92 (82.9)	1			
Did not vomit within 30 m after intake of capsule	140	122 (87.1)	1.49 (0.48–4.61)	0.49		
Vomit within 30 m after intake of capsule	25	20 (80.0)	1			

*Six patients excluded from analysis [=treatment switch for severe adverse events and missing data (because not present at last visit)].

Adherence outcome was dichotomised as poor (<90% intake; $n = 29$) and satisfactory ($n = 142$). Males were more likely to adhere than females (OR 2.87; 95% CI 1.15–7.20; adjusted OR 2.60, 95% CI 1.02–6.67) (Table 2) and so were patients who knew the duration of treatment (OR = 3.39, 95% CI 1.31–8.79; adjusted OR 3.05; 95% CI 1.16–8.04). No significant interaction was found. Adherence was also better for literate (94%; 34/36) than illiterate patients (84%; 108/129). Patients who knew the side effects of treatment showed better adherence to treatment (93%; 50/54) than those who did not (83%; 92/111).

Adherence data versus (late) treatment outcome

We finally verified whether poor adherence was a risk factor for treatment failure, using treatment outcome data from the Kaladrug-R study. Outcome data were available for 49 study patients. There were no treatment-related deaths. Relapse was found in seven and final cure in 42 patients. Patients with poor adherence were more likely to have relapse but the difference was not statistically significant (OR 1.7; 95% CI 0.28–10.41).

Discussion

Our findings show that adherence to MIL treatment in Nepal is a problem and the target of 90% of capsules taken is not reached in at least 17% of the enrolled patients. Though not statistically significant, these patients did have a higher risk of relapse. Reasons for poor adherence were mainly gastrointestinal side effects and negligence once the clinical symptoms of VL had subsided. Side effects were mostly reported in the first 2 weeks, as reported elsewhere (Sundar *et al.* 2002, 2012). In between treatment and outcome, adherence stands as the key link that is often overlooked (Brown & Bussell 2011). In chronic disease in developed countries, adherence is estimated at 50%, assumedly even lower in developing countries (World Health Organization 2003). Good adherence is hindered by side effects of the treatment, treatment fatigue, but also access problems (financial, procurement, quality), condition-related factors (severe illness, concomitant drugs), limited knowledge on the disease and its cure and limited information provided by the healthcare providers.

For VL, treatment duration is limited to 28 days and treatment is provided free of charge in Nepalese government facilities, but adherence remains a major challenge for patients and healthcare providers. In countries with limited resources and often poorly trained and motivated health staff, proper counselling on the importance of treatment adherence is often non-existent. Meanwhile, taking the complete treatment course is not only crucial for successful elimination of the parasite but may also reduce chances of treatment failure (non-response, relapse) and development of drug resistance.

Assessing the level of treatment adherence to MIL is therefore important information on the feasibility of the currently promoted treatment strategy based on unsupervised oral single-drug treatment of VL. To our knowledge, this is the first prospective study on the subject.

Limitations and weaknesses

Like for most drug treatments for which the therapeutic window is not completely clear, there is no gold standard definition or cut-off for good adherence with MIL. The optimal dose and duration of MIL treatment are defined on the basis of a balance between efficacy and toxicity, pharmacokinetic studies are still scarce, cut-off for minimum required MIL drug concentrations in blood has not been defined, and drug clearance of MIL varies much in between individuals (25%, Dorlo *et al.* 2008, 2012a,b). In HIV therapy, where development of resistance is a major issue, 95% is the target (Osterberg & Blaschke 2005), while for other chronic conditions such as antihypertensive treatment (Brown & Bussell 2011) and TB treatment (International Union Against Tuberculosis Committee on Prophylaxis 1982; Nackers *et al.* 2012), 80% is considered as satisfactory. With MIL in VL treatment, it is unknown how many per cent of capsules 'can' be missed before the risk for treatment failure or for development of resistance is increased. For this study, we had set our cut-off arbitrarily at 90%, knowing that the measurements we would use are known to result in an overestimation of adherence behaviour (Norell 1981; Morisky *et al.* 1986; Matsui *et al.* 1994; Farmer 1999).

State of the art in measurement of adherence behaviour requires a multimethod approach combining feasible self-reporting and reasonable objective measures, and no single measurement strategy has been deemed optimal (Vitolins *et al.* 2000; World Health Organization 2003). We assessed adherence combining capsule count, by checking treatment card, interviewing patients about side effects and forgotten or skipped capsule intakes. The true adherence is likely to be lower than assessed through our methods as patients may consciously or unconsciously overestimate their adherence, and we were not able to quantify the number of capsules missed through vomiting.

We included end-of-treatment MIL concentrations, but given the above-mentioned characteristics of MIL pharmacokinetics, these could not provide us an objective

parameter to completely validate the data collected: Treatment interruptions of less than, for example, 8 days may therefore not be detectable by single end-of-treatment concentration measurements.

The frequency of adherence problems reported was different from one hospital to another: problems were reported more at BPKIHS, where patients with VL are attended in the tropical ward, by staff dedicated to VL and VL research. One explanation may be that the more personal contacts between staff and patients may have led to a higher level of openness to report side effects and adherence problems.

Patients report adherence issues when asked even though underreporting in our study is likely. Timeliness for the refill visit after 14 days was good with 94% of patients attending on time; therefore, we believe that this timing for resupply is a good compromise between the obligation of monitoring and strengthening the message on adherence and what is considered acceptable and realistic for the patients. The end-of-treatment visit (on day 28) is equally important to assure completeness of treatment and to assess the outcome. In the current elimination programme, patients are entitled to financial compensation for attending these visits.

Adherence was better in patients who were informed on treatment duration and side effects compared to those who were not. Effective counselling is the best way to prevent poor adherence: during the first day of treatment in hospital, patients should be taught appropriate coping strategies for dealing with gastrointestinal side effects at home, and at discharge, drug supply should be accompanied by short take-home messages on the disease, possible side effects and actions to be taken and the importance of follow-up visits. Guidelines for corrective action in case of severe failure-to-adhere should be designed for the staff. Further research is needed on adherence but also on more patient-friendly and more efficacious drugs and drug regimens for this fatal neglected disease.

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