How better drugs could change kala-azar control. Lessons from a cost-effectiveness analysis

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Summary

Conditional on correct diagnosis and treatment, current drug regimens for visceral leishmaniasis (VL) will only prevent about 90% of deaths. Furthermore, the cost of pentavalent antimonials, the long duration of the regimen and its parenteral administration are major obstacles for patients. Poor patient compliance and the use of counterfeit drugs contribute to therapeutic failure, amplification of the reservoir and the appearance of drug resistance. We assessed the impact of potential improvements in chemotherapy on the cost-effectiveness of VL test-treatment strategies. Competing test-treatment strategies were compared in a formal decision analysis – from the viewpoint of the clinician facing a VL suspect –, with avoided VL-mortality and cost as outcomes of interest. Sensitivity analysis was done involving the following parameters: efficacy, toxicity and cost of treatment including patient care. When safer and more efficacious drugs are considered, they only result in a more cost-effective strategy if the total cost of treatment falls below US$ 390 per patient. A serological test-treatment strategy remains the optimal choice, also when better drugs become available.

keywords visceral leishmaniasis, drug treatment, cost-effectiveness analysis

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Introduction

The current possibilities for visceral leishmaniasis (VL) control are limited: there is no vaccine, no possibility to treat infection in asymptomatic carriers, no effective strategy to control the animal reservoir. While insecticide spraying and impregnated bednets are strategies of proven value to combat the phlebotomine vector (El Naieem et al. 1999), the highest priority should clearly be given to a strategy of diagnosis and treatment of clinical VL cases (Boelaert et al. 2000). However, the currently available tests and drugs have serious limitations, which compromise the success of any control strategy built on case detection and management. Parasitological examination of lymph node and bone marrow aspirates has a weak sensitivity. Splenic aspirates are more sensitive, but are hardly feasible in a primary care setting. Promising serological tests, such as the Direct Agglutination Test (DAT), have been developed (El Harith et al. 1986) and evaluated (Boelaert et al. 1999a), but diagnostic algorithms based on DAT are not yet widely accepted for use by the health services. Pentavalent antimonials have been the therapy of choice for more than 50 years now (Herwaldt & Berman 1992). Therapeutic failure of antimonials, including primary unresponsiveness as well as relapse, require second-line drugs such as amphotericin B, or aminosidine. Worldwide up to 15% therapeutic failures occur with antimonials, but in Bihar, the epicentre of the current Indian epidemic, 37–64% of previously untreated patients fail to respond to them (Sundar 1997; Thakur et al. 1998; Jha et al. 1999). Cases of HIV-VL coinfection are characterized by the same high failure rates (Alvar et al. 1997). The cardio-, hepato- and nephrotoxic effects of antimonials are well known in high doses (Ballou et al. 1987), but recently (Sundar et al. 1997; Thakur et al. 1998) very alarming figures on antimonial cardiotoxicity with the standard WHO regimen in India have been reported.

Ninety per cent of the kala-azar disease burden occurs in regions where health service development is weak: Sudan, India, Bangladesh and Brazil. Drug supply is not at all guaranteed in those endemic areas, and though in high demand, the antimonials are scarce. In eastern Sudan, Pentostam® was a highly demanded commodity in the black market. The dose of antimonials received depended...
on what the patient could afford, and even the quality of the drug was questionable as expired and diluted Pentostam® was circulating in the area (El Safi, unpublished). Poor quality or counterfeit drugs, and poor compliance will contribute to therapeutic failure and the appearance of resistance in parasites. Post-kala-azar dermal leishmaniasis, associated with incomplete treatment, becomes another factor for increased transmission through reservoir amplification (Addy & Nandy 1992).

In this context, the need for better drugs becomes only more pressing. Recently a very promising phase II clinical study was reported on miltefosine (Jha et al. 1999), an antineoplastic agent, which had showed antileishmanial efficacy in animal models. The advantages of miltefosine are that it can be given orally and in shorter duration (2 weeks), while side-effects seem to be moderate (mainly dose-related gastro-intestinal effects: nausea, vomiting and diarrhoea, but also single cases of hepatitis and nephrotoxicity). Teratogenic effects have been described in animals, so it should not be used in pregnancy. The results of miltefosine phase III clinical trials are thus eagerly awaited, and if efficacy is confirmed, this oral agent could potentially constitute a real breakthrough for control.

In a previous study, we compared diagnostic strategies for case detection and management in a formal decision analysis, and recommended a serological test with high sensitivity and reasonable specificity as an alternative for parasitology (Boelaert et al. 1999b). In this paper, we examine whether the potential improvements in chemotherapy would affect the choice of the ‘optimal’ test-treatment algorithm, and under which conditions such newly developed drugs would result in more cost-effective strategies and real improvement of VL-control.

Methods

Decision analysis examined to what extent therapeutic innovation (and other variation in drug related parameters) would affect the optimal choice of test-treatment strategy for VL. Outcomes were assessed from the viewpoint of a clinician facing a patient suspect for VL.

Decision tree

Three alternative strategies, which only differ by diagnostic method, were compared (for full description of decision tree see Boelaert et al. 1999b). Strategy A, ‘treat-all’, treats all clinically suspect patients without testing and leads either to a correctly treated VL or an erroneously treated non-VL case. Strategy B, ‘parasitology’ relies on parasitological diagnosis: only persons with positive parasitology are treated and this leads either to a correctly treated VL or an erroneously treated non-VL case. The latter is almost entirely theoretical, because it is widely accepted that parasitology is 100% specific and produces no false positive results. In case of negative parasitology, the person will not be treated and the decision tree branches either to an untreated VL case, or a correctly ruled out diagnosis in a truly negative person. Strategy C ‘serology’ differs only from the former to the extent that a serological test is used instead of a parasitological one.

In a second step we focused on changes in drug-related parameters, but restricted the comparison to the ‘treat-all’ and the ‘serology’ strategy as the latter was found to be the optimal diagnostic strategy. The cost-effectiveness of treating after serological testing and treating without testing was examined under the hypothesis of a new drug regimen compared with current drugs.

Effectiveness

Each possible outcome of a strategy was judged exclusively on its effectiveness in avoiding VL death. Disregarding all other health benefits or losses of a strategy and its utility (patient’s preference towards quality of life of a health state) the strategy’s overall effectiveness was expressed in terms of deaths averted, compared with no intervention. We assumed that the efficacy of current drugs would be 0.88 in a correctly diagnosed true VL-case (Boelaert et al. 1999b) and examined a range of efficacy values from 36%, the lowest level of antimonial efficacy retrieved in the literature (Sundar et al. 1997), to 100%, as the theoretical maximum a new drug might achieve. We corrected the effectiveness estimate for the negative impact of drug toxicity in the following way. The baseline value of drug toxicity (0.001) was forwarded by an expert panel of four infectious disease specialists, and reflects one iatrogenic death in every 1000 treatment courses dispensed in endemic areas. Subsequently we looked at variation of toxicity over the range 0.0001–0.05, the latter figure reflecting recent and very alarming reports from India on cardiotoxicity of generic stibogluconate (Thakur et al. 1998). Although correctly ruling out VL in a person without the disease may entail psychological benefit, it does not avert death, and effectiveness was rated at 0. A false positive diagnosis exposes a person to a 1-month long treatment and delays correct diagnosis and any other potentially life-saving treatment. Most importantly, it exposes a person unnecessarily to the side-effects of the drug and iatrogenic death, so we related the (negative) effectiveness directly to the toxicity of the drugs. A missed diagnosis of a real VL case was assigned an effectiveness value of 0.
Probabilities

Table 1 shows the baseline estimates used in the comparison of the alternative strategies and a range of plausible values. All computations were made for a prior probability of 40% in clinical suspects.

Cost

Current drug cost was taken at US$ 150 for a full course of antimonials, with a lower value of US$ 16, the cost of generic stibogluconate produced in India. To the price of the drug, the cost of patient care should be added. This cost is variable, from a reported US$ 4000 in Brazil (Marsden 1986), to an estimated US$ 240 in Sudan (Griekspoor et al. 1999). As new drug regimens will influence patient care cost at the same time as drug cost, we used total treatment cost, defined as drug + care cost, as our outcome of interest. We examined variations in total treatment cost (i.e. drug + patient care cost) over the range US$ 0–1000.

Results

Figure 1 shows the relation between cost and effectiveness of a ‘treat-all’, a parasitological and a serological strategy in a context where the prior probability of VL in clinical suspects reaches 40%. Treating all clinical suspects with current drugs would cost US$ 390 per suspect screened (i.e. US$ 150 for antimonials and US$ 240 for patient care), while it would only avert 88% of avoidable VL deaths, i.e. per screened clinical suspect, 0.352 deaths would be averted. This brings the cost-effectiveness ratio of this strategy to US$ 1107.95 per death averted. The effectiveness of a parasitological diagnostic strategy (0.338) is close to that of treating all clinical suspects for a substantial lower cost (US$ 187.4 per clinical suspect screened, i.e. a cost-effectiveness ratio of US$ 554.4 per death averted), whereas a parasitological strategy based on reading of lymph node or bone marrow aspirates is least effective (0.282 deaths avoided per suspect screened), but cheapest (US$ 125.8 per suspect screened, cost-effectiveness US$ 446.7 per death averted). This ranking was robust to variations in the main parameters (including variation of prior probability and in price of antimonials from US$ 150 to 16). Variation in drug efficacy does not affect this ranking, but Figure 2 shows that with newer and more effective drugs (>90% cure rates), the comparative disadvantage of a parasitological screening strategy becomes even clearer. However, the effectiveness ranking of the strategies changes definitely with increasing toxicity of the drug. We simulated a range of toxicity values between 0.0001 and 0.05, and if the proportion of deaths as a result of the antimonial cardiotoxicity exceeds 2.7%, a treat-all strategy will become less effective than a serological

Table 1 Estimates used in the comparison of the alternative strategies

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<tr>
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<th>Baseline estimate</th>
<th>Plausible Range</th>
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<tr>
<td>Prior probability in suspects</td>
<td>0.40</td>
<td>0.10–0.50</td>
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<tr>
<td>Se parasitology</td>
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<td>0.50–0.90</td>
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<tr>
<td>Se DAT</td>
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<tr>
<td>Spe DAT</td>
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<tr>
<td>DAT cost (US$)</td>
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<td>Current drug cost (US$)</td>
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<td>16–150</td>
</tr>
<tr>
<td>Current care cost (US$)</td>
<td>240</td>
<td>240–4000</td>
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<tr>
<td>New treatment cost (US$) (drug + care)</td>
<td>–</td>
<td>1–1000</td>
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n/a, Not applicable.

Figure 1 Cost-effectiveness of three competing test-treatment strategies, at a prior probability of 0.40.

Figure 2 Effectiveness of three competing strategies depending on drug efficacy.
test-treatment strategy, for the high number of iatrogenic deaths caused. The sensitivity analysis thus showed that serology remains the best diagnostic option, and that with increasing drug efficacy and safety, its comparative advantage to parasitology will only become clearer.

Subsequently we examined how cost parameters of a new drug might affect the best strategy choice. As a new drug regimen might also reduce patient care costs in case shorter oral or even single-shot regimens become available, we looked at total treatment cost. Figure 3 shows that a new treatment regimen (open triangles) will only produce a more cost-effective strategy than the current serological test-treatment strategy (full triangles) if its price falls below US$ 390, the current base line cost estimate of drugs and patient care. If the total cost of a new treatment regimen falls below US$ 140, treating all clinical suspects will become more cost-effective than testing patients serologically and treating them with current drugs. However, even at very low cost for future regimens, the serological test-treatment option combined with the new drug stays more cost-effective than ‘treat-all’ with the new drug.

**Discussion**

District doctors in endemic areas treating VL suspects on clinical evidence only, do clearly not use the most cost-effective strategy. Furthermore, this practice might cause considerable harm to patients if the potential cardiotoxicity of generic stibogluconate is considered.

Under current circumstances, whenever a splenic aspirate technique is not feasible, a serological test seems the best diagnostic option for VL suspects and this recommendation will not be altered when better drugs become available. Unless the price of a new (very safe and efficacious) drug combined with the patient care cost drops to virtual zero levels, serology remains the optimal test-treatment strategy for VL, compared with treating-all.

While the cost of the diagnostic test is trivial in the overall cost structure, the cost-effectiveness of case detection and management strategies is very sensitive to changes in the drug-related parameters. The pricing of new drugs will thus be crucial. Today, a full course of Pentostam® for an average 60 kg patient costs about US$ 150 at the manufacturer’s price. However, the actual price of antimonials sold in the endemic regions can be much higher. In Bolivia, e.g. a vial of meglumine antimoniate (Glucantime®) of a value of US$ 2 was sold at US$ 14 in local pharmacies (Le Ray, personal communication). The Sudanese Minister of Health alerted the press in January 1998 saying that antimonial treatment costed locally US$ 330 or eight times the average monthly wage of a government employee. To increase access to drugs, generic antimonials were recently introduced, given their tenfold lower cost. After an equivalence study of generic stibogluconate with branded Pentostam (Veeken et al. 2000), countries in East-Africa registered it for use. But if VL control is really to be improved, it will require more than a shift from branded to generic antimonials, given the long and cumbersome antimonial treatment regimen and the reported increasing resistance in parasites. Ease of administration and the cost of the drug will be the crucial factors in this respect. The pricing of a new drug should be competitive compared with that of generic antimonials.

In conclusion, we emphasize that for VL control there is, further to a clear need for a vaccine, a pressing need for more research into shorter and better drug courses, that can preferably be administered orally. The increasing proportion of patients refractory to stibogluconate as well as the increased toxicity of antimonials observed in India underline the urgency. If the ultimate aim of drug development is to achieve better disease control, it should take into account the epidemiological and economic context of the endemic areas, as well as the features of the local health service organization.

**References**


