Ivermectin worthy of further investigation

We read with interest the article by Ly et al. in the June issue of the *Bulletin of the World Health Organization*.[1] The authors described a randomized controlled trial of treatment of scabies in a community setting in Senegal. They concluded that oral ivermectin is inferior to topical application of benzyl benzoate; indeed the trial was stopped following intermediate analysis because of the apparent superiority of benzyl benzoate and increased rate of bacterial superinfection in the ivermectin group. The findings of this study add to those from several other studies that have investigated the utility of ivermectin for treatment of scabies. A meta-analysis published in 2000 concluded that there were insufficient data from studies comparing ivermectin to benzyl benzoate to determine if either was more effective. Since that meta-analysis, two out of three studies comparing ivermectin to benzyl benzoate have demonstrated significantly higher cure rates for ivermectin (the third study found equivalence of the treatments).[2–4]

This was an equivalence study based on the assumption that the difference in effectiveness between the treatment arms was less than 15%. Ivermectin is known to have limited ovicidal action which means that a single dose may not prevent recrudescence from eggs residing on the skin at the time of treatment (which hatch approximately every four days), compared to benzyl benzoate and permethrin, which have ovicidal activity.[5,6] We recommend two doses of ivermectin for the treatment of scabies separated by 7 to 14 days, an approach supported by other studies.[6,7]

However, from the available data, it appears that ivermectin was used suboptimally in the trial in Senegal. While the authors report in the Methods that treatment was repeated at day 7 if any patient had worsened and repeated again at day 14 if there was treatment failure, the flowchart does not clearly support this. Unfortunately, no detailed outcome data were presented regarding the outcome of the eight patients in the ivermectin arm that were observed to have clinically deteriorated at day 7 (particularly if they were among the 16 patients at day 14 that were cured). Patients in the ivermectin arm of the trial that had not clinically deteriorated at day 7 were not offered any further treatment - because we believe that single dose ivermectin is not optimal, treatment failures beyond day 7 would not be unexpected in this group.

Another important issue in this study was the high rate of non-compliance in the benzyl benzoate group, with 28% and 25% of patients failing to comply with one and two initial applications of benzyl benzoate respectively, compared to just 6% in the ivermectin group. It is our experience that benzyl benzoate can cause considerable skin irritation as was reported in 18% of this group with irritant dermatitis compared to 4% of gastrointestinal side-effects in the ivermectin group. Benzyl benzoate is often very poorly tolerated as was indicated by the high rates of non-compliance.

A further concern was that the number of family contacts included in the study that were given the same treatment as the index case was not provided, yet the number of family members not included in the study that were given benzyl benzoate was stated. This made it difficult to compare the number of family members given benzyl benzoate compared to ivermectin. If more family members with scabies were given a single dose of ivermectin that is known to be subtherapeutic for its effectiveness on scabies eggs, then this would bias the results towards benzyl benzoate as re-infection would be more likely in the ivermectin treated family contacts (unmeasured confounder).

Our last concern with the study relates to observer bias. There was no blinding of outcome assessment and no evaluation of inter-rater reliability. This may suggest a leaning towards benzyl benzoate and raises concern about bias with outcome assessment.

Taken together, the issues outlined above raise concerns about the external validity of the study by Ly et al. We believe that optimally dosed ivermectin is worthy of further investigation in resource-poor settings with endemic scabies infestation. ■

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Ivermectin efficacy still imprecise for scabies treatment

We thank Steer et al. for their comments.[1] We do not agree with the statement that ivermectin was "suboptimally given" in our study.[2] Indeed, a second dose of ivermectin was systematically given when a clinical failure was established at day 14, with the exception of the eight patients with a patent aggravation at day 7 who received a second dose earlier (at day 7). Therefore, all the failures observed with ivermectin at day 28 had received two ivermectin doses.

The 29 "bad compliants" with benzyl benzoate had either performed an excessive number of applications of benzyl benzoate (e.g. every day) or had not respected the scheduled periods of application. When considered separately, all except one were cured at day 28. Cases of irritant dermatitis seen in patients treated with benzyl benzoate were always mild.

When several family members were included simultaneously, all were given the same treatment to avoid confusion (i.e. either ivermectin or benzyl benzoate once or twice). On another hand, family members who were not included (the most likely situation) were all prescribed benzyl benzoate, once. Thus, case contacts in the three arms benefited from identical procedures, with a similar compliance profile ($P = 0.7$), making asymmetric re-infection between arms unlikely.

We agree that blinding might have improved, to a certain extent, our observations' validity. However, we found it difficult to implement in this context, as it was also the case in three of the four studies cited by Steer et al. Above all, our criteria of cure seemed objective, especially superinfection that clearly occurred more commonly in the ivermectin arm, and this favours strongly a greater efficacy of benzyl benzoate at days 14 and 28 – although it is possible that delayed cures with ivermectin might have been missed.

It is striking that, 16 years after the first promising report on ivermectin efficacy in scabies,[3] all the studies reporting high cure rates with that drug had some serious methodological biases,[2,4] making its efficacy range in common scabies – noticeably its speed of action – still imprecise. We hope we contributed to fill in that gap. All that, in addition to higher cost and questionable availability of ivermectin, certainly makes benzyl benzoate the first-line treatment of common scabies in Senegal. ■

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