Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: a randomised non-inferiority trial in Ghana and Papua New Guinea

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Summary

Background A dose of 30 mg/kg of azithromycin is recommended for treatment of yaws, a disease targeted for global eradication. Treatment with 20 mg/kg of azithromycin is recommended for the elimination of trachoma as a public health problem. In some settings, these diseases are co-endemic. We aimed to determine the efficacy of 20 mg/kg of azithromycin compared with 30 mg/kg azithromycin for the treatment of active and latent yaws.

Methods We did a non-inferiority, open-label, randomised controlled trial in children aged 6–15 years who were recruited from schools in Ghana and schools and the community in Papua New Guinea. Participants were enrolled based on the presence of a clinical lesion that was consistent with infectious primary or secondary yaws and a positive rapid diagnostic test for treponemal and non-treponemal antibodies. Participants were randomly assigned (1:1) to receive either standard-dose (30 mg/kg) or low-dose (20 mg/kg) azithromycin by a computer-generated random number sequence. Health-care workers assessing clinical outcomes in the field were not blinded to the patient's treatment, but investigators involved in statistical or laboratory analyses and the participants were blinded to treatment group. We followed up participants at 4 weeks and 6 months. The primary outcome was cure at 6 months, defined as lesion healing at 4 weeks in patients with active yaws and at least a four-fold decrease in rapid plasma reagin titre from baseline to 6 months in patients with active and latent yaws. Active yaws was defined as a skin lesion that was positive for *Treponema pallidum* ssp *pertenue* in PCR testing. We used a non-inferiority margin of 10%. This trial was registered with ClinicalTrials.gov, number NCT02344628.

Findings Between June 12, 2015, and July 2, 2016, 583 (65·1%) of 895 children screened were enrolled; 292 patients were assigned a low dose of azithromycin and 291 patients were assigned a standard dose of azithromycin. 191 participants had active yaws and 392 had presumed latent yaws. Complete follow-up to 6 months was available for 157 (82·2%) of 191 patients with active yaws. In cases of active yaws, cure was achieved in 61 (80·3%) of 76 patients in the low-dose group and in 68 (84·0%) of 81 patients in the standard-dose group (difference 3·7%; 95% CI −8·4 to 15·7%; this result did not meet the non-inferiority criterion). There were no serious adverse events reported in response to treatment in either group. The most commonly reported adverse event at 4 weeks was gastrointestinal upset, with eight (2·7%) participants in each group reporting this symptom.

Interpretation In this study, low-dose azithromycin did not meet the prespecified non-inferiority margin compared with standard-dose azithromycin in achieving clinical and serological cure in PCR-confirmed active yaws. Only a single participant (with presumed latent yaws) had definitive serological failure. This work suggests that 20 mg/kg of azithromycin is probably effective against yaws, but further data are needed.

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