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Multiple-dose versus single-dose ivermectin for *Strongyloides stercoralis* infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial

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Summary

Background ***Strongyloides stercoralis*** **infection is a neglected condition that places people who are immunocompromised at risk of hyperinfection and death. Ivermectin is the drug of choice for the treatment of *S stercoralis* infection, but there is no definitive evidence on the optimal dose. This trial aimed to assess whether multiple doses of ivermectin were superior to a single dose for the treatment of non-disseminated strongyloidiasis.**

Methods **Our study was designed as a multicentre, open-label, phase 3, randomised controlled superiority trial. Participants were enrolled in four centres in Italy, three in Spain, and two in the UK, and recruiting sites were predominantly hospitals. Eligible patients were older than 5 years, weighed more than 15 kg, were residents in an area not endemic for *S stercoralis*, and either were positive for *S stercoralis* in faecal tests and on serology (any titre) or had a positive serological test with high titres, irrespective of the result of faecal tests. Patients were randomly assigned (1:1) using a computer-generated, blinded allocation sequence (with randomly mixed block sizes of six, eight, and ten participants) to receive either one dose of ivermectin 200 µg/kg or four doses of ivermectin 200 µg/kg (given on days 1, 2, 15, and 16). The primary endpoint was the proportion of participants with clearance of *S stercoralis* infection at 12 months, which was assessed in all randomly assigned participants who were not lost to follow-up (modified full-analysis set) and in participants in the modified full-analysis set who did not deviate from the assigned treatment regimen (per-protocol set). All participants were included in the safety analysis. The trial was registered with ClinicalTrials.gov, NCT01570504, and is now closed for recruitment.**

Findings **Of the 351 patients assessed for eligibility, 309 recruited between March 26, 2013, and May 3, 2017, were randomly assigned to one dose (n=155) or four doses (n=154) of ivermectin. At 12 months in the modified full-analysis set, 86% (95% CI 79 to 91; 102 of 118 participants) had responded to treatment in the single-dose group compared with 85% (77 to 90; 96 of 113 participants) in the four-dose group (risk difference 1·48%, 95% CI –7·55 to 10·52; p=0·75); similar results were observed in the per-protocol set. Adverse events were generally of mild intensity and more frequent in the multiple-dose than in the single-dose group. The trial was terminated early due to futility.**

Interpretation **Multiple doses of ivermectin did not show higher efficacy and was tolerated less than a single dose. A single dose should therefore be preferred for the treatment of non-disseminated strongyloidiasis.**

Funding **There was no funding source for this study.**

Introduction

Strongyloides stercoralis is a soil-transmitted helminth with a wide geographical distribution, primarily in tropical and subtropical regions.[1] Previous estimates of prevalence (30–100 million cases) have been questioned, and the real prevalence is probably much higher.[2,3] Unlike other soil-transmitted helminths, *S stercoralis* larvae, generated inside the bowel by parthenogenetic female worms, can reinfect the host (the autoinfection cycle), leading to chronic infection. Acute infection is rarely reported in people who travel to endemic regions, and the index of suspicion for acute infection is usually low because clinical manifestations (mostly fever, cough, and urticaria) are also commonly observed in other infections.[4] Therefore, misdiagnosis is possible. Most individuals who are chronically infected are asymptomatic or have non-specific symptoms affecting mostly the gastrointestinal tract, lungs, and skin.[1] However, strongyloidiasis can transform into a disseminated, life-threatening disease in cases of immunosuppression due to underlying conditions or medical treatment.[1,5]

There is no internationally agreed gold standard for laboratory diagnosis. Stool microscopy has low sensitivity because of the irregular and often low larval output

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Research in context

Evidence before this study

A Cochrane meta-analysis published in 2016 reviewed seven randomised controlled trials (RCTs) comparing ivermectin with either albendazole (in four trials) or thiabendazole (in three trials) for the treatment of strongyloidiasis and concluded that ivermectin should be the drug of choice for the treatment of chronic strongyloidiasis. However, the meta-analysis showed that there was no conclusive evidence on the different dose schedules of ivermectin. In particular, two trials compared one-dose versus two-dose regimens and found no difference. All but one of the trials included in the meta-analysis relied on faecal-based diagnosis only, which is known for poor sensitivity and therefore likely to misclassify the cases included. To identify studies published since the meta-analysis, we searched PubMed and Embase with no language restrictions for RCTs investigating the efficacy of treatment for strongyloidiasis published between Jan 1, 2015, and May 5, 2019 (search strategy reported in the appendix, pp 1–2). We used the search terms "strongyloidiasis" OR "strongyloides" OR "*Strongyloides stercoralis*" AND "ivermectin" OR "stromectol" OR "mectizan" AND "randomized controlled trial" OR "clinical trial". We found one randomised, controlled, non-inferiority trial published in 2017, in which 127 participants were randomly assigned either to ivermectin or moxidectin (a drug not yet registered for the indication of strongyloidiasis). Although the proportions of individuals cured were similar between the two groups (93·7% for moxidectin *vs* 95·2% for ivermectin), non-inferiority could not be shown.

Added value of this study

Before this study, it was unclear if a treatment regimen for strongyloidiasis with repeated doses of ivermectin was superior to a single dose. This RCT was done in a setting (Europe) that ruled out reinfection between treatment and assessment of efficacy. In addition, this RCT is only the second to include serological analyses for monitoring response to treatment, which allows a more accurate estimation of treatment efficacy than faecal tests, which have a low sensitivity for *S stercoralis*.

Implications of all the available evidence

A single dose of ivermectin should be the recommended regimen for the treatment of non-disseminated *S stercoralis* infection. A single dose would be a more feasible regimen, particularly in highly endemic areas, where single drug administration (ivermectin and other drugs) is also used in control programmes for other neglected tropical diseases. More evidence is needed to define the role of moxidectin as an alternative to ivermectin.

in chronic, non-disseminated infection.[6] The Baermann technique and Koga agar plate culture are more sensitive but still miss some infections.[6] Therefore, these methods are arguably not entirely reliable for monitoring treatment efficacy.[7] Nucleic acid amplification tests showed similar sensitivity to the Baermann technique and agar plate culture.[8] Conversely, serology showed high sensitivity.[9] Although cross-reactivity with other helminth infections is possible, serological specificity is close to 100% when antibody concentrations are above defined cutoff values.[10] Serology is also suitable for post-treatment monitoring, and criteria to define response to treatment with this method have been assessed by diagnostic studies.[11–13]

A Cochrane meta-analysis supported ivermectin as the drug of choice for the treatment of strongyloidiasis. Ivermectin has a better safety profile than thiabendazole, which shows similar efficacy to ivermectin and superior efficacy to albendazole. Albendazole has a similar safety profile to ivermectin.[14] Regimens using multiple doses of ivermectin have been tested.[15–18] In particular, a second dose given 2 weeks after the first has been proposed on the basis of the duration of the autoinfection cycle.[17,18] Alternatively, 200 µg/kg ivermectin given on two consecutive days is recommended by some experts,[1,19] although evidence seemed to contradict this suggestion.[18] Overall, there is no conclusive evidence to support any of the multiple-dose regimens.[14] There is even more uncertainty regarding the management of disseminated disease, which is often fatal despite treatment with ivermectin.[20,21] In view of the results of former trials on one versus two doses, and those of a previous trial that showed higher efficacy of multiple doses (on days 1, 2, 15, and 16) compared with a single dose in a small cohort of patients with HIV infection,[22] we chose to test a single-dose versus a four-dose regimen, to provide conclusive evidence as to whether dosage is an issue in the treatment of non-disseminated strongyloidiasis.

This trial aimed to assess whether multiple doses of ivermectin were superior to a single dose for the treatment of non-disseminated strongyloidiasis.

Methods

Study design and participants

This was a multicentre, open-label, phase 3, randomised controlled superiority trial. Recruiting sites comprised four centres in Italy, three in Spain, and two in the UK. The recruiting sites were predominantly hospitals located in Italy (IRCCS Sacro Cuore Don Calabria Hospital, Negrar; ASST Spedali Civili General Hospital, Brescia; Azienda Ospedaliero Universitaria Careggi, Florence; and Anna Meyer Children's University Hospital, Florence), Spain (Hospital de Poniente, Almería; Barcelona Institute for Global Health, ISGlobal-CRESIB, Barcelona; and Unitat de Medicina Tropical Vall d'Hebron-Drassanes, Barcelona), and the UK (University College London Hospitals NHS, London; and Cambridge University Hospital NHS, Cambridge). We also planned to include a site in Latin America (Lima, Peru), but the

site was never opened. The protocol was approved by the local ethics committees for all study sites.

All study sites are referral centres for tropical or parasitic diseases, with well equipped referral laboratories and high expertise in the laboratory methods for parasite diagnosis. Participants presented to the outpatient services either spontaneously or were referred from other health centres, usually for eosinophilia or symptoms that required investigation for potential parasitic disease. All individuals diagnosed with *S stercoralis* infection at the referral site (with any test in use at these sites; case definition for inclusion in the trial is reported in the inclusion criteria) were assessed for eligibility. All participants provided written informed consent before trial entry.

The inclusion criteria were as follows: male and female individuals older than 5 years and weighing more than 15 kg; residence in an area not endemic for *S stercoralis*; and either positive faecal tests for *S stercoralis* and positive serology (at any titre) or a positive serological test at high titre, irrespective of the results of faecal tests. Exclusion criteria were as follows: pregnancy or lactation; disease of the central nervous system; disseminated strongyloidiasis; known immunosuppression; treatment with ivermectin in the previous year; and absence of consent. We included only people living in non-endemic areas because people living in areas endemic for *S stercoralis* might have reinfection, which could affect the response to treatment. We excluded individuals with immunosuppression because they are at higher risk than people who are immunocompetent of developing disseminated infection, which could affect the response to treatment or require a different treatment approach altogether.

For screening and evaluation of eligibility, any diagnostic test for *S stercoralis* infection in use at each site (serology, parasitological examination, agar plate culture or charcoal stool culture, or PCR) was considered valid. None of the sites used the Baermann method. If screening was done by serology at baseline, the same serological assay used for diagnosis had to be repeated at the 6 month and 12 month follow-up visits; participants with positive faecal tests at baseline had to be tested with either PCR or charcoal or agar stool culture at follow-up visits.

The serological assays used were an in-house immunofluorescence test (IFAT)[23] and two commercially available ELISAs (*Strongyloides ratti* ELISA from Bordier Affinity Products, Crissier, Switzerland, and IVD *Strongyloides* serum antibody detection microwell ELISA from IVD Research, Carlsbad, CA, USA). For routine use, positive results for IFAT are indicated by a titre of at least 1:20, which is the lower limit of detection. The manufacturers of the two commercial tests report the following indications for interpretation of the results: for the ELISA from IVD Research, positive samples are defined by absorbance greater than 0·2 optical density units, whereas for the ELISA from Bordier Affinity Products, results are deemed positive when the absorbance of the analysed sample is higher than the absorbance of the weak positive control (provided in the kit). For study purposes, the results of the ELISA tests were reported as normalised optical density (signal-to-cutoff ratio). The cutoff values to define high titre were assessed as at least 160 titres for IFAT, at least 2 normalised optical density for the IVD Research ELISA, and at least 2·5 for the Bordier Affinity Products ELISA.[10] Each study site used (both for inclusion and follow-up) the serological assay available for routine practice. PCR (according to the method developed by Verweij and colleagues[24]) was introduced in 2016 with an amendment to the study protocol, and was used (as an alternative to agar plate culture)[25] for inclusion and follow-up of the participants and was used almost exclusively (except in a few cases) at the IRCCS Sacro Cuore Don Calabria Hospital.

Randomisation and masking

Participants were randomly assigned (1:1) to receive ivermectin (stromectol 3 mg tablets, Merck Sharp & Dohme, Readington, NJ, USA) 200 µg/kg (maximum dose 21 mg) either as a single dose on day 1 or as a multiple dose on days 1, 2, 15, and 16. Randomisation was done centrally with a computer-generated, blinded allocation sequence. Randomisation with permuted blocks (randomly mixed block sizes of six, eight, and ten participants) was stratified by participating study site, and the assignment for each patient was displayed in the electronic case report form. Participants and clinicians were not masked to the intervention, whereas laboratory staff and the study statistician were. Laboratory staff had no information about the treatment allocation of the patients and the statistician did not know what the treatment given to group A and group B was. The trial conduct was overseen by the study steering committee.

Procedures

Participants took ivermectin orally on an empty stomach with water and fasted for 2 h after drug intake. Drug administration on day 1 was done under direct observation. Participants in the multiple-dose group received the remaining tablets for (home) self-administration. All participants received a telephone call on days 2 and 16 to collect information about possible adverse events and to remind participants in the multiple-dose group to take the further doses of ivermectin. On day 17, participants' full blood counts and alanine aminotransferase concentrations were measured, and each participant was invited to report any symptoms that had occurred since the last time they were asked (either through telephone calls or on day 17 when the patient came to the centre for blood tests, in case the participant could not be contacted by phone). Furthermore, adverse events reported during any unscheduled visit were registered in the electronic case report form. Clinical and complete laboratory assessments, including full blood count, strongyloides serology, strongyloides stool culture, or PCR, were repeated at 6 months and 12 months after treatment. Volume of blood

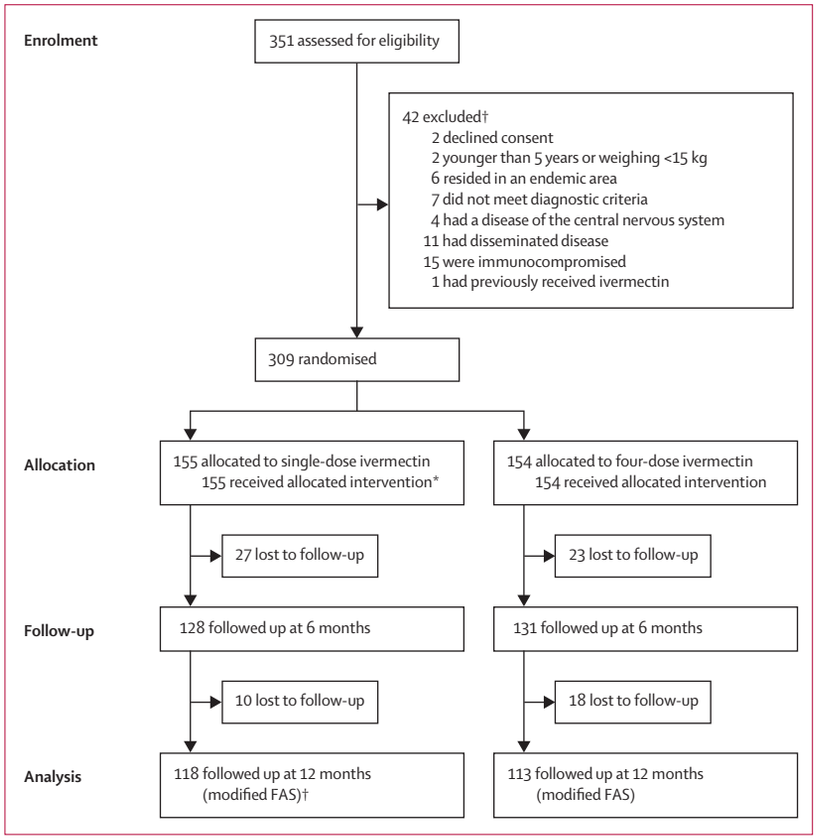

Figure 1: **Trial profile**
FAS=full analysis set. *One patient took a further four doses before the 6-month follow-up visit and was excluded from the per-protocol analysis. †Some participants had more than one reason for exclusion.

withdrawn was 8 mL on day 17, and 13 mL was taken on both follow-up visits.

Outcomes

The primary outcome was the proportion of participants with clearance of *S stercoralis* infection at 12 months, defined by negative agar plate culture or PCR and negative serology or positive serology with a decrease in titre (defined as a decrease of two titres in IFAT, a two-fold reduction of normalised optical density in the case of ELISA).[11]

Secondary outcomes included partial response to treatment at 12 months (defined as negative stool tests and positive serology with a decrease in titre, but remaining higher than the cutoff that defines clearance), all-cause mortality during the 12 months of follow-up, adverse events, the proportion of participants with symptoms cleared or improved at 12 months, increase in alanine aminotransferase to above normal at day 17, mean difference of eosinophil count at 12 months compared with baseline, and decrease in white blood cell count less than the cutoff value at day 17.

We graded adverse events as follows: 0, none; 1, mild (any symptom possibly related to ivermectin, not necessitating medication); 2, moderate (any symptom resolved with medication, not requiring hospital admission); 3, severe (any symptom requiring hospital admission); 4, near fatal (any symptom requiring intensive care); and 5, fatal. Relative tolerability of the two regimens was assessed on the basis of a possible association of the adverse event with ivermectin. This assessment was based on the evaluation by the investigator and on adverse events reported to be related to ivermectin in the literature (according to which we expected high tolerability, with mostly mild symptoms).

Statistical analysis

The sample size was calculated on the basis of an expected 15% increase in efficacy with the multiple-dose compared with the single-dose regimen, which was assumed to have a 70% efficacy on the basis of a previous trial.[26] The study was set with 90% statistical power, a 5% α value, and a two-sided test. To meet these requirements, a sample size of 161 participants in each study group was needed. Allowing for a possible loss to follow-up of 15% of participants and the possible inclusion of an additional 4% false-positive cases (despite the high specificity of high titres of serology,[10] it is possible that some cases were misclassified as positive), the target sample size was 400 participants, with 200 participants per study group.

Statistical analysis was done in the modified full-analysis set (FAS; ie, modified intention to treat), which excluded participants who were lost to follow-up; the primary endpoint analysis was also done in the per-protocol set (PPS). In the modified FAS, participants were classified according to the treatment group assigned by randomisation. The PPS excluded from the modified FAS participants who deviated from the assigned treatment regimen. The treatment response at 6 months and the sustained response from 6 months to 12 months were compared to check for possible biases in the results obtained from the FAS due to losses to follow-up.

Demographic and clinical data were summarised using descriptive statistics. The significance level of statistical tests was fixed at 5%. The unpaired medians of two samples were compared using Mann-Whitney U or Kolmogorov-Smirnov tests, as appropriate, and the Dwass-Steel-Critchlow-Fligner method[27–29] for multiple comparisons. Paired medians were compared using the Wilcoxon signed-rank test, and p values were adjusted for multiple comparisons. The proportion of responders and 95% CIs were summarised in a 2×2 contingency table. χ^2 test or Fisher's test, if appropriate, was used to compare treatment differences. Treatment differences within enrolling countries were also assessed and pooled differences calculated to estimate the contribution of each country to the overall estimation of treatment response.

All clinical and demographical variables were included in the full multivariate logistic regression analysis to

	Single dose (n=155)	Multiple doses (n=154)
Age, years	42 (34–60)	44 (36–65)
Sex		
Female	63 (41%)	59 (38%)
Male	92 (59%)	95 (62%)
Weight, kg	71 (62–80)	71 (64–80)
Eosinophils, per µL	800 (500–1250)	770 (450–1200)
White blood cells, per µL	7160 (5900–8620)	6930 (5950–8370)
ELISA, normalised OD	4·5 (3·0–7·6)	4·1 (3·0–6·6)
IFAT ≥160 titres	46/54 (85%)	51/58 (88%)
Country of enrolment		
Italy	66 (43%)	64 (42%)
Spain	72 (46%)	73 (47%)
UK	17 (11%)	17 (11%)
Continent where infection was presumed to be acquired*		
Europe	28 (19%)	36 (25%)
Asia	13 (9%)	5 (3%)
Latin America	59 (40%)	52 (36%)
Africa	47 (32%)	51 (35%)
Pruritus	56 (18%)	49 (16%)
Skin rash	31 (10%)	23 (7%)
Abdominal pain	41 (13%)	39 (13%)
Respiratory symptoms	18 (6%)	21 (7%)

Data are median (IQR) or number (%). OD=optical density.
IFAT=immunofluorescence test. *18 participants had missing data.

Table 1: **Baseline symptoms and characteristics**

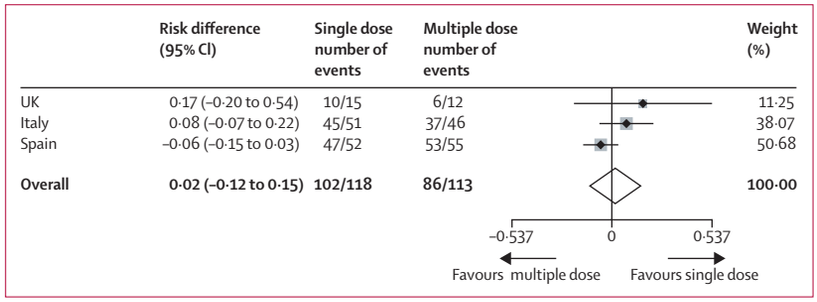

Figure 2: **Risk difference between regimens in primary outcome, overall and by country of enrolment**

model the probability of a participant responding to the treatment. Candidate models were compared, and the final model was selected on the basis of Akaike's information criterion,[30] the clinical and statistical relevance of the candidate variables, and classification tables. Parameters were estimated using Firth's penalisation.[31,32]

The study protocol included indications for an interim analysis in case of slow participant accrual. The analysis was done using the sequential design approach with the O'Brien-Fleming spending functions[33] to establish whether, on the basis of trial interim results, the null or alternative hypotheses fell within the rejection or acceptance regions. Data analysis was done with STATA, version SE14. This trial is registered with ClinicalTrials.gov (NCT01570504).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first participant was randomly assigned to treatment in March 26, 2013, and the last one in May 3, 2017. The study was completed May 18, 2018. Of the 351 patients assessed for eligibility, 309 were randomly assigned to treatment (155 to one dose and 154 to multiple doses; figure 1). The number of missing participants was similar between the two groups at each timepoint.

Recruitment was stopped by the study steering committee before reaching the planned sample size on the basis of an interim analysis at 12 months, which showed that the probability of finding a significant difference favouring the four-dose regimen, in case the study reached the planned 400 participants, was lower than 1%. The complete interim analysis, including the probability analysis, is reported in the appendix (pp 3–4).

See Online for appendix

The baseline characteristics of the participants in the two groups did not differ significantly in terms of demographics, clinical presentation, and laboratory values (table 1). Countries of presumed acquisition of *S stercoralis* infection are shown in table 1 and the appendix (p 5).

146 participants were enrolled on the basis of positive faecal tests, including microscopy (67 participants), stool culture (111 participants), PCR (17 participants), or a combination of faecal tests (96 participants). The remaining 162 participants were enrolled on the basis of positive serology.

259 participants were followed up at 6 months, and 231 attended the 12 month follow-up visit (modified FAS). All participants received their assigned treatment, but one individual in the single-dose group took a further four doses before the 6 month follow-up visit and was excluded from the PPS analysis.

In the modified FAS, the proportion of participants with clearance of *S stercoralis* infection at 12 months was 86% (95% CI 79 to 91; 102 of 118 participants) for the single-dose group and 85% (77 to 90; 96 of 113 participants) for the multiple-dose group, with no significant difference between the groups (proportions absolute difference 1·48%, 95% CI –7·55 to 10·52; p=0·75). In the PPS, the proportion of participants with clearance of *S stercoralis* infection at 12 months was 87% (95% CI 80 to 92; 102 of 117 participants) for the single-dose group and 85% (77 to 90; 96 of 113 participants) for the multiple-dose group (risk difference 2·22%, 95% CI –6·73 to 11·12; p=0·62).

Similarly, an exploratory analysis of clearance of infection at 6 months showed that treatment was effective in 107 (84%, 95% CI 76 to 89) of 128 participants in the single-dose group and in 108 (82%, 75 to 88) of 131 participants in

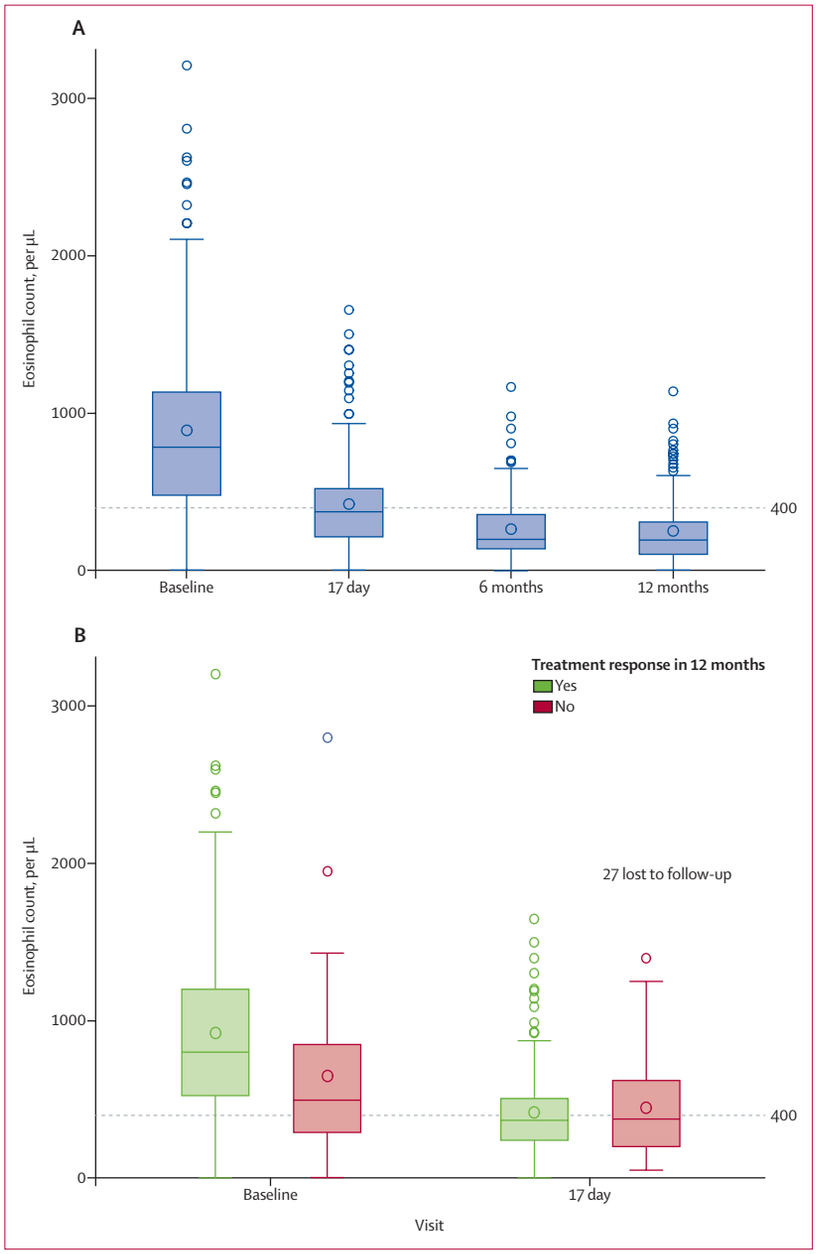

Figure 3: **Eosinophil counts at different timepoints in all recruited participants (A) and from baseline to the 17 day visit by participant cure status at 12 months (B)**
Data are median (IQR). Dotted lines indicate the upper limit for normal eosinophil count. Circles indicate outliers.

the multiple-dose group (proportions absolute difference 1·12%, 95% CI –7·99 to 10·29; p=0·81). In another exploratory analysis, sustained response from 6 months (data available for 215 participants who had infection clearance at 6 months) to 12 months was observed in 169 (96%) of 176 participants overall (88 [96%] of 92 in the single-dose group and 81 [96%] of 84 in the multiple-dose group), and the relative risk associated with non-sustained treatment response calculated as 0·065 (95% CI 0·03–0·14).

We investigated with the meta-analysis the contribution of each country to the treatment proportions difference in the primary outcome (figure 2). From the heterogeneity statistics (χ^2), the difference between and within countries in the primary outcome can be attributed to random variation.

Partial response to treatment (among people who did not respond to treatment according to the primary outcome) at 12 months occurred in 11 (69%, 95% CI 44 to 86) of 16 participants in the single-dose group and in 13 (76%, 53 to 90) of 17 participants in the multiple-dose group B, with a difference in proportions of 7·72% (–22·65 to 38·09).

At 12 months, clearance or improvement of the symptoms reported at baseline was observed in 54 (83%) of 65 participants in the single-dose group and in 55 (82%) of 67 participants in the multiple-dose group. In both study groups, the proportion of participants reporting clearance or improvement of symptoms was higher in the subgroup of participants who had clearance of *S stercoralis* infection at 12 months than in those who did not. In the single-dose group, 46 (85%) of 54 individuals who had symptoms ceased or improved, seven (64%) of 11 with persistent symptons, 100% with new symptoms, and 46 (92%) of 50 that never had symptoms were responders. In the multiple-doses group 45 (82%) of 55 who had symptoms ceased or improved, nine (75%) of 12 with persistent symptoms, 100% with new symptoms and 40 (91%) of 44 that never had symptoms were responders.

The primary analysis was also done by stratifying the study population (modified FAS) into two main subgroups, according to the diagnostic criterion of enrolment (exploratory analysis): participants with positive faecal tests and serology (any titre) and participants with negative faecal tests but high titres on serology. Clearance of *S stercoralis* infection was noted in 34 (94%, 95% CI 82–98) of 36 participants in the single-dose group and 43 (88%, 76–94) of 49 participants in the multiple-dose who had positive faecal tests at baseline, and in 57 (79%, 68–87) of 72 participants in the single-dose group and 45 (80%, 68–89) of 56 participants in the multiple-dose group who had negative faecal tests at baseline. In the subgroup with positive faecal results at baseline, when efficacy was assessed only on the basis of the results of faecal tests, all 36 participants (100%, 90–100) in the single-dose group and 48 (98%, 89–100) of 49 participants in the multiple-dose group had clearance of *S stercoralis* infection at 12 months. Briefly, in all subanalyses, there was no clinical difference between the two regimens.

289 participants (144 in the single-dose group and 145 in the multple-doses group) attended the 17 day visit, and all had white blood-cell counts within the normal range. Only 11 participants in the two groups combined had alanine transaminase values higher than 55 U/L (median 71 U/L, IQR 57–81), but none of these cases were considered clinically relevant. The median

	Variable profile	Univariate model		Multivariate model	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age, years	One unit change	0·98 (0·96–0·99)	0·015	0·97 (0·95–0·99)	0·010
ELISA baseline (54 missing data)	One unit change	1·38 (1·09–1·75)	0·0069	..	..
Sex					
Male	143 (84%)	1 (ref)	..	..	..
Female	88 (89%)	1·46 (0·67–3·20)	0·35	..	..
Has visited endemic country					
Yes	90 (81%)	1 (ref)	..	..	..
No	141 (89%)	1·81 (0·87–3·78)	0·11	..	..
Presence of skin rash					
Yes	42 (76%)	1 (ref)	..	1 (ref)	..
No	189 (88%)	2·29 (1·00–5·23)	0·049	2·97 (1·20–7·33)	0·018
Presence of abdominal pain					
Yes	62 (90%)	1 (ref)	..	..	..
No	169 (84%)	0·60 (0·24–1·49)	0·27	..	..
Presence of pruritus					
Yes	82 (79%)	1 (ref)	..	..	..
No	149 (89%)	2·16 (1·03–4·52)	0·041	..	..
Presence of respiratory symptoms					
Yes	28 (75%)	1 (ref)	..	..	..
No	203 (87%)	2·34 (0·91–5·98)	0·077	..	..
Eosinophil count at baseline					
≤400 cells per µL	50 (74%)	1 (ref)	..	1 (ref)	..
>400 cells per µL	181 (89%)	2·84 (1·30–6·18)	0·0087	4·12 (1·74–9·74)	0·0013
IFAT at baseline (15 missing data)					
≤1:160 titres	70 (84%)	1 (ref)	..	..	..
>1:160 titres	10 (90%)	1·22 (0·18–8·31)	0·84	..	..
Likely region of *S stercoralis* infection* (eight missing data)					
Europe	51 (86%)	1 (ref)	..	..	..
Asia	15 (60%)	0·25 (0·07–0·88)	0·034	..	..
America	80 (89%)	1·27 (0·44–3·55)	0·65	..	..
Africa	77 (91%)	1·58 (0·53–4·75)	0·41	..	..

All variables were taken forward into the multivariate model but only significant variables are reported. IFAT=immunofluorescence test. *Data missing for four people from central America and the Caribbean and from four people from South Africa.

Table 2: **Clinical and demographic characteristics associated with the *Strongyloides stercoralis* infection clearance at 12 months (n=231)**

eosinophil count for all patients in the modified FAS significantly decreased (Wilcoxon signed-rank test adjusted p<0·0004) from baseline (789 cells per µL, IQR 485–1204) to the 17 day visit (371 cells per µL, 220–540; figure 3A) and from baseline to 12 months (196 cells per µL, 100–310; Wilcoxon signed-rank test adjusted p=0·0004). Median eosinophil values were also significantly different (Wilcoxon signed-rank test adjusted p≤0·0004) from the 17 day visit to 6 months follow-up (200 cells per µL, 140–358), but not from 6 months to 12 months follow-up (196 cells per µL, 100–310; Wilcoxon signed-rank test adjusted p=0·13). Moreover, median eosinophil counts were significantly different between those who did and did not have *S stercoralis* infection clearance at 12 months at baseline (Kolmogorov-Smirnov p≤0·0003) but not at the 17 day visit (Kolmogorov-Smirnov p=0·36; figure 3B); the decrease in the median eosinophil count was accentuated in participants who achieved cure at 12 months.

A multivariate logistic regression model was fitted to explore underlying differences in baseline characteristics between people with and without clearance of *S stercoralis* at 12 months (table 2). Clearance at 12 months was associated with younger age, eosinophil counts higher than 400 cells per µL at baseline, and absence of skin rash.

Adverse events were generally of mild intensity and more frequent in the multiple-dose than in the single-dose group (table 3). One participant enrolled in the multiple-dose group died 34 days after the last dose of ivermectin for reasons unrelated to treatment with study drug. The participant, aged 86 years, had underlying chronic conditions that were closely associated with the cause of death.

	Single-dose ivermectin		Multiple-dose ivermectin		Adverse event ratio*
	Number of participants	Day of adverse event†	Number of participants	Day of adverse event†	
Abdominal pain	2	10 (6–13)	2	16 (16–16)	1
Pruritus	2	16 (16–16)	1	16 (16–16)	0·5
Vomiting	1	16 (16–16)	1	14 (8–15)	1
Drowsiness	9	2 (1–2)	16	12 (1–15)	1·8
Fatigue	6	3 (1–16)	6	15 (9–27)	1
Headache	12	1 (1–4)	14	7 (1–15)	1·2
Hypotension	2	3 (2–4)	2	3 (2–9)	1
Nausea	7	2 (1–9)	12	15 (5–15)	1·7
Total	41	..	54	..	1·3

Data are n or n (IQR). All adverse events were reported by the patient via a telephone conversation and during a routine visit except for abdominal pain and pruritus, which were reported during a routine visit only, and vomiting, which was reported via telephone conversation only. All adverse events were graded as mild, except for two participants in the single-dose group and two in the multiple-dose group who had moderate fatigue, and two participants in the single-dose group and one in the multiple-dose group who had moderate headache. *Ratio of adverse events in the multiple-dose group to adverse events in the single-dose group. †Day on which the participant reported to have experienced the symptoms, which did not necessarily occur on the same day as the report.

Table 3: **Complete description of adverse events**

Discussion

This randomised controlled trial showed that a four-dose ivermectin regimen offers no advantage in terms of efficacy over single-dose treatment and is less well tolerated. These findings are consistent with the results of two previous smaller trials that compared one dose with two doses of ivermectin, given either on 2 consecutive days[16] or 2 weeks apart.[18] In both studies, efficacy was assessed with faecal tests and was close to 100% for both regimens, similar to the efficacy observed in our study when the same criterion of infection clearance was applied.

Diagnosing strongyloidiasis and measuring treatment efficacy is challenging. Negative faecal tests cannot reliably rule out *S stercoralis* infection, so the efficacy of an intervention tends to be overestimated when assessed by these methods only.[7] To our knowledge, only one previous trial of treatment for strongyloidiasis used serology to assess the efficacy of the intervention.[26] Compared with that trial, in this study the possible inclusion of false-positive cases was limited by the introduction of serological cutoff values for inclusion of participants who had negative stool samples. Nevertheless, it is still possible that some participants were erroneously classified as infected, and this might have partly contributed to underestimation of treatment efficacy.

Although concentrations of antibodies targeting *S stercoralis* tend to decrease over time in patients who are cured,[11] we found that the proportions of patients with clearance of infection were similar at 6 and 12 months, hence 6 months of follow-up might be sufficient to judge response to treatment. The eosinophil count rapidly decreased from baseline, and the decline was substantially accentuated in participants who had clearance of infection at 12 months. However, a decrease in eosinophil counts, albeit smaller, was also observed in participants who did not have infection clearance at 12 months, which might suggest a partial response to treatment in these patients. Thus, it is not possible to predict treatment efficacy on the basis of a reduction in eosinophil count shortly after treatment.

In this study, a single dose was better tolerated than multiple doses, another factor to favour the single dose. Overall, including the four-dose group, adverse events were few and of mild intensity, confirming the excellent tolerability profile of ivermectin. A raised eosinophil count and younger age were associated with a better outcome; both parameters might indicate that a robust immune system is required for a good response to treatment.

The strengths of our study include the use of sensitive diagnostic methods to assess cure and the long follow-up period compared with previous trials.[14] Furthermore, the study was done in non-endemic countries, excluding the possibility of reinfection as a confounder. Despite this, the results are also relevant for endemic countries: the ability to use a single dose of a well tolerated, safe drug argues for provision of easier access to treatment where the infection is prevalent. Single-dose treatment is more convenient for patients, with an option for directly observed administration. Moreover, community treatment of other soil-transmitted helminths (namely, hookworm, *Ascaris lumbricoides*, and *Trichuris trichiura*) is based on a single dose of albendazole.[34] Co-administration with ivermectin would enhance the effectiveness of community control programmes by targeting *S stercoralis* as well.

The main limitation of our study is that the sample size was smaller than originally planned. Although this small sample size did not affect the results of the primary outcome (as the probability analysis showed; appendix pp 3–4), it possibly limited the interpretation of some subanalyses. Another limitation is that we cannot assure adherence to the dose schedule for participants in the four-dose group, although telephone contact might have increased compliance. It must also be stressed that in real clinical practice, no directly observed treatment would be feasible. Finally, we could not assess the human T-lymphotropic virus (HTLV-1) status of the participants (this infection has been associated with a reduced response to treatment),[1] but we believe that the randomisation method allowed us to balance the possible presence of individuals with HTLV-1 between the study groups. Moreover, although the overall efficacy of the intervention might have been partly reduced in case of inclusion of participants with HTLV-1 infection, the influence on the primary outcome is presumably irrelevant, because the prevalence of HTLV-1 infection is low.[35] The results of this study are not generalisable to patients who are immunocompromised who are exposed to the severe complications of strongyloidiasis.

In conclusion, single-dose ivermectin should be the preferred regimen for the treatment of chronic, non-severe strongyloidiasis in patients who are immunocompetent.

Contributors

DB contributed to the study design, supervised the study sites, contributed to data collection, data analysis, and data interpretation, and wrote the first draft of the manuscript. JS-C, JM, BTM, PR, FC, LZ, LB, FG, TC-F, AR-M, and GG contributed to data collection, data interpretation, and revised the manuscript critically. PLC contributed to the study design, data collection, and data interpretation and revised the manuscript critically. RS did the statistical analysis and revised the manuscript critically. MR contributed to data management, data analysis, and data interpretation and revised the manuscript critically. ZB conceived and supervised the study, contributed to the study design, data analysis, and data interpretation and wrote the first draft of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified participant data, the key for reading the variables in the database, and informed consent forms (English, Italian, and Spanish) will be made available upon publication in Mendeley Data in September, 2019.

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