ORIGINAL ARTICLE

Oral Ivermectin versus Malathion Lotion for Difficult-to-Treat Head Lice

Olivier Chosidow, M.D., Ph.D., Bruno Giraudeau, Ph.D., Jeremy Cottrell, M.S., Arezki Izri, M.D., Robert Hofmann, M.D., Ph.D., Stephen G. Mann, M.D., and Ian Burgess, Ph.D.

ABSTRACT

BACKGROUND

Head-lice infestation is prevalent worldwide, especially in children 3 to 11 years old. Topical insecticides (i.e., pyrethroids and malathion) used as a lotion, applied twice at an interval of 7 to 11 days, are typically used for treatment. Resistance of lice to insecticides, particularly pyrethroids, results in treatment failure. The efficacy of alternative agents is controversial.

METHODS

We conducted a multicenter, cluster-randomized, double-blind, double-dummy, controlled trial comparing oral ivermectin (at a dose of 400 μg per kilogram of body weight) with 0.5% malathion lotion, each given on days 1 and 8, for patients with live lice not eradicated by topical insecticide used 2 to 6 weeks before enrollment. The cluster was defined as the household. Infestation was confirmed and monitored by means of fine-toothed combing. Patients were at least 2 years of age and weighed at least 15 kg; all were treated at the study sites. The primary end point was the absence of head lice on day 15.

RESULTS

A total of 812 patients from 376 households were randomly assigned to receive either ivermectin or malathion. In the intention-to-treat population, 95.2% of patients receiving ivermectin were lice-free on day 15, as compared with 85.0% of those receiving malathion (absolute difference, 10.2 percentage points; 95% confidence interval [CI], 4.6 to 15.7; P<0.001). In the per-protocol population, 97.1% of patients in the ivermectin group were lice-free on day 15, as compared with 89.8% of those in the malathion group (absolute difference, 7.3 percentage points; 95% CI, 2.8 to 11.8; P=0.002). There were no significant differences in the frequencies of adverse events between the two treatment groups.

CONCLUSIONS

For difficult-to-treat head-lice infestation, oral ivermectin, given twice at a 7-day interval, had superior efficacy as compared with topical 0.5% malathion lotion, a finding that suggests that it could be an alternative treatment. (ClinicalTrials.gov number, NCT00819520.)

From Université Pierre et Marie Curie Paris 6 and Assistance Publique–Hôpitaux de Paris (O.C.), and INSERM Unité 738 (B.G.) — all in Paris; the Department of Dermatology, Hôpital Henri-Mondor, Créteil (O.C.); INSERM, Centre d'Investigation Clinique 202, Université François-Rabelais, Tours, and Centre Hospitalier Régional Universitaire de Tours — all in Tours (B.G.); and Université Paris 13 and the Department of Parasitology, Hôpital Avicenne, Bobigny (A.I.) — all in France; McNeil, High Wycombe, United Kingdom (J.C., S.G.M.), and the Medical Entomology Centre, Insect Research and Development, Cambridge (I.B.) — both in the United Kingdom; and Johnson and Johnson, Neuss, Germany (R.H.). Address reprint requests to Dr. Chosidow at Hôpital Henri-Mondor, 51 Ave. du Maréchal de Lattre de Tassigny, 94010 Créteil, France, or at olivier.chosidow@hmn.aphp.fr.

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Head lice are universal human parasites, affecting over 100 million people worldwide each year. In the developed world, children 3 to 11 years of age are most likely to be affected.[1] Since the withdrawal in 2007 of the Cochrane review of head-lice treatments,[2] the only review available is a systematic review[3] published in 1995; it concluded that sufficient evidence of efficacy existed only for the pyrethroid insecticide permethrin (1% formulation), which had a cure rate with a lower 95% confidence limit of more than 90%. However, because of emerging pyrethroid resistance, malathion (0.5% formulation), an organophosphate insecticide, is now widely considered an effective alternative and was reintroduced into the U.S. market in 1999.[4] Regardless of which topical insecticide is used, management of head lice should include the use of a lotion that delivers a high insecticide concentration in one application, with a sufficient quantity of the lotion applied to ensure thorough coverage, a second application no fewer than 7 and no more than 11 days after the first in order to kill lice that may have hatched from eggs surviving the first treatment, and concomitant treatment of all infested family members.[5] Strict adherence to these recommendations controls head-lice infestation, at least in the absence of insecticide resistance.

Clinical and parasitologic resistance to pyrethroids was first suspected in the early 1990s in France[6] and was subsequently confirmed elsewhere (e.g., in the United Kingdom,[7] Israel,[8] United States,[9,10] Australia,[11] and Argentina[12]). The resistance results from the amino acid mutations Thr929Ile and Leu932Phe, involving the sodium-channel pathway that alters the sensitivity of the head-louse nervous system to pyrethroids.[13] Malathion resistance also seems to be increasing,[14] and nonpesticide alternatives, such as dimethicone lotion (4% or 92% formulations) and physical removal of the lice ("bug-busting"), are controversial or not sufficiently effective.[15-19] Consequently, infestations of head lice with insecticide resistance are considered difficult to treat.

Ivermectin, a semisynthetic derivative of the avermectin family of macrocyclic lactones, interrupts γ-aminobutyric acid–induced neurotransmission in invertebrates and has been used to treat onchocerciasis, lymphatic filariasis, helminthiases, and ectoparasite infestations, mainly scabies.[20,21] Head lice must feed on blood two to six times a day, and body lice must do so at least once daily. Ivermectin works systemically,[22] but a single, standard dose of oral ivermectin — 200 μg per kilogram of body weight — eradicated head-lice infestation in only 6 of 26 subjects (23%) in a noncontrolled study.[23] This trial was designed to assess the efficacy and safety of oral ivermectin at a dose of 400 μg per kilogram, as compared with malathion (0.5%) lotion in patients with difficult-to-treat head-lice infestation.

METHODS

STUDY DESIGN

The trial was a cluster-randomized, double-blind, double-dummy, controlled trial. Clusters were defined as households. Once an eligible patient was identified and recruited as an index patient, we randomly assigned the households, rather than the patients, to a treatment group to prevent contamination between the two groups within a household.

The trial was planned as a two-stage study: at the end of the primary stage (day 15), any patients who still had an infestation entered an extension stage, during which they were switched to the alternative treatment regimen in a double-blind, crossover fashion. The investigators who recruited patients for the study are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org).

The trial was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation, the Declaration of Helsinki, and local laws and regulations, and the protocol was reviewed and approved by the ethics committees of participating centers. Participants who were at or over the legal age for consent provided written informed consent before any study procedure was performed and before randomization. Simplified, age-appropriate information sheets were used to explain the study to children and adolescents who were under the legal age of consent. Their assent was recorded, and written informed consent was given on their behalf by parents or guardians.

The trial was funded by Johnson & Johnson–Merck Sharp & Dohme–Chibret, which provided

the study medications. Two academic authors and the sponsor designed the study; a contract research organization collected the data on behalf of the sponsor. The academic authors had full access to the data and made the decision to submit the manuscript for publication. Two academic authors and one industry author wrote the manuscript. All the authors vouch for the completeness and accuracy of the data, analyses, and reported findings.

STUDY SITES

The study was conducted from March 9 through September 14, 2004, at seven study centers: four in the United Kingdom and one each in Ireland, France, and Israel. The U.K. and Irish centers are small, dedicated clinical-research sites; the centers in France and Israel are local hospital departments.

STUDY PATIENTS

Patients were recruited from the community by means of advertising or outreach by nurses. Initial contact with a prospective household consisted of a telephone response to an advertisement or contact by outreach nurses during home visits. Initial contact was followed by a baseline visit (day 1) at the study site in all cases. All household members suspected to be infested were encouraged to attend the appointment; if all household members at the appointment met the inclusion criteria, randomization proceeded.

The inclusion criteria were an age of at least 2 years, weight of at least 15 kg, and head-lice infestation (defined as the presence of live lice) confirmed by study staff by combing the dry hair with a dedicated fine-toothed comb, as previously described.[24] Live lice seen during this examination were counted, to provide baseline data. The other inclusion criterion was previously failed treatment in either the index patient or a household member, defined as persistence of head-lice infestation, despite topical application of a pyrethroid-based or malathion insecticide 2 to 6 weeks before the day 1 visit, as reported by the patient (or parent or guardian) at the day 1 visit. Exclusion criteria are listed in the Supplementary Appendix.

Within a household, all infested members who met the inclusion criteria on day 1 were eligible. To be enrolled in the study, all the infested members had to be present at the day 1 visit. A household could not comprise more than six infested members.

STUDY TREATMENTS AND BLINDING

On days 1 and 8, either oral ivermectin (at a dose of 400 μg per kilogram, in 3-mg tablets; Stromectol, Merck) or 0.5% alcoholic malathion lotion (Prioderm, Viatris) was administered by staff on site. To ensure that treatment remained blinded, a double-dummy technique was used. All patients received tablets, either ivermectin or a visually identical placebo tablet (of identical composition except for the ivermectin, which was replaced by cellulose), and lotion, either 0.5% malathion or a placebo lotion containing 100% isopropanol. Before the trial, isopropanol was found to exert no relevant pediculicidal activity in vitro against body lice (for details, see the Supplementary Appendix).

All patients were weighed on day 1 to calculate the number of ivermectin tablets required to achieve the dose of 400 μg per kilogram. Patients who were unable to swallow whole tablets were given ivermectin or placebo tablets crushed and mixed with applesauce.

On days 1 and 8, according to the manufacturer's instructions, an investigator applied lotion to each patient's dry hair until all the hair and scalp were thoroughly moistened. The hair was allowed to dry naturally (without the aid of a hair dryer or other artificial heat) in a well-ventilated room. When the hair was dry, the patient was allowed to leave the center, with instructions to leave the lotion in place for 10 to 12 hours and then to wash the hair with the mild shampoo provided by the investigation team in a treatment kit and to rinse as usual.

Patients who still had a head-lice infestation on day 15 (i.e., those in whom the primary end point of absence of head lice at day 15 had not been achieved) entered the extension stage, in which the randomized treatment was switched to the alternative treatment, administered at the same dose used in the primary stage.

No other pediculicidal treatments (including nit combing and trimethoprim–sulfamethoxazole) were permitted throughout the study. Patients were advised not to share items that were ordinarily in contact with the head (e.g., hats, combs, and hair accessories) and to avoid head-

to-head contact with others. Patients were asked not treat their hair (e.g., with dyes or bleach) or cut it very short or otherwise style it in a way that would prevent effective fine-toothed combing during the 2-week study period (see the Supplementary Appendix for details).

OUTCOMES AND ADVERSE EVENTS

The primary end point was the absence of live head lice on day 15, determined with the use of a standardized combing procedure (as on day 1): combing was performed until a live head louse was discovered or the entire scalp had been examined and was determined to be free of live lice. Secondary outcomes were the absence of live head lice on days 2 and 8, as well as on days 22 and 29 for patients who entered the extension stage. Each patient's treatment preference, an oral tablet or lotion, was also recorded.

All patients who received at least one application or dose of the study drug were evaluated for efficacy and safety (the intention-to-treat population). Patients (or, for children and adolescents, a parent or guardian) were questioned about adverse events at each study visit. All patients with serious adverse events were followed for the outcome, regardless of the determined cause of the event.

SAMPLE SIZE

We planned a two-step trial, using the approach of Morikawa and Yoshida,[25] with the first objective of establishing noninferiority and the second objective of establishing superiority. At each step, the hypothesis was subjected to a one-sided test at a 2.5% level. A priori true rates of efficacy were assumed to be 85% for malathion lotion and 95% for ivermectin. A 1.4 inflation factor was applied to adjust for the cluster design. For a total of 700 patients, we calculated that the study would have a statistical power of more than 99% for the noninferiority step (with a noninferiority margin of 5 percentage points) and a power of more than 96% for the superiority step. Sensitivity analyses were conducted to explore different efficacy rates for ivermectin and malathion lotion.

RANDOMIZATION

The randomized units were households (clusters), and randomization was stratified according to the number of persons with infestation within the household (three or fewer or four or more). Using permuted blocks of four, we randomly assigned households (not patients) to receive ivermectin or malathion (in a 1:1 ratio). The randomization schedule was generated by the Merck Research Laboratories statistical group and was delivered to the contractor who provided the treatment kits. Eligible households were assigned the next available treatment kit. The schedule was not revealed to investigators until after the database was finalized.

STATISTICAL ANALYSIS

The primary objective of establishing noninferiority required data to be analyzed according to both the intention-to-treat and per-protocol principles. For the intention-to-treat analysis, missing data were handled by means of the last-observation-carried-forward approach, which is generally applied to dropouts from longitudinal trials. Estimation of the two-sided 95% confidence interval for the difference between the rates of freedom from lice in the two treatment groups was performed with the use of a normal approximation. A ratio-estimator approach (based on a simple adjustment of the standard Pearson chi-square statistic) was applied to account for clustering.[26] The lower limit of the 95% confidence interval was compared with a noninferiority margin of −5 percentage points (the noninferiority objective), and we also determined whether it was greater than 0% (the superiority objective). Moreover, superiority was assessed with the use of z-tests and cluster-adjusted standard errors. Finally, intraclass correlation coefficients (to assess the clustering effect) were estimated for each of the two treatment groups.[27]

RESULTS

STUDY PARTICIPANTS AND TREATMENT

A total of 376 households, comprising 812 patients, were enrolled in the study (Fig. 1). The ivermectin group consisted of 398 patients in 185 households; the malathion group consisted of 414 patients in 191 households. On day 15 (the time at which the primary end point was assessed), 35 of the 812 patients (4.3%) had been lost to follow-up, and 53 of the 812 patients (6.5%) did not complete the study.

At baseline, the two treatment groups were

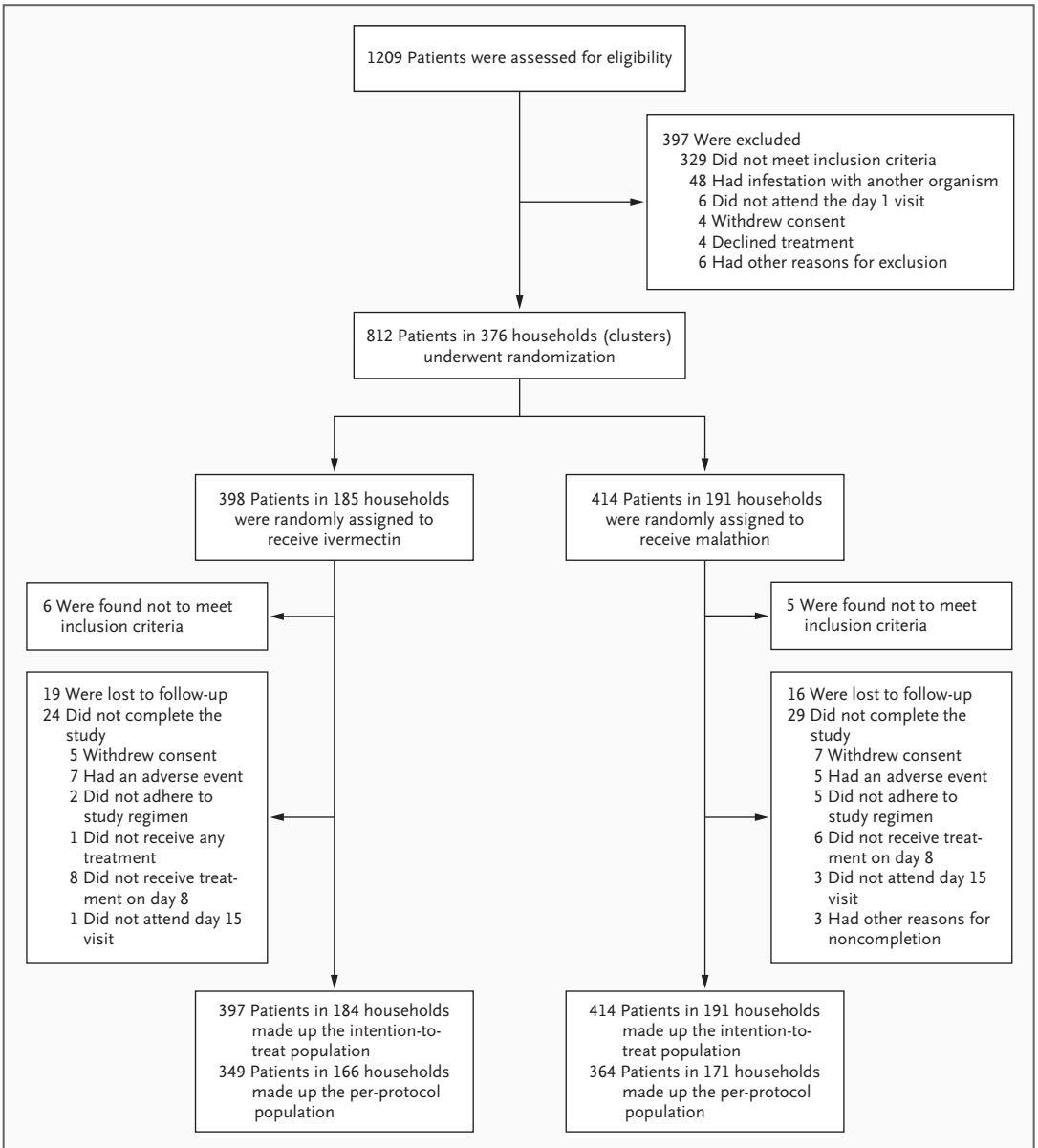

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients.

Recruitment of patients, provision of consent, and randomization took place at the study sites. The median number of members with a head-lice infestation per household in each of the two treatment groups was two (range, one to six). The one patient (the sole participant in that household) in the ivermectin group who did not receive any treatment was also not seen on day 15; the patient and the household were excluded from follow-up, and no data were included in the intention-to-treat analysis.

similar with regard to characteristics of households and patients (Table 1) (for details, see Table 1 in the Supplementary Appendix). Approximately 15% of randomized households had more than three family members with an infestation. The two treatment groups had nearly equivalent distributions of households according to the severity of infestation at the time of enrollment (mild [<12 live lice] or moderate or severe [≥12 live lice]) in the member with the most severe infestation. The study population was predominantly female (86.9%), with a median age of 10 years (interquartile range, 7 to 14) and a mean (±SD) weight of 40±22 kg.

One patient in the ivermectin group did not receive any treatment. The mean volumes of malathion lotion used in patients with thin, average, and thick hair density were 28.5±15.9 ml, 41.1±25.0 ml, and 59.4±32.6 ml, respectively, for each of the two applications.

OUTCOMES

Analysis of the primary end point in the intention-to-treat population, according to the last-observation-carried-forward approach, showed that on day 15, 378 of the 397 patients (95.2%) in the ivermectin group were free of head lice, as compared with 352 of the 414 patients (85.0%) in the malathion group (absolute difference, 10.2 percentage points; 95% confidence interval [CI], 4.6 to 15.7; P<0.001) (Table 2). In the per-protocol population, the estimated absolute difference between the two treatment groups was 7.3 percentage points (95% CI, 2.8 to 11.8; P=0.002). At the clusters level, 171 of the 185 households (92.4%) in the ivermectin group were free of head lice, as compared with 151 of the 191 households (79.1%) in the malathion group (absolute difference, 13.4 percentage points; 95% CI, 6.4 to 20.4). On days 2 and 8, ivermectin was also superior to malathion, with absolute differences between the two groups of 10.1 percentage points and 29.8 percentage points, respectively, and with efficacy sustained through days 22 and 29 (Table 2). (See Fig. 2 in the Supplementary Appendix for the results of detailed exploratory subgroup analyses.)

On day 15, 39 patients (8 in the ivermectin group and 31 in the malathion group) had persistent infestation and therefore entered the extension phase, with a switch to the other treatment. At day 29, 8 of the 8 patients (100%) receiving malathion and 30 of the 31 patients (96.8%) receiving ivermectin no longer had head lice.

Regarding treatment preference, 78.3% of the patients preferred tablets, 13.0% preferred lotion, and 8.7% had no preference.

ADVERSE EVENTS

Two serious clinical adverse events were reported (Table 3; see also Table 3 in the Supplementary Appendix for detailed information about adverse events). A total of 7 of the 398 patients (1.8%) in the ivermectin group and 5 of the 414 patients (1.2%) in the malathion group discontinued treatment because of an adverse event; only three events were judged to be severe. The frequencies

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	Ivermectin Group	Malathion Group
Study households	N=185	N=185
No. of members per household — median (interquartile range)	5 (4–6)	5 (4–6)
No. of members with infestation — median (interquartile range)	2 (1–3)	2 (1–3)
Household size — no. (%)†		
Small	157 (84.9)	159 (83.2)
Large	28 (15.1)	32 (16.8)
Severity of household infestation — no. (%)‡		
Mild or moderate	85 (45.9)	90 (47.1)
Severe	100 (54.1)	101 (52.9)
Study patients	N=398	N=414
Age — yr		
Median	10	10
Interquartile range	7–14	7–14
Sex — no. (%)		
Male	53 (13.3)	53 (12.8)
Female	345 (86.7)	361 (87.2)
Weight — kg	40±22	40±20
Race group — no. (%)§		
Asian	69 (17.3)	48 (11.6)
Black	1 (0.3)	0
White	323 (81.2)	361 (87.2)
Other	5 (1.3)	5 (1.2)
Hair density — no. (%)		
Thin	59 (14.8)	50 (12.1)
Average	164 (41.2)	156 (37.7)
Thick	175 (44.0)	208 (50.2)
Hair length — no. (%)		
Well above earlobe	65 (16.3)	57 (13.8)
Between earlobe and shoulder	70 (17.6)	69 (16.7)
Below shoulder	263 (66.1)	288 (69.6)
No. of live lice on visual inspection — no. (%)		
<12	265 (66.6)	268 (64.7)
≥12	133 (33.4)	146 (35.3)

* Plus–minus values are means ±SD.
† A small household was one with three or fewer members with infestation; a large household was one with four or more members with infestation.
‡ The severity of household infestation was assessed in the member of each household with the most severe infestation. Mild or moderate was defined as fewer than 12 live lice per infestation; severe was defined as 12 or more live lice per infestation.
§ Race group was reported by either the investigator or the patient or, if the patient was a child, by the child's parent or guardian.

Table 2. Rates of Freedom from Live Lice at Various Time Points, According to Treatment Group.

Day of Study	Ivermectin Group (N=397)	Malathion Group (N=414)	Absolute Difference	P Value*	No. Needed to Treat with Ivermectin (95% CI)†
	no. (% [95% CI])		*percentage points (95% CI)*		
Day 15 (primary end point)					
Intention-to-treat analysis with LOCF‡	378 (95.2 [92.3–98.1])	352 (85.0 [80.3–89.8])	10.2 (4.6–15.7)	<0.001	9.8 (6.4–21.7)
Per-protocol analysis§	339 (97.1 [95.1–99.2])	327 (89.8 [85.8–93.9])	7.3 (2.8–11.8)	0.002	13.9 (8.5–35.7)
Day 2¶	367 (92.4 [88.8–96.1])	341 (82.4 [78.0–86.8])	10.1 (4.3–15.8)	<0.001	9.9 (6.3–23.3)
Day 8¶	332 (83.6 [78.7–88.6])	223 (53.9 [48.2–59.5])	29.8 (22.4–37.3)	<0.001	3.4 (2.7–4.5)
Day 22¶	380 (95.7 [93.0–98.4])	365 (88.2 [83.6–92.7])	7.6 (2.3–12.8)	0.003	13.2 (7.8–43.5)
Day 29¶	382 (96.2 [93.6–98.8])	364 (87.9 [83.4–92.5])	8.3 (3.1–13.5)	<0.001	12.0 (7.4–32.3)

* P values were calculated with the use of tests of superiority.
† The number needed to treat with ivermectin, which was derived from the intention-to-treat analysis, is the number of patients who would need to be treated with oral ivermectin to prevent a recurrence of head-lice infestation in one patient.
‡ The intention-to-treat analysis included data from patients who received at least one dose or application of the study drug. The last-observation-carried-forward (LOCF) method was used to handle missing data. The estimated intraclass correlation coefficients for the ivermectin and malathion groups were 0.62 (95% CI, 0.27 to 0.83) and 0.44 (95% CI, 0.24 to 0.62), respectively.
§ The per-protocol analysis was based on 349 patients in the ivermectin group and 364 patients in the malathion group.
¶ The intention-to-treat analysis included this day.

of adverse events were generally similar among the age groups of 2 to 5 years, 6 to 12 years, and more than 12 years, but in absolute terms, the youngest group had the fewest events.

DISCUSSION

The results of this multicenter, cluster-randomized, double-blind, double-dummy, controlled trial showed the noninferiority and superiority of oral ivermectin (at a dose of 400 μg per kilogram) to 0.5% malathion lotion, each given on days 1 and 8, for eradicating head-lice infestation. Given the rising prevalence of head-lice infestation, the target population of persons with difficult-to-treat infestation, defined by a previous failure of topical insecticides, represents an emerging medical need. Moreover, failure to clear the infestation leads to frequent misuse of various products or devices, such as repeated use of insecticidal shampoos, which is suspected of increasing resistance to insecticides[5]; there is preliminary epidemiologic evidence linking exposure to insecticidal shampoos to acute leukemia in children.[28]

More households were lice-free after receipt of oral ivermectin than after receipt of malathion lotion, showing that ivermectin effectively controls infestations in close contacts and suggesting that it would be useful at the classroom level as well. The real-life effect size is likely to be even greater, because adherence to topical-insecticide regimens is poor.[17]

The superiority of ivermectin was seen at both day 2 and day 8 (since day 2 was included to measure the true effect of the study drug, administered on day 1, on live lice present at the time of enrollment, not those that hatched thereafter). The efficacy of ivermectin was also confirmed during the double-blind, extended phase (when patients in whom malathion failed to eradicate the infestation received ivermectin). Ivermectin has a long plasma half-life (12 to 16 hours), as does its active metabolite, which is a potential explanation for why the rate of freedom from live lice with ivermectin remained stable through day 29 and why the rate associated with ivermectin was 8.3 percentage points higher than the rate associated with malathion at day 29, in spite of the potential residual local effect of malathion.

The primary end point — the absence of live head lice — was scheduled to be assessed on day 15, because the study drugs (and all those available for lice infestation) generally have poor ovicidal activity, and nits can continue to hatch until 11 days after the first administration. A standard-

Table 3. Clinical Adverse Events, According to Age Group and Primary-Stage Treatment Group.

Adverse Event	Total			2–5 Yr		6–12 Yr		>12 Yr	
	Ivermectin (N=398)	Malathion (N=414)	P Value*	Ivermectin (N=54)	Malathion (N=58)	Ivermectin (N=228)	Malathion (N=226)	Ivermectin (N=116)	Malathion (N=130)
	no. of patients (%)			*no. of patients (%)*					
Serious adverse event†	1 (0.3)	1 (0.2)	1.00	0	0	1 (0.4)	1 (0.4)	0	0
Adverse event the primary reason for discontinuation‡	7 (1.8)	5 (1.2)	0.57	0	0	6 (2.6)	4 (1.8)	1 (0.9)	1 (0.8)
Any adverse event	91 (22.9)	100 (24.2)	0.68	17 (31.5)	10 (17.2)	45 (19.7)	56 (24.8)	29 (25.0)	34 (26.2)
Treatment-related adverse event§	30 (7.5)	45 (10.9)	0.12	2 (3.7)	1 (1.7)	20 (8.8)	27 (11.9)	8 (6.9)	17 (13.1)
Severe adverse event¶	1 (0.3)	2 (0.5)	1.00	0	0	1 (0.4)	1 (0.4)	0	1 (0.8)

* P values were calculated with the use of Fisher's exact test.

† Adverse events were classified as serious according to prespecified criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org). A 7-year-old girl in the ivermectin group had a seizure 6 days after the first dose of ivermectin and was hospitalized; a right rolandic (centrotemporal) focus was found. She recovered and was discharged with a prescription for oxcarbazepine. An 11-year-old girl in the malathion group had a severe headache 6 days after the first application of malathion lotion and was hospitalized overnight as a precautionary measure; she recovered fully.

‡ The following specific adverse events led to discontinuation: in the ivermectin group, impetigo (in two patients), nausea or vomiting (in one), gastroenteritis (in three), and convulsions (in one), and in the malathion group, rash or urticaria (in three patients) and gastroenteritis (in two).

§ Treatment-related adverse events were those classified as possibly, probably, or definitely related to the study drug by the investigator.

¶ Severe adverse events were adverse events classified by the investigator as being severe, using a scale of mild, moderate, or severe (see the Supplementary Appendix). These included the convulsions in one patient in the ivermectin group and headache in two patients in the malathion group.

ized procedure for fine-toothed combing was used to assess both trial eligibility and study end points, and the combing was performed by trained study staff on dry hair. To accurately measure the effect of treatment on head-lice infestation, we controlled for confounding factors: cluster randomization was used to avert reinfestation of the index patient by an untreated household member; both study treatments were administered twice on site, on days 1 and 8; and sufficient amounts of malathion lotion were applied.

Ivermectin may be a good alternative to malathion when topical insecticide resistance is suspected. The patients included in our large trial were recruited from the community in four countries, as a realistic sample of the general population, in which the degree of resistance and the type of resistance (i.e., resistance to a pyrethroid, malathion, or both) may vary from one place to another.

The main limitations of our study were that the previous failure of an insecticide to eradicate a head-lice infestation was reported by patients only; parasitologic tests and genotyping were not performed. However, in real life, the persistence of live lice 1 day after insecticide application strongly suggests resistance. Pyrethroid resistance is the type of resistance that has been studied most extensively, and a phenotype–genotype correlation has been documented.[29] In an in vitro assay, a topical ivermectin lotion has been found to kill permethrin-resistant head lice that infest humans.[30]

The fact that fewer adverse events were reported in children 2 to 5 years of age than in other age groups in our study could reflect variation due to the relatively small size of this group or perhaps its lower propensity for self-reporting (by a parent or guardian). An increased risk of death has been reported among elderly patients with scabies infestation who were treated with ivermectin,[31,32] but this has not been confirmed in long-term studies of resident populations and thus is not considered a risk for patients with head-lice infestation. The mechanism of action of ivermectin is quite species-specific. Among mammals, sudden death has been reported only in collies with a multidrug resistance protein 1 gene (*MDR1*)–deficient genotype, rendering them hypersensitive to the P-glycoprotein substrate.[33] Encephalopathy associated with infestation has

been observed only in patients heavily infected with *Loa loa* microfilariae and is therefore not expected to occur in patients with head-lice infestation.[34] The seizure that occurred in one of our patients took place 6 days after the first dose of ivermectin and was attributed to a rolandic (centrotemporal) focus. Finally, in the general population, approximately 45 million people in more than 30 countries have received 150 million doses of ivermectin[35] with no reported severe adverse events, although the dose was lower than that used to eradicate head lice in this study.

Ivermectin has been used extensively to treat onchocerciasis since 1987. It is worrisome that it was recently shown to drive the genetic selection of resistant *Onchocerca volvulus*.[36] Mass treatment with ivermectin has been used for ectoparasitic diseases (e.g., scabies and pediculosis), but to date, resistance has been documented in only two patients who were given more than 30 doses of ivermectin each.[37-40] However, a recent longitudinal study showed increasing scabies-mite tolerance to ivermectin, as measured in vitro, in communities in regions where scabies is endemic.[41] Restricting the use of ivermectin for head-lice infestation to the target population in our study (i.e., patients with infestation in whom a topical insecticide failed) should limit the risk of the emergence of resistance, but long-term surveillance will be mandatory.

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REFERENCES

1. Roberts RJ. Head lice. N Engl J Med 2002;346:1645-50.
2. Dodd CS. Withdrawn: interventions for treating head lice. Cochrane Database Syst Rev 2007;4:CD001165.
3. Vander Stichele RH, Dezeure EM, Bogaert MG. Systematic review of clinical efficacy of topical treatment for head lice. BMJ 1995;311:604-8.
4. Malathion for treatment of head lice. Med Lett Drugs Ther 1999;41:73-4.
5. Chosidow O. Scabies and pediculosis. Lancet 2000;355:819-26.
6. Chosidow O, Chastang C, Brue C, et al. Controlled study of malathion and *d*-phenothrin lotions for *Pediculus humanus* var *capitis*-infested schoolchildren. Lancet 1994;344:1724-7.
7. Burgess IF, Brown CM, Peock S, Kaufman J. Head lice resistant to pyrethroid insecticides in Britain. BMJ 1995;311:752.
8. Mumcuoglu KY, Hemingway J, Miller J, et al. Permethrin resistance in the head louse *Pediculus capitis* from Israel. Med Vet Entomol 1995;9:427-32.
9. Pollack RJ, Kiszewski A, Armstrong P, et al. Differential permethrin susceptibility of head lice sampled in the United States and Borneo. Arch Pediatr Adolesc Med 1999;153:969-73.
10. Meinking TL, Serrano L, Hard B, et al. Comparative in vitro pediculicidal efficacy of treatments in a resistant head lice population in the United States. Arch Dermatol 2002;138:220-4.
11. Hunter JA, Barker SC. Susceptibility of head lice (*Pediculus humanus capitis*) to pesticides in Australia. Parasitol Res 2003; 90:476-8.
12. Vassena CV, Mougabure Cueto G, González Audino P, Alzogaray RA, Zerba EN, Picollo MI. Prevalence and levels of permethrin resistance in *Pediculus humanus capitis* De Geer (Anoplura: Pediculidae) from Buenos Aires, Argentina. J Med Entomol 2003;40:447-50.
13. Lee SH, Yoon KS, Williamson MS, et al. Molecular analysis of *kdr*-like resistance in permethrin-resistant strains of head lice, *Pediculus capitis*. Pestic Biochem Physiol 2000;66:130-43.
14. Kristensen M, Knorr M, Rasmussen AM, Jespersen JB. Survey of permethrin and malathion resistance in human head lice populations from Denmark. J Med Entomol 2006;43:533-8.
15. Burgess IF, Brown CM, Lee PN. Treatment of head louse infestation with 4% dimeticone lotion: randomized controlled equivalence trial. BMJ 2005;330:1423-6.
16. Heukelbach J, Pilger D, Oliveira FA, Khakban A, Ariza L, Feldmeier H. A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial. BMC Infect Dis 2008;8:115.
17. Roberts RJ, Casey D, Morgan DA, Petrovic M. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomised controlled trial. Lancet 2000;356:540-4.
18. Elston DM. Controversies concerning the treatment of lice and scabies. J Am Acad Dermatol 2002;46:794-6.
19. Chosidow O. Bug Buster for head lice: is it effective? Arch Dermatol 2006;142: 1635-7.
20. Meinking TL, Taplin D, Hermida JL, Pardo R, Kerdel FA. The treatment of scabies with ivermectin. N Engl J Med 1995; 333:26-30.
21. Foucault C, Ranque S, Badiaga S, Rovery C, Raoult D, Brouqui P. Oral ivermectin in the treatment of body lice. J Infect Dis 2006;193:474-6.
22. Mumcuoglu KY, Miller J, Rosen LJ, Galun R. Systemic activity of ivermectin on the human body louse (Anoplura: Pediculidae). J Med Entomol 1990;27:72-5.
23. Glaziou P, Nyguyen LN, Moulia-Pelat JP, Cartel JL, Martin PM. Efficacy of ivermectin for the treatment of head lice (*Pediculosis capitis*). Trop Med Parasitol 1994;45: 253-4.
24. Mumcuoglu KY, Friger M, Ioffe-Uspensky I, Ben-Ishai F, Miller J. Louse comb versus direct visual examination for the diagnosis of head louse infestation. Pediatr Dermatol 2001;18:9-12.
25. Morikawa T, Yoshida M. A useful test-

ing strategy in phase III trials: combined test of superiority and test of equivalence. J Biopharm Stat 1995;5:297-306.
26. Donner A, Klar N. Design and analysis of cluster randomization trials. London: Arnold, 2000.
27. Giraudeau B. Model mis-specification and overestimation of the intraclass correlation coefficient in cluster randomized trials. Stat Med 2006;25:957-64.
28. Menegaux F, Baruchel A, Lescoeur B, et al. Household exposure to pesticides and risk of childhood acute leukaemia. Occup Environ Med 2006;63:131-4.
29. Yoon KS, Gao JR, Lee SH, Clark JM, Brown L, Taplin D. Permethrin-resistant human head lice, *Pediculus capitis*, and their treatment. Arch Dermatol 2003;139:994-1000.
30. Strycharz JP, Yoon KS, Clark JM. A new ivermectin formulation topically kills permethrin-resistant human head lice (Anoplura: Pediculidae). J Med Entomol 2008; 45:75-81.
31. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. Lancet 1997;349:1144-5.
32. del Giudice P, Marty P, Gari-Toussaint M, Le Fichoux Y. Ivermectin in elderly patients. Arch Dermatol 1999;135:351-2.
33. Roulet A, Puel O, Gesta S, et al. *MDR1*-deficient genotype in Collie dogs hypersensitive to the P-glycoprotein substrate ivermectin. Eur J Pharmacol 2003;460:85-91.
34. Gardon J, Gardon-Wendel N, Demanga-Ngange, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. Lancet 1997;350:18-22.
35. Ottesen EA, Hooper PJ, Bradley M, Biswas G. The global programme to eliminate lymphatic filariasis: health impact after 8 years. PLoS Negl Trop Dis 2008; 2(10):e317.
36. Bourguinat C, Pion SD, Kamgno J, et al. Genetic selection of low fertile *Onchocerca volvulus* by ivermectin treatment. PLoS Negl Trop Dis 2007;1(1):e72.
37. Heukelbach J, Winter B, Wilcke T, et al. Selective mass treatment with ivermectin to control intestinal helminthiases and parasitic skin diseases in a severely affected population. Bull World Health Organ 2004;82:563-71.
38. Chosidow O. Scabies. N Engl J Med 2006;354:1718-27.
39. Badiaga S, Foucault C, Rogier C, et al. The effect of a single dose of oral ivermectin on pruritus in the homeless. J Antimicrob Chemother 2008;62:404-9.
40. Currie BJ, Harumal P, McKinnon M, Walton SF. First documentation of in vivo and in vitro ivermectin resistance in *Sarcoptes scabiei*. Clin Infect Dis 2004;39(1): e8-e12.
41. Mounsey KE, Holt DC, McCarthy JS, Currie BJ, Walton SF. Longitudinal evidence of increasing in vitro tolerance of scabies mites to ivermectin in scabies-endemic communities. Arch Dermatol 2009;145:840-1.