

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010;362:896-905.

Exclusion criteria

Any of the following criteria rendered patients ineligible: 1) pregnant or breastfeeding; 2) active scalp disease (e.g., bacterial infection); 3) use of any pediculicidal treatment (including trimethoprim–sulfamethoxazole) or any potentially interacting drug within the 2 weeks before the study; 4) a hair style (e.g., tight plaiting) that would preclude fine-toothed combing, or use of hair dyes, bleaches or permanent wave or hair relaxing solutions during the preceding 2 weeks; 5) prior residence in areas of Africa known to be endemic for onchocerciasis, lymphatic filariasis, *Loa loa* or any other microfilaremic disease; 6) known or suspected intestinal helminth infection; 7) known hypersensitivity to any component of either study treatment.

In vitro preclinical study

The malathion topical treatment (Prioderm™, Viatrix, France) contained around 16% terpenoid (*d*-limonene, alpha-terpineol and pine needle oil) along with isopropanol and malathion. Usually, the vehicle minus the active agent is used as the topical placebo. However, the Prioderm™ vehicle, i.e., terpenes and isopropanol, was suspected of having pediculicidal activity, with the active product probably being the terpenes. Therefore, lotions with lower terpene levels (2.5% and 5%) were developed and tested in an in vitro study using human body lice, *Pediculus humanus humanus*, obtained from the culture colony maintained by the Medical Entomology Centre (IB). A 60% isopropanol base was used for the controls. Despite these lower concentrations, both terpene-containing lotions showed significant activity after overnight exposure: 100% mortality (n=60 for each group) vs 11.5% (n=61) for the isopropanol base. Finally, the placebo lotion used in the trial was 100% isopropanol, which was intended, as far as was possible, to mimic the Prioderm™ formulation (for blinding purposes) and simultaneously to eliminate all the known or suspected active components (malathion and terpenes).

Subgroup analyses

METHODS

Subgroup post-hoc analyses were performed on the intention-to-treat principle, using the last-observation-carried-forward approach to handle missing data. Statistical analyses were independently re-run for each subgroup and interaction significance was examined through hierarchical logistic-regression models (SAS PROC GLIMMIX, SAS Institute Inc, Cary, NC). In the absence of convergence, subgroup between-arm differences were compared using a normal approximation.

RESULTS

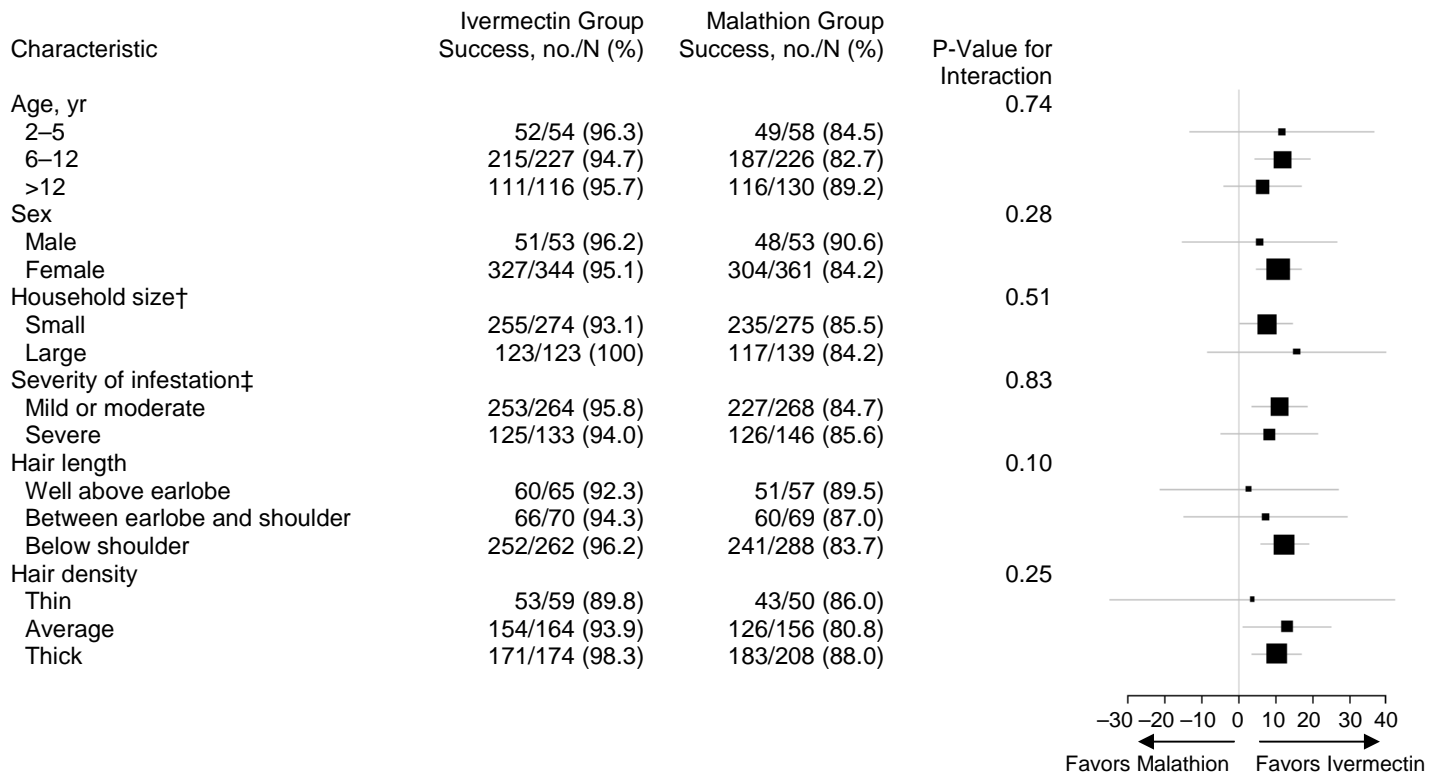
Exploratory subgroup analyses (Fig. 2) showed greater ivermectin efficacy in patients ≤ 12 years old and girls. When >3 household members were infested or infestation was severe (≥ 12 live lice), ivermectin superiority was not reached (differences vs. malathion group, 15.8% and 8.4%, respectively). None of the between-subgroup interactions and between-arm differences reached statistical significance.

DISCUSSION

The too small subgroups for exploratory analyses might explain why ivermectin superiority could not be reached when >3 household members were infested or infestation was ≥ 12 live lice.

Figure 2. Analyses of Treatment Subgroups Defined According to Baseline Individual-Patient Characteristics

Subgroup analyses were performed according to the intention-to-treat principle. Missing data were handled using the last-observation-carried-forward method.



† 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 infestation was assessed individually for each patient. Mild or moderate infestation was defined as the patient having fewer than 12 live head lice; severe was defined as the patient having 12 or more live head lice.

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

Characteristic	Ivermectin Group	Malathion Group
Study Households	N = 185	N = 191
Country – no. (%)		
United Kingdom	41 (22.2)	46 (24.1)
Ireland	80 (43.2)	81 (42.4)
France	42 (22.7)	42 (22)
Israel	22 (11.9)	22 (11.5)
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
Country – no. (%)		
United Kingdom	91 (22.9)	114 (27.5)
Ireland	145 (36.4)	155 (37.4)
France	117 (29.4)	94 (22.7)

Israel	45 (11.3)	51 (12.3)
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 or ethnic group - no. (%)§		
Asian	69 (17.3)	48 (11.6)
Black	1 (0.3)	0 (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)	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 \pm 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 the household infestation was assessed for 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 or ethnic group was reported either by the investigator or the patient or, if the patient was a child, by the child's parent or guardian.

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

	Total		P Value*	2–5 Yr		6–12 Yr		>12 Yr	
	Ivermectin	Malathion		Ivermectin	Malathion	Ivermectin	Malathion	Ivermectin	Malathion
Adverse event	(N=398)	(N=414)		(N=54)	(N=58)	(N=228)	(N=226)	(N=116)	(N=130)
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)	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)
Adverse event in ≥1% of patients									
Abdominal pain	18 (4.5)	19 (4.6)	1.00	1 (1.9)	2 (3.4)	12 (5.3)	10 (4.4)	5 (4.3)	7 (5.4)

Diarrhea	8 (2.0)	7 (1.7)	0.80	2 (3.7)	2 (3.4)	3 (1.3)	2 (0.9)	3 (2.6)	3 (2.3)
Nausea	8 (2.0)	4 (1.0)	0.25	0	0	3 (1.3)	2 (0.9)	5 (4.3)	2 (1.5)
Vomiting	9 (2.3)	5 (1.2)	0.29	2 (3.7)	0	4 (1.8)	2 (0.9)	3 (2.6)	3 (2.3)
Application site									
pain/irritation	1 (0.3)	4 (1.0)	0.37	0	1 (1.7)	1 (0.4)	3 (1.3)	0	0
Pyrexia	2 (0.5)	4 (1.0)	0.69	1 (1.9)	2 (3.4)	1 (0.4)	1 (0.4)	0	1 (0.8)
Gastroenteritis	4 (1.0)	2 (0.5)	0.44	2 (3.7)	0	2 (0.9)	2 (0.9)	0	0
Nasopharyngitis	4 (1.0)	5 (1.2)	1.00	1 (1.9)	2 (3.4)	3 (1.3)	2 (0.9)	0	1 (0.8)
Tonsillitis	0	4 (1.0)	0.12	0	1 (1.7)	0	2 (0.9)	0	1 (0.8)
Headache	17 (4.3)	21 (5.1)	0.62	0	1 (1.7)	10 (4.4)	11 (4.9)	7 (6.0)	9 (6.9)
Psychomotor									
hyperactivity	3 (0.8)	5 (1.2)	0.73	2 (3.7)	0	1 (0.4)	5 (2.2)	0	0
Cough	8 (2.0)	8 (1.9)	1.00	2 (3.7)	4 (6.9)	5 (2.2)	2 (0.9)	1 (0.9)	2 (1.5)
Pharyngolaryngeal									
pain	4 (1.0)	8 (1.9)	0.39	1 (1.9)	0	0	7 (3.1)	3 (2.6)	1 (0.8)
Rash/erythema	6 (1.5)	8 (1.9)	0.79	2 (3.7)	0	2 (0.9)	6 (2.7)	2 (1.7)	2 (1.5)

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

†Serious adverse events were classified as serious according to prespecified criteria (cf infra). 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 (cf infra).

These included the convulsions in one patient in the ivermectin group and headache in two patients in the malathion group.

|| Reported side effects had a frequency $\geq 1\%$ (overall population) in at least one treatment group during the first phase of the trial.

Seriousness of adverse event

A serious adverse experience was defined as any adverse experience occurring at any dose that resulted in death, was life threatening (this did not include an adverse experience that, had it occurred in a more severe form, might have caused death), resulted in a persistent or significant disability/incapacity (substantial disruption of ability to conduct normal life functions), resulted in or prolonged an existing inpatient hospitalisation (hospitalisation was defined as an inpatient admission, regardless of length of stay, even as a precautionary measure for continued observation), was a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis), cancer or an overdose (whether accidental or intentional).

Hospitalisation for a pre-existing condition that had not worsened or for an elective procedure did not constitute a serious adverse experience.

Any overdose, whether or not associated with an adverse experience, was to be reported within 24 hours.

Other important medical events that did not result in death, were not life threatening or did not require hospitalisation could be considered a serious adverse experience when, based upon appropriate medical judgment, the event jeopardised the patient or required medical or surgical intervention to prevent one of the outcomes previously listed.

Intensity of adverse event

- 1 = Mild (awareness of sign or symptom, but easily tolerated).
- 2 = Moderate (sufficient discomfort to interfere with usual activity).
- 3 = Severe (incapacitating, resulting in the inability to work or perform usual activity).

The investigators who recruited patients for the study are listed below.

United Kingdom: Dr Hilary Shaw, Synexus Reading Clinical Research Centre, 11 Glebe Road, Reading, RG2 7AG. Dr John Robinson, Synexus Crosby Clinical Research Centre, Burlington House, Crosby, L22 0LG. Dr Caroline Naik, Synexus Manchester Clinical Research Centre, 1st Floor Williams House, Manchester Science Park, Lloyd Street North, Manchester, M15 6SX. Dr Jean Fraser, Synexus Wigan Clinical Research Centre, Buckingham Row, Brick Kiln Lane, Wigan WN1 1XX. **Ireland:** Prof W.P. Leary, Shandon Clinic, 9 John Redmond Street, Cork. **France:** Dr Arezki Izri, Department of Parasitology, Hopital Avicenne, 125, route de Stalingrad, 93009 Bobigny. **Israel:** Dr Avner Shemer, Dermatology Department, Chaim Sheba Medical Centre, Tel Hashomer Hospital, Tel Hashomer 52621.