EDITORIAL

Topical Ivermectin — A Step toward Making Head Lice Dead Lice?

Olivier Chosidow, M.D., Ph.D., and Bruno Giraudeau, Ph.D.

Head-louse infestation stigmatizes hundreds of millions of people worldwide, predominantly children 3 to 11 years of age of all socioeconomic levels. It is commonly perceived as a sign of poor hygiene, which often engenders excessive management responses (e.g., repeated hair shaving and improper pediculicide use). Medical consequences of infestation can include itching and scratching, which may lead to cutaneous bacterial superinfection (i.e., pyoderma and impetigo) and possible transmission of *Bartonella quintana*, the trench-fever pathogen that is usually transmitted by body lice and that has been isolated from head lice.[1] The estimated annual direct and indirect cost of head-louse infestation in the United States is $1 billion.

Only a live louse on the head should define infestation, with detection enhanced by fine-toothed combing of hair (avoiding underdiagnosis by simple visual inspection or overdiagnosis by the use of nits as a criterion). The head louse, *Pediculus humanus* var. *capitis*, is an obligate, blood-sucking ectoparasite that feeds three to six times daily. The female lives 1 month and lays up to 300 eggs, whose hatching releases nymphs that become adults 7 to 10 days later. Thus, the relevant primary end point of studies is the louse-free rate of the infested population, ideally at the end of the louse's life cycle, because not all drugs are active against all developmental stages (e.g., eggs). Direct head-to-head contact is the most common transmission mode, and simultaneous treatment of all infested contacts (e.g., household members and classmates) should prevent reinfestation, a frequent cause of treatment failure. Indirect transmission through fomites such as linens is rare and easily preventable: the female dies within hours after being separated from her host, and machine laundering at a temperature of at least 50°C (122°F) kills all lice and nits.

In the mid-1980s, pyrethrin and pyrethroid insecticides, with claimed efficacy (of up to 95%), safety, convenience, cost-effectiveness, and a supposedly favorable environmental-safety profile, were marketed for head lice and progressively replaced other insecticides (e.g., dichlorodiphenyltrichloroethane [DDT], lindane, carbaryl, and malathion, a cholinesterase inhibitor twice withdrawn from the U.S. market). Available formulations include 1% permethrin and pyrethrins plus piperonyl butoxide. In the early 1990s, a randomized, controlled trial involving French schoolchildren showed that 24 hours after application, 0.5% malathion lotion, an infrequently used insecticide at that time, achieved a better louse-free rate (92%) than 0.3% *d*-phenothrin (40%). Ex vivo parasitologic testing of freshly sampled lice gave the same results, raising the possibility that lice might have acquired a pyrethroid-resistant phenotype.[2]

Pyrethroids are neurotoxins that modify louse voltage-gated sodium channels (VGSC), causing spastic paralysis and death. These agents have a rapid immobilizing effect, called knockdown, that often precedes lethality. DNA sequencing showed that "knockdown resistance" (kdr) to permethrin was linked to a three-point mutation (M815I–T917I–L920F) in the louse VGSC α-subunit gene, conferring nerve insensitivity.[3] The frequency of resistant kdr-like louse alleles varies according to geographic area, with values ranging from 0% in Thailand to 33 to 100% in California, Florida, and Texas, 97% in Canada, and 98.7% in Paris.[4,5] However, genetic resistance might not be predictive of clinical or parasitologic failure.

Resistance of head lice to insecticides led researchers to look for alternatives. Malathion was reintroduced to the U.S. market in 1999; formulations differ in the United States and Europe, and resistance has been reported in Europe. Other potential topical agents are detailed in the table in the Supplementary Appendix, available with the full text of this article at NEJM.org. Ivermectin is an antiparasitic drug used for onchocerciasis and lymphatic filariasis. It induces arthropod and nematode paralysis and death by interrupting neurotransmission, acting on glutamate-gated or γ-aminobutyric acid–gated chloride channels. A recent cluster-randomized, controlled trial showed that a single oral dose (400 μg per kilogram of body weight) repeated within 7 days achieved higher louse-free rates on day 15 than 0.5% malathion among patients with head lice refractory to insecticides (95.2% vs. 85.0%) and their household members (92.4% vs. 79.1%).[6]

In this issue of the *Journal*, Pariser et al. describe two randomized, controlled trials comparing a single application of 0.5% ivermectin lotion with vehicle control in patients 6 months of age or older.[7] The louse-free rate at day 15 was 73.8% among index patients (vs. 17.6% among vehicle-control recipients), and, remarkably, patients were deloused rapidly (94.9% on day 2). The infested household members were treated as well, but cluster analysis is not mentioned. Only local adverse events were reported (similar in both groups). A topical drug formulation is indeed welcome and is expected to have less risk of systemic adverse events. The Food and Drug Administration approved topical ivermectin lotion in February 2012.

Although oral ivermectin (at a dose of 400 μg per kilogram) is used off-label, its safety for patients with head-louse infestation remains unknown. However, more than 45 million people have taken oral ivermectin at a dose of 200 μg per kilogram for other infections. The lotion is convenient (i.e., applied to dry hair, left for 10 minutes, then rinsed with water), which should increase compliance. Notably, in a randomized, controlled trial in which malathion lotion was applied for 8 to 10 hours on parent and child volunteers, compliance reached only 50%. In an in vitro experiment, topical ivermectin acted as a posteclosion nymphicide by reducing head-louse blood-feeding, a finding that explains the single-application protocol of the current studies. However, the louse-free rate on day 15 was lower than on day 2, suggesting less in vivo activity.

The two randomized, controlled trials reported raise the question of the placebo-controlled design, because head lice is an infectious condition, albeit relatively benign, with still-infested children at risk of transmission in the community. Moreover, the use of an active comparator group would have been more relevant with regard to global head-louse management. Finally, strong ivermectin selection pressure in a population requires prudence, because it will eventually select resistant lice. Indeed, phenotypic and genotypic studies have shown emerging ivermectin resistance in *Onchocerca volvulus* in countries (e.g., Ghana and Cameroon) where ivermectin is widely used to control onchocerciasis.[8] In Australia, increasing in vitro scabies-mite tolerance of ivermectin in scabies-endemic communities has also been reported.[9]

How should head-louse infestation be managed? With good comparative-effectiveness research still lacking, indirect comparisons (see the table in the Supplementary Appendix) support the 2010 American Academy of Pediatrics recommendations to use 1% permethrin or pyrethrin insecticide as first-line therapy.[10] If resistance in the community has been proven or live lice are present 1 day after the completion of treatment, a switch to malathion may be necessary. Other options include wet combing or treatment with dimethicone or other topical agents, depending on the availability of the agents in the country. Nit removal is useful. Ivermectin should be the last choice, whether topical (for still-infested persons) or oral (especially for mass treatment). Management should also include more frequent checking for head-louse infestation in families and schools.

From the Department of Dermatology, Assistance Publique–Hôpitaux de Paris, Hôpital Henri-Mondor, Université Paris-Est Créteil Val de Marne, and INSERM, Centre d'Investigation Clinique (CIC) 006, Créteil (O.C.); INSERM, CIC 202, Université François-Rabelais, and Centre Hospitalier Régional Universitaire de Tours, Tours (B.G.); and INSERM Unité 738, Paris (B.G.) — all in France.

1. Bonilla DL, Kabeya H, Henn J, Kramer VL, Kosoy MY. *Bartonella quintana* in body lice and head lice from homeless persons, San Francisco, California, USA. Emerg Infect Dis 2009;15:912-5.
2. 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.
3. SupYoon K, Symington SB, Lee SH, Soderlund DM, Marshall Clark J. Three mutations identified in the voltage-sensitive sodium channel alpha-subunit gene of permethrin-resistant human head lice reduce the permethrin sensitivity of house fly

Vssc1 sodium channels expressed in *Xenopus* oocytes. Insect Biochem Mol Biol 2008;38:296-306.
4. Hodgdon HE, Yoon KS, Previte DJ, et al. Determination of knockdown resistance allele frequencies in global human head louse populations using the serial invasive signal amplification reaction. Pest Manag Sci 2010;66:1031-40.
5. Bouvresse S, Berdjane Z, Durand R, Bouscaillou J, Izri A, Chosidow O. Permethrin and malathion resistance in head lice: results of ex vivo and molecular assays. J Am Acad Dermatol 2012 May 22 (Epub ahead of print).
6. 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. [Erratum, N Engl J Med 2010;362:1647.]
7. Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med 2012;367:1687-93.
8. Osei-Atweneboana MY, Awadzi K, Attah SK, Boakye DA, Gyapong JO, Prichard RK. Phenotypic evidence of emerging ivermectin resistance in *Onchocerca volvulus.* PLoS Negl Trop Dis 2011;5(3):e998.
9. 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.
10. Frankowski BL, Bocchini JA Jr, Council on School Health and Committee on Infectious Diseases. Head lice. Pediatrics 2010;126:392-403.

DOI: 10.1056/NEJMe1211124