

## THE TREATMENT OF SCABIES WITH IVERMECTIN

TERRI L. MEINKING, B.A., DAVID TAPLIN, JORGE L. HERMIDA, M.D., RUBE PARDO, M.D., PH.D.,  
AND FRANCISCO A. KERDEL, M.D.

**Abstract Background.** Ivermectin is an anthelmintic agent that has been a safe, effective treatment for onchocerciasis (river blindness) when given in a single oral dose of 150 to 200  $\mu\text{g}$  per kilogram of body weight. Anecdotal reports of improvement in patients who suffered from infestation with the mite *Sarcoptes scabiei* suggest that the ectoparasitic disease scabies might be treated with ivermectin.

**Methods.** We conducted an open-label study in which ivermectin was administered in a single oral dose of 200  $\mu\text{g}$  per kilogram to 11 otherwise healthy patients with scabies and to 11 patients with scabies who were also infected with the human immunodeficiency virus (HIV), 7 of whom had the acquired immunodeficiency syndrome. All patients received a full physical and dermatologic examination; scrapings from the skin of all patients tested positive for scabies. Patients were reexamined two and four weeks after treatment, when the scrapings for scabies

were repeated. The patients used no other scabicides during the 30 days before ivermectin treatment or during the 4-week study period.

**Results.** None of the 11 otherwise healthy patients had evidence of scabies four weeks after a single dose of ivermectin. Of the 11 HIV-infected patients, 2 had  $\leq 10$  scabies lesions before treatment, 3 had 11 to 49 lesions, 4 had  $\geq 50$  lesions, and 2 had heavily crusted skin lesions. In eight of the patients the scabies was cured after a single dose of ivermectin. Two patients received a second dose two weeks after the first. Ten of the 11 patients with HIV infection (91 percent) had no evidence of scabies four weeks after their first treatment with ivermectin.

**Conclusions.** The anthelmintic agent ivermectin, given in a single oral dose, is an effective treatment for scabies in otherwise healthy patients and in many patients with HIV infection. (N Engl J Med 1995;333:26-30.)

**I**N the 1970s, during an intensive search for natural substances with anthelmintic properties, over 40,000 cultures of actinomycetes were screened in a collaboration between the Kitasato Institute in Japan and the Merck Institute for Therapeutic Research in the United States.<sup>1</sup> *Streptomyces avermitilis*, isolated from Japanese soil, was the only organism tested that produced a class of compounds known as avermectins. One of these, avermectin B<sub>1</sub> (abamectin), was later chemically modified to form ivermectin, a macrocyclic lactone structurally similar to the macrolide antibiotics but devoid of antibacterial activity. Ivermectin did, however, act strongly against a wide variety of insect, nematode, and acarine parasites of animals<sup>2</sup> and humans.<sup>3</sup> Ivermectin is used worldwide to control these infections and infestations, including sarcoptic mange in domesticated animals. In veterinary medicine, it is formulated for both topical and oral delivery, for administration in feed, and as a subcutaneous injection. Oral preparations are of well-established benefit as prophylaxis against the heartworm *Dirofilaria immitis* in dogs.<sup>4</sup>

In humans, ivermectin is used extensively to control onchocerciasis, a disfiguring and blinding disease caused by the filarial worm *Onchocerca volvulus*.<sup>3,5</sup> It is estimated that more than 6 million people in over 30 countries have been treated with ivermectin to control this disease, for which over 30 million people are considered to be at risk.<sup>6</sup> Oral ivermectin is also highly effective for the treatment and chemoprophylaxis of loiasis and bancroftian filariasis.<sup>3,7,8</sup>

In 1992, Glaziou et al. conducted an investigator-

blinded trial in French Polynesia, comparing a single oral dose of ivermectin (100  $\mu\text{g}$  per kilogram of body weight) with topical therapy with a 10 percent benzyl benzoate preparation for the treatment of scabies.<sup>9</sup> One month later, 70 percent of the patients treated with ivermectin had been cured, as compared with only 48 percent of the patients treated with benzyl benzoate. In India, Kar et al. treated one patient with scabies with a single oral dose of 100  $\mu\text{g}$  of ivermectin per kilogram, and a second patient with a dose of 20  $\mu\text{g}$  per kilogram. Although the itching and eruptions of the disease were reduced, the authors suggested that these doses were inadequate.<sup>10</sup> The results were much poorer than those expected from the best topical remedies.<sup>11-15</sup>

Dunne et al., working in Sierra Leone, could find no difference in the prevalence of scabies two months after 13 patients had been given either a single oral dose of ivermectin (100 to 200  $\mu\text{g}$  per kilogram) or placebo.<sup>16</sup> In a double-blind study conducted in Mexico, 23 of 29 patients were considered cured of scabies one week after being given a single dose of 200  $\mu\text{g}$  of ivermectin per kilogram, as compared with 4 of 26 patients in the placebo group.<sup>17</sup>

In the clinical trial of oral ivermectin that we are now reporting, one study group consisted of otherwise healthy patients with scabies. The second group comprised patients infected with the human immunodeficiency virus (HIV), the majority of whom had already been given a diagnosis of the acquired immunodeficiency syndrome (AIDS).

## METHODS

### Patients with Uncomplicated Scabies

The subjects assigned to the study group with uncomplicated scabies were healthy, mentally competent patients from 18 to 80 years of age who had received no topical or systemic antibiotic therapy in the week before entry into the study nor any topical antiscabietic treatment in the month before entry (or during the study).

From the Department of Dermatology and Cutaneous Surgery (T.L.M., D.T., R.P., F.A.K.) and the Department of Epidemiology and Public Health (D.T., J.L.H.), University of Miami School of Medicine, Miami. Address reprint requests to Ms. Meinking at the Department of Dermatology and Cutaneous Surgery, P.O. Box 016960, R-117, Miami, FL 33101.

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The patients in this group were also required to have clinical evidence of scabies and the microscopically demonstrated presence of live *Sarcoptes scabiei* mites, their eggs, or their fecal pellets (scybala). Subjects who were taking medications for other conditions or for whom antihistamines, antidepressants, or sleeping therapy had been prescribed for pruritus or anxiety were enrolled in the study only if they met the other inclusion criteria and were considered to be in good health at the time of the pretreatment physical examination. The patients in this group ingested a single oral dose of ivermectin (200  $\mu\text{g}$  per kilogram) in the presence of one or more investigators.

### Patients with Scabies and HIV Infection

Patients who were seropositive for HIV and those with AIDS were accepted as a separate group in the study under a compassionate-use protocol approved by the Food and Drug Administration. In this second group, as in the first, we required a positive microscopical demonstration of live mites or their byproducts. None of the patients with HIV infection had used a scabicide in the month before entry into the trial. No restriction, however, was placed on the use of medications required for problems associated with the immunologic deficiency of these patients. The number of ivermectin treatments in this group was determined by the patient's clinical response, the degree of pruritus, or the presence of live mites on the patient's skin, but the drug was always administered under supervision in an oral dose of 200  $\mu\text{g}$  per kilogram.

### Study Design

For each participant the distribution of scabies lesions was plotted on a body diagram, and the severity of disease was recorded as mild (10 or fewer lesions), moderate (11 to 49 lesions), severe (50 or more lesions), or crusted. Immediately before treatment, a history was taken and a physical examination was conducted that included measurement of the patient's blood pressure, pulse, temperature, height, and weight. Skin scrapings were examined for mites, eggs, or scybala. Because of the extensive record of safe use of ivermectin in humans with systemic parasitic diseases, no blood, urine, or stool analysis was required unless abnormal findings were noted on the physical examination.<sup>3,4,7</sup> Patients were seen two and four weeks after the first dose of ivermectin, and all examination procedures, including the collection of skin scrapings, were repeated. Patients who had clinical signs of active scabies or had new lesions either two or four weeks after the initial treatment were given another dose of ivermectin. For all participants, any medications used during the 30 days before treatment were recorded. No new medications were prescribed after the initial visit, but maintenance therapy for other conditions was not discontinued.

Ivermectin was administered as scored 6-mg tablets taken with water. The total dose ranged from 9 to 18 mg, depending on body weight. During the three days after treatment, the patients were interviewed about any symptoms or subjective evidence of adverse reactions. People known to be in close contact with the study patients were treated with a topical 5 percent permethrin cream to reduce the chance of reinfestation. Patients with no pruritus, no dermatologic evidence of scabies, and no positive signs of infestation in skin scrapings were considered to be cured.

The study was conducted in Miami between June 24, 1992, and May 24, 1993, after approval by the University of Miami Institutional Review Board. Participation was voluntary, and all patients gave written informed consent.

## RESULTS

### Patients with Uncomplicated Scabies

In the group with uncomplicated scabies, 13 patients received a single oral dose of 200  $\mu\text{g}$  of ivermectin per kilogram. No side effects were reported during interviews or at any follow-up visit. One woman was lost to follow-up. A 28-year-old man, paralyzed by a spinal cord injury, was the only person in this group who had crusted scabies. During the two weeks after receiving

ivermectin he was treated four times with 1 percent lindane lotion, a routine therapy in the nursing home where he lived. Two weeks after his ivermectin treatment his condition had improved but he was not cured, and his case was excluded from our results as a protocol violation. Because of the two exclusions, 11 otherwise healthy patients, 7 men and 4 women, ranging from 24 to 78 years of age, completed the study. Nine had moderate scabies, one had mild disease, and one severe disease. Five of them (45 percent) were cured two weeks after treatment. The rest were cured by the time of the four-week visit. All had received only a single oral dose of ivermectin.

### Patients with Scabies and HIV Infection

All 11 patients in the group with scabies and HIV infection, 9 men and 2 women, completed the study. They ranged from 28 to 48 years of age. Two had mild cases of scabies, three had moderate disease, four had severe disease, and two had crusted scabies. Seven had AIDS as defined by the Centers for Disease Control and Prevention and had CD4 counts below 200 per cubic millimeter.<sup>18</sup> Four others were seropositive for HIV, with CD4 counts of 200 to 500 per cubic millimeter and no history of opportunistic infections.

Six of the 11 patients (55 percent) were completely free of scabies two weeks after a single dose of ivermectin. Two others had skin scrapings that tested negative for scabies and had clinical improvement two weeks after treatment; we did not consider that their condition warranted a second dose. At the four-week follow-up examination they were completely cured. In contrast, two other patients had scrapings that tested negative after two weeks, but still had substantial pruritus and new lesions consistent with scabies; they were therefore given a second dose. They were also cured four weeks after their first evaluation. Thus, 8 of 11 (73 percent) of the patients seropositive for HIV were cured with a single dose of ivermectin. Two of the remaining three (18 percent of the treatment group) required a second dose two weeks after the first treatment and were cured by the time of the four-week follow-up evaluation.

The last case was a therapeutic challenge. The patient, a 34-year-old woman, was seriously ill with advanced AIDS, tuberculosis, and extensive, heavily crusted scabies (Fig. 1A and 2A). Her pruritus was severe, and she was constantly excoriating herself. The widespread dispersal of her mite-laden scales (Fig. 3) was visibly evident, so much so that the examining room had to be temporarily closed for cleaning and decontamination. She was an intravenous-drug user, and those in close contact with her declined to be identified or treated.

Two weeks after initial therapy, her crusts had diminished in size. Although we could not recover any live mites from skin scrapings, she still had severe pruritus and was given a second dose of ivermectin. Two weeks later, her condition had dramatically improved. The lesions on her hands had resolved (Fig. 1B), but she still had crusts on her elbows. At this time, four



Figure 1. The Hands of a Patient with AIDS before and after Treatment for Scabies.

The patient had heavily crusted scabies on her hands before treatment (Panel A). A photograph taken one month after an initial dose of ivermectin and two weeks after a second dose reveals that the lesions had resolved (Panel B).

weeks after her initial visit, we recovered live mites from her arms and administered a third dose of oral ivermectin. In addition, a total-body treatment with topical 5 percent permethrin cream was applied under supervision. Two weeks later she was cured. Her crusts had fallen off, or been picked off, to reveal newly formed, nonpigmented skin (Fig. 2B).

#### DISCUSSION

The 10-year history of the use of oral ivermectin to control onchocerciasis indicates that it is an extremely safe drug. In previous studies, hematologic values, blood chemistry, and urine composition were unaffected by ivermectin in doses of 100 to 400  $\mu\text{g}$  per kilogram.<sup>3,5,7,19</sup> In onchocerciasis and other filarial diseases, the majority of side effects of the drug involve eosinophilia<sup>7</sup> and Mazzotti reactions associated with the sudden death of the microfilaria or the release of their toxic products.<sup>3,5</sup> This was well demonstrated by Cartel et al., who used ivermectin for mass prophylaxis against

lymphatic filariasis.<sup>8</sup> Adverse reactions were reported in 29 of 122 patients with microfilaremia (24 percent), but in only 4 of 831 patients without microfilaremia (0.5 percent). Side effects in the group with microfilaremia included asthenia, fever, myalgia, headache, arthralgia, anorexia, and chills. In most cases, the reactions were transient and mild. In the group without microfilaremia a severe headache in one patient was the only side effect that prevented normal daily activities.

In our study, neither patients nor investigators noted any adverse reactions. All the patients reported beneficial effects, particularly diminished pruritus, which in several patients occurred less than 48 hours after treatment. The patients' emotional well-being was dramatically improved. The relief afforded by the cessation of itching and the ability to sleep soundly are benefits of any successful scabies therapy. We had the impression that these effects occurred more quickly after ivermectin treatment than in the several thousand



Figure 2. The Left Elbow of a Patient with AIDS before and after Treatment for Scabies.

The patient had heavily crusted elbows before treatment (Panel A), but was cured of scabies six weeks after the initial visit (Panel B). She required three doses of oral ivermectin and topical treatment with 5 percent permethrin cream.

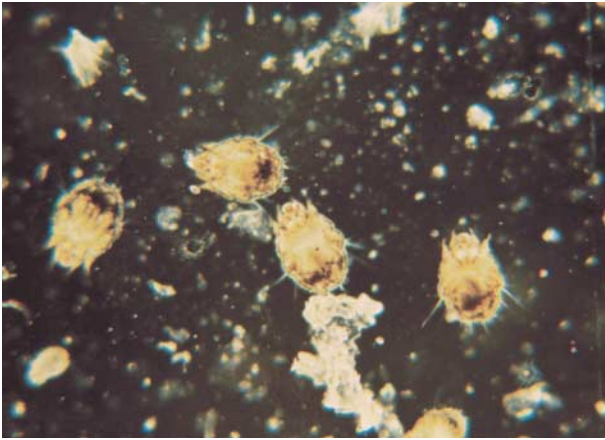


Figure 3. Scrapings from the Skin of a Patient with AIDS, Showing Live Scabies Mites on Darkfield Microscopy ( $\times 40$ ).

cases that we and others have treated with topical medications.<sup>11-15</sup> Five patients who had been treated with topical therapy for previous episodes of scabies expressed a strong preference for oral ivermectin, since it facilitated treatment and led to a more rapid resolution of their pruritus.

Our results suggest that a single treatment with oral ivermectin at a dose of 200  $\mu\text{g}$  per kilogram is a safe and effective therapy for uncomplicated scabies. Since an oral dose of the drug can be administered under supervision at the time of diagnosis, it has the additional advantage of avoiding the problems of noncompliance, misuse, and inadequate application associated with topical therapy.

We were particularly impressed with ivermectin as a treatment for immunocompromised patients. Curing scabies is difficult in such patients and usually requires several applications of different topical agents or combinations of therapy over a period of weeks. Eight of our 11 patients with HIV infection (73 percent) were cured after a single dose of ivermectin. We gave a second dose at two weeks to two patients who were still symptomatic, although we found no mites. They might well have been cured without a second dose.

Our most difficult case illustrated a challenge all too familiar to dermatologists and others who deal with crusted scabies in patients with AIDS. We believe the presence of live mites in our patient's skin after ivermectin treatment was due to the inadequate penetration of the drug into her thick crusts (Fig. 2A). Optimal treatment in such cases must await results from studies of larger numbers of patients, but our experience suggests that a combination of an effective topical treatment, such as 5 percent permethrin cream, and oral ivermectin leads to the best outcome. Topical treatment is wise in all cases of crusted scabies, to avoid contamination of the environment and the infestation of others, including health care providers.

In previous attempts to control scabies in communities, nursing homes, or institutions, success has depended on treating all persons at risk at the same time,

whether or not they show or admit signs or symptoms of scabies.<sup>12-15,20-22</sup> Control programs currently rely on head-to-toe application of creams and lotions, with particular attention to body crevices and genital areas. Accomplishing this on a community basis, or in institutions, is difficult, since the treatments need to be administered simultaneously to large numbers of patients to avoid reinfection. Some people may refuse to participate because they do not believe they have scabies — or are reluctant to admit it — or simply because they wish to avoid the embarrassment and fuss of treatment.

An oral medication with an excellent safety record, such as ivermectin, offers important benefits in the control of scabies on a large scale, in addition to the benefits of treatment in individual cases and families. In many areas of the world, scabies and infections with intestinal helminths are commonplace. Oral ivermectin has the additional advantage of being an effective antihelmintic agent against these parasites.<sup>19,23</sup> It has also been used successfully to treat infection with *Strongyloides stercoralis*, a frequent and important pathogen in patients with AIDS.<sup>19,24</sup>

One patient in our study became reinfested with *S. scabiei* two months after treatment, three patients three months after treatment, and one patient nine months after treatment. From our limited experience, it appears that ivermectin may have no residual activity against scabies two months after a single dose. This may account for the poor response seen by Dunne et al., who conducted their first follow-up examination two months after ivermectin treatment.<sup>16</sup> We have consistently noted that it may take a month after any single scabies treatment for all cutaneous signs to resolve.<sup>12,14,15</sup> This delay may well explain the disappointingly high number of treatment failures in the study conducted by Macotela-Ruiz and Peña-Gonzalez,<sup>17</sup> who evaluated their patients only one week after treatment with ivermectin. Our study also suggests that a single oral dose of 200  $\mu\text{g}$  of ivermectin per kilogram cures most cases of scabies, but that crusted or other stubborn cases may require additional treatments. In previous studies lower doses of ivermectin were less efficacious.<sup>9,10,16</sup> Aubin and Humbert recently reported the effectiveness of a single 12-mg dose of ivermectin in two patients in France with crusted scabies.<sup>25</sup>

Ivermectin is not approved for use in children under five years of age, nor yet for the treatment of scabies in humans. Prospective clinical trials are planned in several centers. The results of these trials should further define the role of ivermectin, the first oral treatment for a disease that affects many millions worldwide. We agree with Lawrence et al., who state that it will be unfortunate if ivermectin does not become available for the treatment of scabies in humans, since our domestic animals already have access to this simple, cheap, safe oral therapy for the same condition.<sup>26</sup>

This article is dedicated to the memory of Debra Chester Kalter, M.D.

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