Tolerability of Antimalaria Drugs

Sir—The multicenter randomized trial reported by Overbosch and colleagues [1] is important for 2 reasons. First, the study shows that when taken as malaria prophylaxis, mefloquine is not well tolerated by many travelers. Of the study participants randomized to receive mefloquine, 67.1% reported ≥1 adverse event, and, in 6% of mefloquine users, these events were severe (defined as requiring medical advice). The most common category of unwanted effects in the mefloquine treatment arm were neuropsychiatric adverse effects, which were reported by one-third of all mefloquine users [1]. This disturbing finding contradicts the advice in the most recent guidelines on malaria prevention for US travelers issued by the Centers for Disease Control and Prevention (CDC; Atlanta, Georgia); the guidelines state that “mefloquine is the drug of choice for chemoprophylaxis for most travelers [and] is well tolerated at prophylactic dosages” ([2], p. 1767). This assurance, which is plainly incorrect, was based on findings from uncontrolled studies of tourists and Peace Corps volunteers and from mefloquine trials that involved young, healthy soldiers. The CDC guidelines urgently need to be revised now that a randomized trial involving heterogeneous, nonimmune travelers has provided good evidence that mefloquine prophylaxis has the potential to cause harm.

Second, the article by Overbosch and colleagues [1] shows that, although earlier studies of atovaquone-proguanil therapy given to lifelong residents of areas where malaria is endemic may indeed have demonstrated that, in those populations, this drug combination has a safety profile that is “similar to placebo” [3, 4], the same is not true of atovaquone-proguanil therapy for nonimmune Western travelers. Of the Overbosch study participants randomized to receive atovaquone-proguanil, 64.5% reported ≥1 adverse event [1]. If one categorizes headache as a neuropsychiatric adverse event, then neuropsychiatric effects are again the most common category of unwanted effects in users of atovaquone-proguanil, as they are in users of mefloquine.

On a point of detail, Overbosch and colleagues refer to trial “subjects” and to “compliance” with appropriate chemoprophylaxis. These terms are obsolete. In modern scientific terminology, those who consent to take part in trials are “participants,” and those consumers who are offered therapy may or may not choose to “adhere” to it. If the therapy involves use of a new or relatively untried drug, they may be wise not to do so [5].

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References


Reply

Sir—We read with interest the letter to the editor by Croft and Herxheimer [1] regarding the results of our randomized, double-blind study comparing atovaquone-proguanil with mefloquine as prophylaxis for malaria [2]. We would like to respond to the issues that specifically pertain to the study.

The primary study end point was the overall frequency of adverse events, regardless of whether they were attributable to one of the study drugs. There is a high rate of adverse events overall among travelers, so the adverse events that we considered to be related to treatment are of particular interest. When only adverse events attributed to 1 of the study drugs were evaluated, 6 subjects (1%) who were receiving atovaquone-proguanil and 24 (5%) who were receiving mefloquine discontinued their drug therapy (P = .001). Further analysis revealed that subjects who received atovaquone-proguanil also experienced fewer treatment-related neuropsychiatric adverse events than did subjects who received mefloquine (69 [14%] vs. 139 [29%], respectively; P = .001). Croft and Herxheimer [1] correctly note that we did not include headache as a neuropsychiatric adverse event; however, subjects who received atovaquone-proguanil also reported fewer treatment-related headaches than did subjects who received mefloquine (19 [4%] vs. 34 [7%], respectively; P = .040).

To assess the efficacy of an antimalarial,
a trial with a placebo-controlled comparator arm is required. However, in studies of nonimmune travelers, it is unethical to use a placebo arm; therefore, studies have been conducted with semi-immune populations. Studies in this population are well accepted as surrogates for studies of nonimmune travellers. In studies of the semi-immune population that have evaluated placebo versus atovaquone-proguanil as prophylaxis, the side effect profiles have been similar [2, 3].

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Uveitis Due to Leishmania major as Part of HAART-Induced Immune Reconstitution Syndrome in a Patient with AIDS

Although it is not an AIDS-defining illness, visceral leishmaniasis (VL) is a severe opportunistic infection in HIV-infected patients. VL is common in southern Europe [1]. Most reported cases of HIV-VL coinfection involve Leishmania infantum and generally occur when the patient’s CD4 cell count is <200 cells/mm³. Leishmaniasis amastigotes are found in atypical locations (mostly in the gastrointestinal and respiratory tracts) in severely immunocompromised patients [2]. Cutaneous lesions in patients with VL are being reported with increasing frequency; however, exclusively cutaneous leishmaniasis has remained rare in patients with HIV infection [3].

We describe a patient with AIDS and diffuse cutaneous and ganglionary leishmaniasis, without visceral involvement, due to Leishmania major. The patient developed isolated severe uveitis due to leishmaniasis while receiving highly active antiretroviral therapy (HAART), which led to the loss the right eye, despite the administration of antiparasital therapy.

In September 1997, an HIV-infected, 34-year-old man from Burkina Faso (CD4 cell count, 4 cells/mm³; plasma virus load, 381,000 RNA copies/mL) had diffuse cutaneous and ganglionar biopsy smears. The results of cultures of blood, bone marrow, and gastrointestinal tract samples were negative. PCR amplification of a repetitive noncoding sequence and additional molecular typing by sequence analysis contributed to the diagnosis of Leishmania major zymodeme MON-26 infection—the second case reported in a patient from Burkina Faso and the second case reported in association with HIV infection [4].

Treatment with amphotericin B (50 mg/day given iv for 28 days) led to complete regression of the patient’s lesions. The patient received primary prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX; 80/400 mg/d) and secondary prophylaxis with meglumine antimoniate (1200 mg im per month). Two weeks after he started receiving therapy, cultures of blood and bone marrow samples were positive for Mycobacterium avium, and treatment with clarithromycin (1 g/day), ethambutol (1200 mg/day), and rifabutin was started. The patient began to receive HAART in November 1997. Since January 1998, his plasma virus load has been <50 copies/mL.

Bilateral granulomatous anterior uveitis appeared in March 1998, when the patient’s CD4 cell count was 91 cells/mm³. Rapid resolution of the inflammation in the left eye occurred after the patient was treated with topical dexamethasone. Mild uveitis persisted in the right eye. Rifabutin-induced uveitis was suspected. In May 1998, despite an interruption in rifabutin therapy, visual acuity of the right eye quickly worsened to light perception and pain became intense. Slit-lamp examination revealed granulomatous uveitis with diffuse mutton-fat keratic precipitates, anterior chamber cell reactions (3+ [severe]), and flare reactions (3+). Intraocular pressure increased to 40 mm Hg, and examination of the fundus of the eye became impossible. A nodule was also noted in the iris and resected. No other trouble was noted.

Despite receiving treatment with IFN-γ (75 µg/day) and daily doses of lipid-associated amphotericin B (150 mg/day), the patient’s uveitis worsened, with extension of the inflammation to the orbit and scleral necrosis. This led to enucleation in December 1998, when the patient’s CD4 cell count was 198 cells/mm³. Pathological examination of the resected nodule and the resected eye showed inflammation that contained the amastigot form of Leishmania, but the results of cultures for Leishmania species remained negative. Three weeks later, treatment with lipid-associated amphotericin B and IFN-γ was stopped. Clarithromycin and ethambutol were stopped in October 1998 without relapse of mycobacterial infection. TMP-SMX was stopped in October 2000. No relapse of uveitis or dermatitis occurred during a 38-month follow-up period, during which time the patient was receiving HAART, IL-2 (started in February 2000), and meglumine antimoniate (1200 mg per month). In November 2000, the patient’s CD4 cell count was 528 cells/mm³.

The HAART-induced immune restitution syndrome, in which CD4 T cell reaction-against opportunistic pathogens oc-