High Risk of Infectious Disease Caused by Salmonellae and Mycobacteria Infections in Patients with Crohn Disease Treated with Anti–Interleukin-12 Antibody

Sir—Mannon et al. [1] reported a promising treatment of Crohn disease with anti–IL-12p40 antibody in a recent issue of the New England Journal of Medicine. This treatment had response and remission rates of 75% and 38%, respectively. Decreases in IL-12 and IFN-γ levels and TNF-α production by lamina propria mononuclear cells were documented but were not correlated with clinical response. Surprisingly, the authors did not discuss the possible risk of mycobacteriosis and salmonellosis in patients receiving anti-IL-12p40–specific antibody.

Patients with autosomal recessive complete deficiency of the p40 subunit of IL-12 (which is shared by IL-23) or the β1 chain of the IL-12/IL-23 receptor have impaired IL-12– and IL-23–dependent IFN-γ–mediated immunity. These patients have clinical disease caused by weakly virulent mycobacteria (i.e., bacille Calmette-Guérin substrains and environmental species) and nontyphoid Salmonella species and have severe forms of tuberculosis [2]. Since the first description in 1998 of inherited disorders associated with IL-12p40 and IL-12Rβ1 deficiency, the number of patients for whom these conditions were diagnosed has steadily increased, providing invaluable clinical information [3, 4]. These inherited conditions are mimicked in patients who are receiving anti–IL-12p40 antibody treatment.

Patients with Crohn disease who were treated with anti–TNF-α antibody were found to be at risk for reactivation of latent tuberculosis—an unexpected complication, given that no heritable disease associated with TNF-α–mediated immunity in humans was known at the start of clinical trials. Because these infections frequently induce intestinal manifestations, which may remain unrecognized in patients with Crohn disease, we wish to draw attention to the high risk of severe disease caused by even weakly virulent salmonellae or mycobacteria in patients with Crohn disease treated with anti–IL-12p40 antibody [5].

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2005;40:1381
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Anti–Interleukin-12 Antibody Treatment for Crohn Disease: Potential Risk of Invasive Disease Due to Mycobacteria and Salmonellae Infection

Sir—In a recent study published in the New England Journal of Medicine, Mannon et al. [1] showed that a 7-week course of
anti–IL-12 antibody therapy produced a higher clinical response rate than placebo for patients with active Crohn disease. Mannon et al. [1] stated that safety was the primary objective in their trial. We are therefore surprised by the lack of discussion concerning the most common problems associated with inherited deficiency of IL-12 signaling: invasive disease due to mycobacteria and salmonellae infection [2, 3]. The first patient with IL-12 deficiency who was described had disseminated bacille Calmette-Guérin and Salmonella serotype Enteritidis infections [4]. In an unselective study of 71 subjects with complete deficiency of the IL-12 or IL-12 receptors, we found that 55 (77%) of 71 individuals had a history of mycobacterial disease and that 31 (44%) of 71 had a history of Salmonellosis disease [5]. Fortunately, no patient in the trial by Mannon et al. [1] had either infection. This might be a consequence of incomplete IL-12 blockade, limited duration of treatment, and/or small enrollment (n = 79). Nevertheless, because disease with mycobacteria and salmonellae in IL-12–deficient subjects is often severe, is difficult to treat, and may have an unusual presentation (e.g., lymphadenitis and osteomyelitis), clinicians should be alerted to the possibility of these infections in anyone receiving anti–IL-12 antibody.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Mismanagement of Malaria among Travelers in Developing Countries

SIR—I write to respond to the article by Causer et al. [1], which reported on the poor management of exchange students and faculty from the United States who were visiting Ghana, Africa. This article is important not only for the Centers of Disease Control and Prevention, physicians offering travel advice, and potential US-based persons planning to travel to areas where malaria is endemic, but also for health practitioners in the recipient developing countries.

The first issue I would like to address is the why the health system in the United States is perceived to be better than that in Ghana. There are many reasons, one being that the US system is properly manned, as opposed to that of Ghana and other African countries, where there are low numbers of physicians and the health system is driven by medical assistants and clinical officers with only basic medical training. Unfortunately, the resilience and usefulness of such lower-level health staff is seen as a justification for the continued reliance on them [2]. It is the medical assistants and clinical officers who are told to consider all fever as malaria unless proven otherwise, yet the tools and skill to prove otherwise are rarely available.

Despite the need of developing countries to attract tourist dollars to help sustain their economies, in addition to other pressing needs, travelers’ malaria may not be perceived as a public health threat. Deaths of children <5 years of age, preterm and underweight deliveries, and poor maternal outcomes that are caused by malaria may be perceived as more important problems to spend time and resources on than the prevention and control of travelers’ malaria. Approximately 2 years ago, we experienced a situation in which our final-year medical students had little understanding of malaria prophylaxis for travelers when asked during the final viva voce examinations. We have started to correct this anomaly, although probably too late for some previous travelers.

In Malawi, the National Malaria Policy identifies travelers from nonmalarious areas, such as the United States, as a vulnerable group, and such travelers are expected to “comply with drug regimens in accordance with recommendations from their countries of origin” [3, p. ix]. In essence, our Malaria Policy does not recommend any regimen for foreign travelers and leaves that decision to physicians from the traveler’s country of origin. Another policy statement says, “Visitors traveling to Malawi without having taken any prophylaxis will be given chemoprophylaxis as set out in a brochure to be produced and updated from time to time” [3, p. ix]. It is now almost 3 years since that policy was written, and the brochure is yet to be developed. The key message is that there are pressing issues other than travelers’ malaria to attend to at the moment.

I sympathize with the health workers in Ghana who may have to work with minimal skills, poor laboratory support, and sweeping malaria guidelines. I wish to illustrate such sweeping guidelines with the Malawi Policy, which may be similar to that of Ghana: “The Government of Malawi encourages presumptive treatment for the first episode of febrile illness...