at least 1 statistically significant result by chance alone is elevated. However, our analyses were not 15 independent comparisons. We performed a univariate analysis of 5 variables to compare 2 treatment groups. To clarify the results, we stratified patients into 2 severity classes. We agree with Kraus et al. [1] that a primary end point should have been specified. We consider the primary end point to be the development of complications.

With respect to the second point made by Kraus et al. [1], we are unsure whether an outbreak situation provides an excellent opportunity to perform a randomized trial. Although focal outbreaks of legionnaires disease continue to occur worldwide, no randomized trials have been published. Several reasons could explain this. First, outbreaks are often identified retrospectively and may remain unsuspected at the moment when they occur [3]. Second, at the time that physicians initiate treatment for pneumonia, they rarely know whether the patient has legionnaires disease or, instead, has some other infectious or noninfectious pulmonary process, with the exception of patients who have a positive result of a Legionella urinary antigen test. Third, when a sudden and explosive outbreak occurs, there are a large number of affected patients who seek quick assistance at a hospital. Management of this situation requires the prioritization of care. Implicated medical personnel are usually worried about meeting the needs of patients, and every effort is made to provide high quality care.

We are in strong agreement with the third point of Kraus et al. [1]. The question of optimal therapy for legionnaires disease should be answered using appropriately designed randomized trials. Unfortunately, as stated in our article [2], the lack of randomized trials that study antibiotic treatments of this disease means that decisions about the use of antimicrobial agents have to be made on the basis of the results of laboratory studies and uncontrolled clinical studies [4–6].

We know the potential limitations of our study (i.e., that it is observational and not randomized) [2]. It is obvious that such a study cannot provide conclusive results. Despite these limitations, we believe the study provides useful data for clinicians. The large number of patients given treatment allowed us to confirm that monotherapy with levofloxacin is a safe and effective treatment for patients with legionnaires disease, including patients with severe disease [2].

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References


Progressive Multifocal Leukoencephalopathy as a Complication of Hepatitis C Virus Treatment in an HIV-Negative Patient

Sir—It is estimated that >170 million individuals are infected with hepatitis C virus (HCV) worldwide. To date, combination therapy with pegylated IFN-α 2a or 2b and ribavirin has been shown to be the most effective treatment and can eradicate HCV in >50% of affected individuals [1]. However, serious side effects are associated with this treatment, including leukopenia and a potential risk of opportunistic infections [2, 3]. We describe a patient who developed progressive multifocal leukoencephalopathy (PML) while receiving pegylated IFN-α and ribavirin therapy for HCV infection.

A 55-year-old man was admitted to the hospital because of progressive neurological symptoms. His past medical history included a diagnosis of HCV infection 4 years previously. Six months before admission, he began receiving pegylated IFN-α 2a (180 µg once a week) and ribavirin (1200 mg/day). His HCV load was 1,416,000 IU/mL. Four months later, he developed progressive multifocal leukoencephalopathy (PML) while receiving pegylated IFN-α and ribavirin therapy for HCV infection.

At admission, neurological examination showed left homonymous hemianopia and left mild hemiparesis. Later, the patient developed dysarthria, dysphagia, and left-side weakness. Laboratory tests revealed a hemoglobin level of 12.5 g/dL and leukopenia (leukocyte count, 3600 cells/μL). The total T cell count was 516 cells/mm³, and the absolute CD4+ cell count was 144 cells/mm³. Findings of serological tests for HIV-1 and HIV-2 were negative. HCV RNA was undetectable. Findings of
cranial MRI showed disseminated hyperintense lesions on fluid attenuation inversion recovery (FLAIR) (figure 1A) and T2-weighted images in the white matter of both hemispheres, the splenium of the corpus callosum, the right thalamus, the pons, and the right cerebellar hemisphere. No contrast enhancement or mass effect was observed. Pegylated IFN-α and ribavirin therapy was discontinued. The patient underwent a stereostatic brain biopsy, and histological examination of the specimen showed areas of demyelination in the white matter associated with the presence of atypical reactive astrocytes and oligodendroglial cells with enlarged nuclei. Results of immunostaining for JC virus (JCV) were positive, and a diagnosis of PML was established (figure 1B). The patient received a 5-day course of intravenous cytarabine (2 mg/kg) [3], and, on the basis of a recent discovery that JCV entry into cells is mediated by 5HT2A receptors [4], empiric treatment with mirtazapine (a serotonin receptor antagonist) at a dosage of 15 mg/day was started [5]. Despite these treatments, the patient’s neurological condition worsened, and he died 5 months after diagnosis.

PML is a devastating disease of the CNS caused by JCV and is usually seen in patients with severe cellular immunodeficiency, such as those with AIDS, leukemia, or an organ transplant [6]. This disease has been previously described in association with HCV infection [7, 8], although the precise mechanism of JCV reactivation in this situation is unclear. In the present case, the patient’s immunosuppression was most likely caused by leukopenia secondary to IFN-α therapy. Leukopenia is more prevalent among patients receiving pegylated IFN-α than among those receiving standard IFN-α (20% vs. 5%) [2]. Additionally, in a recent study of patients with HIV-HCV coinfection, decreased levels of cytomegalovirus-specific and HIV-specific T helper cells were observed during treatment with IFN-α and ribavirin, suggesting that this therapy might compromise virus-specific immune responses [9].

In conclusion, treatment with pegylated IFN-α and ribavirin for HCV infection can lead to severe immunosuppression and the development of PML. With the increasing use of this combination therapy worldwide, clinicians should be aware of this possibility and should follow WBC counts to prevent fatal opportunistic infections.

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Treatment of Brain Abscess Due to *Listeria monocytogenes*

Str—Comparative studies of antimicrobial treatments for human listeriosis are lacking, as are studies to define appropriate treatment duration for listerial infection. Case reports are useful to suggest newer agents that might have efficacy against human listeriosis.

In the report by Leiti et al. [1], a claim is made for cure of listerial brain abscess using linezolid and rifampin in a patient who was able to complete standard therapies because of allergic reactions to both ampicillin and trimethoprim-sulfamethoxazole. The linezolid and rifampin regimen was initiated after the patient had completed 76 days of parenteral ampicillin treatment.

Most authorities recommend 6–8 weeks of antimicrobial treatment for listerial brain abscess [2, 3]. Many patients who are successfully treated for listerial brain abscess still have visible lesions on CTs of the brain at the end of the 6–8 week course [4]. It is clearly not necessary to treat abscesses—whether located in the brain, lung, liver, or elsewhere—until complete radiographic resolution of lesions.

Leiti et al. [1] reasonably considered the use of linezolid on the basis of in vitro and animal model data. Rifampin was added to the treatment regimen on the basis of in vitro activity. The utility of adding rifampin to other agents in the treatment of listeriosis is unclear. In vitro studies have shown synergism in some instances [5], but in others, antagonism has been demonstrated [6–8]. In an animal model of listerial meningitis, treatment with the combination of rifampin and ampicillin was no more effective than treatment with ampicillin alone [9].

It is plausible—and, I believe, likely—that in a patient who demonstrated clinical and radiographic improvement while receiving ampicillin therapy, treatment with ampicillin alone for 76 days was curative and that the CT findings lagged behind the clinical cure. Linezolid may prove to be a useful agent for treatment of listeriosis, but caution must be exercised before assuming its value on the basis of this report. The economic cost of 107 days of linezolid therapy must have been consid-

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