Moxifloxacin Monotherapy in Severe Pneumonia: Do We Really Need It?

To The Editor—The study by Torres et al. [1] possibly has loosened the brick in the wall of treatment of severe pneumonia. This study is unlikely to have an impact on the landscape of medical opinion about the equivalency of moxifloxacin monotherapy. The strength of the study is weakened by some recent conflicting outcomes. In a parallel publication describing patients hospitalized with community-acquired pneumonia who, during the first 3 days of hospitalization, were intravenously given levofloxacin daily at a dosage of 750 mg (instead of 1g [1]) or were intravenously given moxifloxacin daily at a dosage of 400 mg, initial treatment with levofloxacin (750 mg) was associated with a significantly shorter mean length of hospital stay and improved outcomes, compared with treatment with moxifloxacin (400 mg) [2].

In another study, patients with severe pneumonia who were receiving mechanical ventilation were given fluoroquinolone monotherapy, which was not associated with superior outcomes. Fluoroquinolone alone has not been established as a treatment of choice for severe community-acquired pneumonia [3]. “Combined medication with a macrolide and third-generation cephalosporin may be preferred over fluoroquinolones as first-line therapy of hospitalized patients with community-acquired pneumonia to minimize the development of multiresistant nosocomial Gram-negative bacilli” [4, p. 329].

Torres et al. [1] also confirmed the non-inferiority of moxifloxacin in the intention-to-treat population. The intention-to-treat principle overlooks the fact that patients may not always receive all their allotted treatment. Intention-to-treat analysis of noninferiority trials is not conservative, because the inclusion of patients who violate the protocol will tend to minimize differences between study arms, thereby increasing the possibility of results showing noninferiority.

Extensively drug-resistant tuberculosis (TB) is defined by resistance to any fluoroquinolones and at least 1 of 3 injectable second-line antitubercular drugs in addition to the resistance that defines multidrug-resistant TB (i.e., resistance to isoniazid and rifampicin). Thus, resistance to any fluoroquinolone is an essential criterion of extensively drug-resistant TB. The fluoroquinolones have excellent in vitro and in vivo activity against Mycobacterium tuberculosis [5]. High-level phenotypic resistance to fluoroquinolones among clinical isolates of M. tuberculosis, which appears to be caused predominantly by gyrA mutations, exhibits cross-resistance to all 6 important fluoroquinolones [6]. Patients with past exposure to any of the fluoroquinolones are prone to develop cross-resistance to other fluoroquinolones. The newer fluoroquinolone moxifloxacin is an alternative anti-TB drug, on the basis of results from a large clinical trial [7]. Patients who receive fluoroquinolones before starting standard anti-TB treatment have poorer outcomes than do patients who do not receive fluoroquinolones, possibly because of the emergence of drug-resistant TB [8, 9]. The global threat of extensively drug-resistant TB has revealed weaknesses in TB control and also has revealed the lack of new tools for TB control [10]. No better drugs are in the pipelines, and we are left with few bacteriostatic antitubercular drugs. By misusing the fluoroquinolones, we are facilitating an increase in the emergence of extensively drug-resistant TB. The future with regard to multidrug-resistant TB and extensively drug-resistant TB in the coming decades looks to be grim, because we are rapidly losing very effective drugs, like quinolones, for their management. Fluoroquinolones should not be the first-line antibiotics in areas where TB is endemic. We should treat severe pneumonia, but we must find better ways to prevent the emergence of extensively drug-resistant TB.

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Prasanta Raghag Mohapatra, Monica Gupta, and Ashok K. Janmeja
Government Medical College and Hospital, Chandigarh, India

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Reprints or correspondence: Dr. Prasanta Raghab Mohapatra, Government Medical College and Hospital Chandigarh, Pulmonary Medicine, Sector-32, Chandigarh, 160012, India (prmohapatra@hotmail.com).

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Reply to Mohapatra et al.

To The Editor—We thank Dr. Mohapatra and colleagues [1] for their response to our article, and we concur with the essence of their argument, which is that fluoroquinolones are a valuable resource that should be used when necessary and not used when unnecessary. However, the purpose of our study was not to encourage liberal use of fluoroquinolones in the treatment of serious community-acquired pneumonia (CAP) but was to determine whether sequential intravenous and oral moxifloxacin monotherapy (400 mg once daily) is safe and effective for hospitalized patients who have CAP with pneumococcal severity index classes III–V. In our large, prospective, randomized, double-blind study, moxifloxacin was indeed noninferior to a combination of ceftriaxone (2 g once daily) plus sequential intravenous and oral levofloxacin (500 mg twice daily) [2]. We did this study because although fluoroquinolones are recommended by current international guidelines for the treatment of CAP [3], there is no general agreement as to whether they can be used to treat moderate-to-

severe CAP requiring hospitalization. Mohapatra et al. [1] make the point that there have been other studies of the use of fluoroquinolone monotherapy for CAP. However, it should be noted that the study by Schein and colleagues [4], which showed a small reduction (5.8 vs. 6.4 days) in mean length of hospital stay among patients who had received intravenous levofloxacin versus intravenous moxifloxacin during the first 3 days of hospital treatment, was a retrospective database study with no prospective stratification by severity. The study by Lery et al. [5] was an open-label study in which it was concluded that levofloxacin (500 mg every 12 h) was at least as effective as cefotaxime plus ofloxacin for the treatment of CAP in a subset of patients without septic shock who required admission to the intensive care unit. In that study, there was no prospective stratification by Fine score. The study by Zer vos et al. [6] was also an open-label study. Although we accept the shortcomings of all studies that are powered only to demonstrate noninferiority of one drug compared with another, our study had the benefit of being rigorously controlled. Noninferiority was demonstrated in both the per-protocol and the intention-to-treat analyses.

We do not agree that appropriate use of intravenous fluoroquinolones for patients with serious pneumonia treated in the hospital will inevitably encourage the spread of extensively drug-resistant tuberculosis. In most populations, the incidence of hospitalization with pneumonia that is sufficiently severe to require use of intravenous antibiotics is relatively low. Theoretically, treatment of CAP with fluoroquinolone monotherapy for an individual patient who has unrecognized latent or active tuberculosis might encourage the generation of resistance, but we would hope that clinicians would be alert to this possibility, especially in regions where tuberculosis is endemic. In contrast, inappropriate use of orally administered fluoroquinolones in community practices should always be discouraged, as is the case for all antibiotics. In this regard, the recent article by Jeon et al. [7] is of considerable interest. They investigated risk factors for presentation with extensively drug-resistant tuberculosis and found that the strongest predictors were the cumulative duration of prior therapy for tuberculosis and the number of different second-line drugs used previously. The occurrence of ofloxacin-resistant Mycobacterium tuberculosis was most common among individuals with no prior exposure to fluoroquinolones, although the difficulties inherent in the study of the relationships between antibiotic resistance and community prescribing habits should be acknowledged [8].

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Robert C. Read,¹ Javier Garau,² and Antoni Torres²

¹Section of Infection and Immunity, Sheffield University Medical School, Sheffield, United Kingdom; and ²Servei de Pneumologia i Allergia Respiratoria, Institut Clínic del Tòrax, Hospital Clinic de Barcelona, and ³Hospital Mútua de Terrassa, University of Barcelona, Barcelona, Spain

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