Moxifloxacin Treatment of Tuberculosis

We are pleased to see that the study of Pletz et al. (6) confirms our earlier observations that moxifloxacin is active in patients with pulmonary tuberculosis with positive sputum smears (3). However, some of their results differ from ours, and we believe that this is due to the method that they adopted. In our study, we recruited groups of 15 subjects (3) and found that moxifloxacin was significantly less active than isoniazid when the time to reduce the viable bacillus count by 50% (vt50) was calculated (1), but like Pletz et al., we found no significant difference between the two drugs when early bactericidal activity (EBA) was calculated (3, 5, 6). The most important reason for this difference is the number of patients in the groups recruited by Pletz et al. is small, and thus, the absence of a statistically significant difference cannot be construed as indicating biological equivalence. Second, the EBA methodology that Pletz et al. use is a variation of the standard method (4), which calculates the value for EBA over 5 days rather than 2 days and has limited power to distinguish between different drugs (5). The EBA methodology produces large confidence intervals, and for this reason, studies have shown that the results for isoniazid are poorly reproducible between centers (7). Third, by grouping the data from different patients together, the errors are enlarged. Viable counts of mycobacteria from sputum vary enormously between patients (often by more than 1 order of magnitude) and from day to day. As the EBA measure is half (or a fifth) of the ratio between the day 0 and day 2 (or day 5) values expressed logarithmically, small variations in sputum mycobacterial viable counts result in large variations in the EBA values as found in the study of Pletz et al.

We agree with the authors’ strategy of measuring the sputum mycobacterial viable count over 5 days, but by recording only three values and not calculating a regression line, they lose much of the benefit of the longer period of observation. As discussed in our previous papers (1–3), by taking measurements daily over the 5-day trial period, it is possible to use nonlinear regression, which permits discrepant values to be identified and removed. Moreover, vt50 has been shown to be a measure which is comparable in different countries (2).

For these reasons, we believe that, although this paper is useful in that it confirms that moxifloxacin is bactericidal in patients with pulmonary tuberculosis with positive smears, its conclusion that this compound is as active as isoniazid is misleading. Further studies are required to understand the optimal use of new highly active quinolones, such as moxifloxacin, in pulmonary tuberculosis and whether they add to the activity of isoniazid.

REFERENCES


Roland Gosling*
Stephen Gillespie
Department of Medical Microbiology
Royal Free and University College
Pond Street
London NW3 2PF
United Kingdom
*Phone: 44 2077940500
Fax: 44 2077940333
E-mail: rolygos@aol.com

Authors’ Reply

Both the study of Gosling et al. (1) and our study (4) used isoniazid as a comparator to moxifloxacin, but different analyses were performed in the two studies. Our study was based on the classical parameter of EBA over 5 days. When the EBAs of moxifloxacin and isoniazid were compared, there was no statistically significant difference. Our conclusion was that the activity of moxifloxacin is comparable—we did not write equal—to that of isoniazid. This was not based on the absence of a statistically significant difference but rather on the following data. (i) The reduction in the number of CFU per milliliter over 5 days was more pronounced in the moxifloxacin group than in the isoniazid group (from 14±17.2 to 0.7±0.9 CFU/ml for moxifloxacin versus 11.5±8.7 to 1.2±0.15 CFU/ml for isoniazid). (ii) The EBA of moxifloxacin was greater than the EBA of isoniazid (0.273 for moxifloxacin and 0.209 for isoniazid). (iii) Calculating 95% confidence intervals revealed that moxifloxacin had at least 61.6% of the antimycobacterial activity of isoniazid despite the deviation of the data.

Our conclusion is also supported by results of animal studies which showed that the bactericidal activity of moxifloxacin is comparable to that of isoniazid (2, 3). Furthermore, Nuerberger et al. showed in a mouse model that the replacement of isoniazid by moxifloxacin in the standard regimen increased the activity dramatically, resulting in earlier culture negativity (E. Nuerberger, T. Yoshimatsu, S. Tyagi, W. Bishai, and J. Grosset, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1035, 2003).

In conclusion, we agree with Gosling et al. that the discrepancy in our studies regarding the comparison of moxifloxacin to isoniazid is caused by the different parameters (EBA versus vt50) used, but on the basis of our results and the results of several animal studies, we maintain that moxifloxacin and isoniazid have comparable activities. However, larger studies using clinical endpoints, such as time to culture negativity, are required to identify the drug with the best clinical activity.
REFERENCES


Mathias W. R. Pletz*
Department of International Health
Rollins School of Public Health
Emory University
Atlanta, Georgia

Hartmut Lode
Department of Chest and Infectious Diseases
Chest Hospital Heckeshorn
Berlin, Germany

*Phone: (404) 727-3984
Fax: (404) 712-8419
E-mail: mpletz@sph.emory.edu