

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/152723>

Please be advised that this information was generated on 2017-12-05 and may be subject to change.

CORRESPONDENCE



Shorter Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

TO THE EDITOR: Gillespie et al. (Oct. 23 issue)¹ report that two moxifloxacin-containing regimens for the treatment of tuberculosis were not effective with a shortened treatment period of 4 months. The authors used a moxifloxacin dose of 400 mg per day, which may have contributed to the unfavorable results. Rifampin decreases the average exposure to moxifloxacin (assessed according to the area under the curve [AUC]) by approximately 30%,² which can be compensated for by an increase in the dose of moxifloxacin.³ In addition, preclinical data combined with pharmacokinetic and pharmacodynamic modeling showed that a higher moxifloxacin dose, of 800 mg per day, is likely to achieve better *Mycobacterium tuberculosis* microbial killing and suppression of drug resistance.⁴ Limited data have shown that moxifloxacin at a dose of 800 mg can be given safely.^{3,5} The inclusion of moxifloxacin

drug exposure as a covariate would have been of additional value, considering that the ratio of the AUC to the minimum inhibitory concentration is the driver of moxifloxacin efficacy and that the AUC for moxifloxacin can vary among patients by a factor of 7.⁶ Such a pharmacokinetic and pharmacodynamic analysis could have shown whether the results of this trial could have been explained by a drug exposure to moxifloxacin that was too low.

Jan-Willem Alffenaar, Pharm.D., Ph.D.

University of Groningen
Groningen, the Netherlands
j.w.c.alffenaar@umcg.nl

Tawanda Gumbo, M.D., Ph.D.

University of Texas Southwestern Medical Center
Dallas, TX

Rob Aarnoutse, Pharm.D., Ph.D.

Radboud University Medical Center
Nijmegen, the Netherlands

No potential conflict of interest relevant to this letter was reported.

1. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014;371:1577-87.
2. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007;45:1001-7.
3. Ruslami R, Ganiem AR, Dian S, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. *Lancet Infect Dis* 2013;13:27-35.
4. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis*, by use of an in vitro pharmacodynamic infection model and mathematical modeling. *J Infect Dis* 2004;190:1642-51. [Erratum, *J Infect Dis* 2004;190:2059.]
5. Alffenaar JW, van Altena R, Bökkerink HJ, et al. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. *Clin Infect Dis* 2009;49:1080-2.
6. Pranger AD, van Altena R, Aarnoutse RE, et al. Evaluation of moxifloxacin for the treatment of tuberculosis: 3 years of experience. *Eur Respir J* 2011;38:888-94.

DOI: 10.1056/NEJMc1414718

THIS WEEK'S LETTERS

- 576 Shorter Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis
- 578 Monocarboxylate Transporter 1 Deficiency and Ketone Utilization
- 579 Management of Withdrawal Delirium
- 581 A Woman with Fever, Pharyngitis, and Double Vision
- 582 Elevated Sweat Chloride Levels Due to Arsenic Toxicity
- 584 West African Ebola Epidemic after One Year
- 587 Ebola in Freetown Area, Sierra Leone

TO THE EDITOR: The Rapid Evaluation of Moxifloxacin in Tuberculosis (REMoxTB) study did not show the noninferiority of two moxifloxacin-containing regimens, shortened to 4 months, as compared with a control regimen, for the treatment of tuberculosis. Failures during the treatment phase occurred in less than 2% of patients. More unfavorable outcomes in the two groups with shorter regimens, as compared with the control group, were driven by more relapses after conversion to culture-negative status after the end of treatment. Relapse strains were those shown to be identical on 24-locus mycobacterial-interspersed-repetitive-unit (MIRU) analysis. First, whole-genome sequencing enables the differentiation between relapse and reinfection with greater resolution than MIRU analysis.¹ Second, differentiation between relapse and reinfection with the same strain from a close relative² might be impossible if the diversity of circulating clones is limited.³ Reinfection with the same strain from a close relative can occur frequently⁴ in areas with a high prevalence of tuberculosis (where this study was conducted). The results could be different in areas with a low prevalence of tuberculosis.

Pierre O. Sellier, M.D., Ph.D.

Philippe Clevenbergh, M.D., Ph.D.

Jean-François Bergmann, M.D., Ph.D.

Hôpital Lariboisière

Paris, France

pierre.sellier@lrb.aphp.fr

No potential conflict of interest relevant to this letter was reported.

1. Bryant JM, Harris SR, Parkhill J, et al. Whole-genome sequencing to establish relapse or re-infection with *Mycobacterium tuberculosis*: a retrospective observational study. *Lancet Respir Med* 2013;1:786-92.
2. Walker TM, Ip CL, Harrell RH, et al. Whole-genome sequencing to delineate *Mycobacterium tuberculosis* outbreaks: a retrospective observational study. *Lancet Infect Dis* 2013;13:137-46.
3. Niemann S, Köser CU, et al. Genomic diversity among drug sensitive and multidrug resistant isolates of *Mycobacterium tuberculosis* with identical DNA fingerprints. *PLoS One* 2009;4(10):e7407.
4. Wood R, Lawn SD, Caldwell J, Kaplan R, Middelkoop K, Bekker LG. Burden of new and recurrent tuberculosis in a major South African city stratified by age and HIV-status. *PLoS One* 2011;6(10):e25098.

DOI: 10.1056/NEJMc1414718

THE AUTHORS REPLY: We agree that an increased dose of moxifloxacin might be of interest and has proved to be valuable in patients with limited treatment options. We aimed to register a new shortened regimen for susceptible disease, and our approach was to repurpose an existing licensed preparation at its approved dose. This strategy has the advantage that the safety charac-

teristics of all the regimen components were well understood. Because the proposed 800-mg dose is outside the current license and the adverse-event profile among an unselected population is unpredictable, the incorporation of such a dose would require intensive preclinical and clinical testing before it could be used in a regulatory phase 3 study. Moreover, as shown in Table S3B in the Supplementary Appendix, available with the full text of the article at NEJM.org, patients receiving moxifloxacin who had a higher body-mass index (BMI) had a better outcome than did those with a low BMI, which argues against the supposition that a higher dose might have been successful. This result contrasts with the OFLOTUB study, in which the opposite was found.¹

Next-generation whole-genome sequencing provides increased granularity to differentiate relapse from reinfection, as we found in a subset of patients from the REMoxTB cohort.² Among the many sensitivity analyses that we performed, we evaluated the effect of calling all reinfections “unfavorable” (instead of “not able to be assessed”), which resulted in proportions of unfavorable outcomes of 17%, 25%, and 26% in the control, isoniazid, and ethambutol groups, respectively. Thus, this different interpretation did not alter the overall outcome of the study. Whole-genome sequencing will have an important effect on our understanding of tuberculosis infection, and these insights will have consequences for the design of clinical trials. Similarly, enumerating the number of mixed infections and improving recognition of laboratory cross-contamination could reduce sample size.

Stephen H. Gillespie, M.D., D.Sc.

University of St. Andrews

St. Andrews, United Kingdom

shg3@st-andrews.ac.uk

Carl M. Mendel, M.D.

TB Alliance

New York, NY

Patrick P.J. Phillips, Ph.D.

University College London

London, United Kingdom

for the REMoxTB Consortium

Since publication of their article, the authors report no further potential conflict of interest.

1. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014;371:1588-98.
2. Bryant JM, Harris SR, Parkhill J, et al. Whole-genome sequencing to establish relapse or re-infection with *Mycobacterium tuberculosis*: a retrospective observational study. *Lancet Respir Med* 2013;1:786-92.

DOI: 10.1056/NEJMc1414718