Early bactericidal activity of new drug regimens for tuberculosis

Andreas Diacon and colleagues (Sept 15, p 986)[1] have undertaken a most needed study with a new treatment regimen for tuberculosis: PA-824, bedaquiline, pyrazinamide, and moxifloxacin. However, sputum sensitivity testing was done only for these four drugs. The sensitivity to isoniazid and rifampicin was not known. Without including patients resistant to isoniazid and rifampicin, the effectiveness of the new regimen in patients with multidrug-resistant (MDR) tuberculosis can only be guessed at. The pharmacokinetics and probability of pharmacodynamic target attainment (ratio of area under the time curve to minimum inhibitory concentration) are likely to be altered in patients with MDR tuberculosis.[2]

Thus, current clinical speculation about the effectiveness of the new regimen on MDR tuberculosis seems to be overoptimistic and should be based on the outcome data of a randomised clinical trial in patients with MDR tuberculosis. Such patients must be included in future clinical trials of the new regimen to confirm its efficacy.

We declare that we have no conflicts of interest.

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1 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14 day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; **380:** 986–93.
2 Chigutsa E, Meredith S, Wiesner L, et al. Population pharmacokinetics and pharmacodynamics of ofloxacin in South African patients with multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2012; **56:** 3857–63.

New drugs for tuberculosis, in isolation, are of little use to patients with multidrug-resistant (MDR) forms of the disease. Drug combinations are needed, and Andreas Diacon and colleagues[1] are to be congratulated for acting on this need in their ground-breaking study.

However, to claim that PA-824, moxifloxacin, and pyrazinamide can cure MDR tuberculosis is a leap of faith at best. The types of strain encountered in many parts of the world are seldom resistant to just isoniazid and rifampicin. At the Hinduja Hospital in Mumbai, India, we have been treating MDR tuberculosis for the past two decades, and have witnessed first hand the relentless amplification of our patients' resistance patterns from MDR to extensively drug-resistant to totally drug-resistant tuberculosis.[2,3] The fluoroquinolones are among the most widely prescribed groups of antibiotics in India, and around 50% of all MDR tuberculosis strains we see are resistant even to moxifloxacin.[4] An analysis of our last 100 patients' drug susceptibility reports showed that a third of these patients were resistant to both pyrazinamide and moxifloxacin (in addition to isoniazid and rifampicin). Thus to give Diacon and colleagues' triple-drug regimen to these patients with MDR tuberculosis would be tantamount to monotherapy with PA-824, ensuring that resistance rapidly develops to yet another new and promising agent.

Great caution will need to be exercised in treating patients with the extreme forms of resistance almost routinely encountered in some MDR hot spots. New regimens with three novel agents are what these patients desperately need to cure them of their disease.

I declare that I have no conflicts of interest.

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1 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14 day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; **380:** 986–93.
2 Udwadia ZF. MDR, XDR, TDR tuberculosis: ominous progression. *Thorax* 2012; **67:** 286–88.
3 Udwadia ZF, Amale RA, Abjani KK, et al. Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 2012; **54:** 579–81.
4 Agarwal D, Udwadia ZF, Rodrigues C, et al. Increasing incidence of fluoroquinolone resistant Mycobacterial tuberculosis in Mumbai, India. *Int J Tuberc Lung Dis* 2009; **13:** 79–83.


Corbis

Andreas Diacon and colleagues[1] report equivalent 2-log reductions in sputum colony-forming units (CFU) during 2 weeks of tuberculosis treatment with PA-824, moxifloxacin, and pyrazinamide versus isoniazid, rifampicin, pyrazinamide, and ethambutol. We question the significance of the finding.

Two studies[2,3] (totalling 64 patients) describe the effects on sputum CFU of well characterised tuberculosis drug combinations over 14 days (figure, right). One[2] found equal 2-log reductions with the combination of isoniazid plus rifampicin versus isoniazid alone. A second[3] found the combination of isoniazid, rifampicin, streptomycin, and pyrazinamide to be at the threshold of superiority over the combination of isoniazid, streptomycin, and thiacetazone, but only during days 2–28; equal 2-log reductions occurred at earlier timepoints. Isoniazid, rifampicin, streptomycin, and pyrazinamide given for 6 months cures tuberculosis with a relapse rate of 3%.[4] By contrast, 22% of patients relapse if similarly treated with isoniazid, streptomycin, and thiacetazone; 18 months of treatment are required to reduce the relapse rate to 3%.[5]

The failure of 2-week trials to capture clinically important differences between groups of prospective controlled trials seems not to arise from variability, because independent similarly sized studies of 7–14 days' duration show very similar results (figure, left).[2,3,6,7] It seems instead to be an intrinsic limitation of

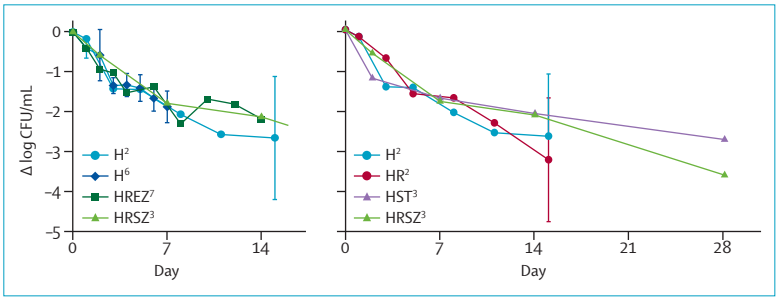

Figure: **Published trials of quantitative sputum microbiology in patients with pulmonary tuberculosis of 7–28 days' duration**

Left: Across-trial comparisons of similar treatments, showing similar results. Right: Within-trial comparisons of distinct treatments, showing similar results during first 14 days. H=isoniazid; R=rifampicin, E=ethambutol; S=streptomycin, Z=pyrazinamide; T=thiacetazone. CFU=colony-forming units.

short-duration trials. The concept that such trials can inform the required duration of treatment is unsupported by clinical data.

RSW is an employee and shareholder of Pfizer. CN is an employee and Chief Executive Officer of Sequella.

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1 Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. 14 day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; **380:** 986–93.

2 Wallis RS, Phillips M, Johnson JL, et al. Inhibition of INH-induced expression of *M tuberculosis* antigen 85 in sputum: a potential surrogate marker in TB chemotherapy trials. *Antimicrob Agents Chemother* 2001; **45:** 1302–44.

3 Brindle R, Odhiambo J, Mitchison DA. Serial counts of *Mycobacterium tuberculosis* in sputum as surrogate markers of the sterilising activity of rifampicin and pyrazinamide in treating pulmonary tuberculosis. *BMC Pulm Med* 2001; **1:** 2.

4 East and Central African-British Medical Research Council. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis. *Tubercle* 1983; **64:** 153–66.

5 East African-British Medical Research Councils. Results at 5 years of a controlled comparison of a 6-month and a standard 18-month regimen of chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1977; **116:** 3–8.

6 Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC 207 in pulmonary tuberculosis. *Antimicrob Agents Chemother* 2008; **52:** 2831–35.

7 Diacon AH, Dawson R, Hanekom M, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. *Antimicrob Agents Chemother* 2010; **54:** 3402–07.

Authors' reply

We agree with Prasanta Mohapatra and colleagues and Zarir Udwadia that the efficacy of the PA-824-moxifloxacin-pyrazinamide regimen must be shown in clinical trials that include patients with multidrug-resistant (MDR) tuberculosis. Obviously, this regimen cannot be appropriate for all such patients because their isolates can harbour resistance beyond that to isoniazid and rifampicin, including moxifloxacin and pyrazinamide. A study of PA-824-moxifloxacin-pyrazinamide over 8 weeks, which includes patients with MDR tuberculosis susceptible to moxifloxacin and pyrazinamide, is currently underway (ClinicalTrials.gov identifier NCT01498419). The results of our published study[1] suggest that patients who receive PA-824-moxifloxacin-pyrazinamide, but neither isoniazid nor rifampicin, hitherto regarded as essential, will not be therapeutically disadvantaged in the ongoing study.

Udwadia shares our enthusiasm for constructing a combination of at least three novel chemical entities that can be combined safely and to which resistance would be unlikely to occur naturally. Such a universal regimen would treat all forms of tuberculosis, thereby obviating the necessity for susceptibility testing for drugs currently in use. Until such a regimen becomes available, it remains important to use several drugs to which a patient's *Mycobacterium tuberculosis* isolate is sensitive, and susceptibility testing is essential for the correct treatment of all drug-resistant tuberculosis.

Robert Wallis and Carol Nacy seem to misunderstand the role of early bactericidal activity studies in our development pathway. All our current first-line antituberculosis drugs and regimens have shown efficacy, when appropriately tested, in mouse models, in 2-week early bactericidal activity studies, in 2-month clinical trials, and in long-term clinical trials.[2,3] The mouse relapse model forms the initial basis for constructing any new regimen to advance into clinical evaluation. Hypotheses based on mouse studies must then continue to be supported by findings in short-term, intermediate-term, and long-term trials to remain viable. Our 2-week trial of the early bactericidal activity of PA-824-moxifloxacin-pyrazinamide[1] represents the first step in this systematic process. It remains an open, but extremely important, question as to exactly how well data based on sputum sampling in the early phase of treatment (whether for 2 weeks or for 2 months) predict long-term outcomes; unfortunately there is no single biomarker or short-term study to provide definitive evidence of the necessary treatment duration to achieve cure.[4] We believe that only after rigorous, methodical studies, such as our completed 2-week trial,[1] our ongoing 2-month trial, and hopefully a future phase 3 trial, will we better understand the predictive capability of short-term clinical studies.

We declare that we have no conflicts of interest.

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