# Should gatifloxacin be included in the model list of essential medicines?

*To the Editor:*

We read with great interest the paper by Falzon *et al.* [1], which reported that gatifloxacin and moxifloxacin have been recommended by the World Health Organization (WHO) for both longer and shortened regimens in the treatment of rifampicin-resistant (RR) and multidrug-resistant (MDR) tuberculosis (TB). Gatifloxacin and moxifloxacin belong to the latest generation of fluoroquinolones that have comparable early bactericidal and sterilising activity in the treatment of TB. Gatifloxacin has been used in the treatment of bacterial infections and MDR-TB [2]. Gatifloxacin was also used in a clinical trial (OFLOTUB) comparing a 4-month gatifloxacin-based regimen with the standard 6-month regimen for the treatment of rifampicin-susceptible pulmonary TB [3]. The gatifloxacin-based shortened treatment was highly effective, achieving >84% treatment success among MDR-TB patients in Bangladesh, Cameroon and Niger [2].

On May 4, 2006, Bristol Myers Squibb announced that it was withdrawing gatifloxacin from the market because an observational study reported that gatifloxacin was associated with dysglycaemia in the treatment of pneumonia among the elderly [2]. Consequently, moxifloxacin replaced gatifloxacin in the treatment of MDR-TB in observational studies [4] and in a clinical trial (STREAM) comparing a 9-month moxifloxacin-based regimen with WHO recommended 20–24-month regimens.

Noting that gatifloxacin was not included in the WHO Essential Medicines List (EML), the Global TB Programme and the Global Drug Facility submitted an application for gatifloxacin to be included in the updated EML as an alternative to levofloxacin and moxifloxacin [5], which is an essential step in making gatifloxacin available for the treatment of RR/MDR-TB. Unfortunately, gatifloxacin was not included in the 20th WHO EML or the sixth WHO EML for Children updated in March 2017, due mainly to opposition from two internationally renowned organisations [5]. Concerns raised included that 1) gatifloxacin may cause dysglycaemia, 2) other fluoroquinolones (for example, moxifloxacin) are safer alternatives and 3) there was no known quality-assured product from generic manufacturers. These were important concerns. However, we would like to respectfully point out that concerns about gatifloxacin in terms of safety and efficacy should be balanced against those about moxifloxacin, and that there remains uncertainty about gatifloxacin and moxifloxacin in the treatment of MDR-TB.

First, moxifloxacin may not necessarily be safer than gatifloxacin. Park-Wyllie *et al.* [6] reported that gatifloxacin, but not moxifloxacin, was significantly associated with dysglycaemia [2]. This was not supported by findings from: 1) a recent study from Taiwan, which reported that moxifloxacin was associated with both hyperglycaemia and hypoglycaemia [7]; and 2) the OFLOTUB trial, which reported that the vast majority of the patients had normal blood glucose levels throughout the course of treatment, and that there was no significant difference in the risk of hyperglycaemia between the 4-month gatifloxacin-based regimen and the standard 6-month regimen [3]. It might be appropriate to indicate that both moxifloxacin and gatifloxacin may potentially cause dysglycaemia and close monitoring is needed in the use of either. Of note is that dysglycaemia was manageable and reversible in all cases treated with gatifloxacin in Bangladesh, Cameroon and Niger [2]. Another major issue was not mentioned: both moxifloxacin and gatifloxacin have been reported to be associated with ECG QT prolongation. The OFLOTUB study reported that a 4-month gatifloxacin-based regimen did not have a sizable risk of QT prolongation [8]. But the psychological fear of QT prolongation with moxifloxacin has resulted in the use of normal-dose moxifloxacin in a recent observational study on the shortened MDR regimen, which



**Cite this article as:** Chiang C-Y, Trébucq A, Piubello A, *et al.* Should gatifloxacin be included in the model list of essential medicines? *Eur Respir J* 2018; 51: 1702329 [https://doi.org/10.1183/13993003.02329-2017].

observed a higher frequency of treatment failure and acquisition of resistance to fluoroquinolones than was observed in Bangladesh using high-dose gatifloxacin [4].

Second, moxifloxacin may not necessarily be quite as efficacious as gatifloxacin even if both give excellent results for short-course MDR-TB regimens. A multi-country surveillance project reported that of the 282 ofloxacin-resistant *Mycobacterium tuberculosis* strains, 7% were resistant to moxifloxacin but only 2% were resistant to gatifloxacin [9]. Another study has reported that the minimum inhibitory concentration distribution ratio of gatifloxacin to ofloxacin is higher than that of moxifloxacin to ofloxacin [10]. Meta-analyses of the effectiveness and safety of standardised shorter regimens for MDR-TB reported that moxifloxacin was not associated with hyperglycaemia. However, moxifloxacin was significantly associated with greater odds of failure/relapse compared to gatifloxacin [11].

Finally, there is interest among generic manufacturers to produce gatifloxacin for MDR-TB should countries show interest (personal communication; E. Jaramillo, Global TB Programme, WHO, Geneva, Switzerland). It might be easier to use gatifloxacin than moxifloxacin in resource-limited settings where the burden of MDR-TB is high but the capacity for monitoring and management of QT prolongation is limited, and monitoring plasma glucose is required with either medication anyway. Moxifloxacin may not necessarily be a valid alternative to gatifloxacin, and therefore we would like to call for support to endorse the inclusion of gatifloxacin in the WHO EML.

**Chen-Yuan Chiang[1,2,3], Arnaud Trébucq[1], Alberto Piubello[1,4], Hans L. Rieder[5,6] and Armand Van Deun[1,7]**
[1]International Union Against Tuberculosis and Lung Disease, Paris, France. [2]Division of Pulmonary Medicine, Dept of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. [3]Division of Pulmonary Medicine, Dept of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. [4]Damien Foundation, Niamey, Niger. [5]Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zurich, Switzerland. [6]Tuberculosis Consultant Services, Kirchlindach, Switzerland. [7]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium.

Correspondence: Chen-Yuan Chiang, 111 Hsin-Long Road, Section 3, Taipei, 116, Taiwan.
E-mail: cychiang@theunion.org

Received: Nov 11 2017 | Accepted after revision: Dec 04 2017

Conflict of interest: None declared.

## References

1 Falzon D, Schünemann HJ, Harausz E, *et al.* World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *Eur Respir J* 2017; 49: 1602308.
2 Chiang C-Y, Van Deun A, Rieder HL. Gatifloxacin for short, effective treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2016; 20: 1143–1147.
3 Merle CS, Fielding K, Sow OB, *et al.* A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; 371: 1588–1598.
4 Trébucq A, Schwoebel V, Kashongwe Z, *et al.* Treatment outcome with a short MDR-TB regimen among patients with rifampicin-resistant TB in nine African countries. *Int J Tuberc Lung Dis* 2018; 22: 17–25.
5 World Health Organization. Gatifloxacin – EML and EMLc. 21st Expert Committee on the Selection and Use of Essential Medicines. www.who.int/selection_medicines/committees/expert/21/applications/gatifloxacin_ad/en/ Date last accessed: November 10, 2017.
6 Park-Wyllie LY, Juurlink DN, Kopp A. Outpatient gatifloxacin therapy and dysglycemia in older adults. *N Engl J Med* 2006; 354: 1352–1361.
7 Chou HW, Wang JL, Chang CH, *et al.* Risk of severe dysglycemia among diabetic patients receiving levofloxacin, ciprofloxacin, or moxifloxacin in Taiwan. *Clin Infect Dis* 2013; 57: 971–980.
8 Olliaro PL, Merle C, Mthiyane T, *et al.* Effect on the QT interval of a gatifloxacin-containing regimen *versus* standard treatment of pulmonary tuberculosis. *Antimicrob Agents Chemother* 2017; 61: e01834–e01816.
9 Zignol M, Dean AS, Alikhanova N, *et al.* Population-based resistance of *Mycobacterium tuberculosis* isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. *Lancet Infect Dis* 2016; 16: 1185–1192.
10 Rigouts L, Coeck N, Gumusboga M, *et al.* Specific *gyrA* gene mutations predict poor treatment outcome in multidrug-resistant tuberculosis. *J Antimicrob Chemother* 2016; 71: 314–323.
11 Ahmad Khan F, Salim MAH, du Cros P, *et al.* Effectiveness and safety of standardized shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017; 50: 1700061.