Group 5 drugs for multidrug-resistant tuberculosis: is the glass half full or half empty?

Giovanni Sotgiu [1] and Giovanni Battista Migliori [2]

Affiliations: [1]Clinical Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences – University of Sassari, Sassari, Italy. [2]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Maugeri Institute, IRCCS Tradate, Tradate, Italy.

Correspondence: Giovanni Sotgiu, Clinical Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences – University of Sassari, via Padre Manzella 4, Sassari 07100, Italy. E-mail: gsotgiu@uniss.it

@ERSpublications
Coordinated effort in the fight against MDR-TB is needed to develop new drugs and better use existing ones http://ow.ly/bsxD306sPsw

Cite this article as: Sotgiu G, Migliori GB. Group 5 drugs for multidrug-resistant tuberculosis: is the glass half full or half empty? *Eur Respir J* 2017; 49: 1602273 [https://doi.org/10.1183/13993003.02273-2016].

The 2016 World Health Organization (WHO) tuberculosis (TB) report, published after the approval of the End TB Strategy, shows that, because of the improved surveillance/survey figures from India, the global 2015 TB incidence and mortality reached 10.4 and 1.4 million, respectively [1–5]. Together with India, China, Nigeria, Pakistan, Indonesia, Pakistan and South Africa contribute most to the global TB burden.

In 2015, 1.2 million individuals were estimated to be TB/HIV co-infected and 580 000 patients were affected by multidrug-resistant (MDR)-TB (half of the global cases being in China, the Russian Federation and India), of whom, ~125 000 were treated with a success rate <60%. Although about 49 million lives have been saved between 2000 and 2015 as a result of the enormous effort by WHO and its partners, much work is ahead us in the future if the United Nations Sustainable Development and End TB Strategy goals are to be reached.

The present prevalence of resistance to the available anti-TB drugs plays a crucial role in fighting the MDR-TB epidemic. A systematic review and individual patient data meta-analysis by Dick Menzies and colleagues, published in the recent past, demonstrated that cases harbouring *Mycobacterium tuberculosis* strains with an extensively drug-resistant (XDR)-TB profile (*i.e.* resistance to isoniazid, rifampicin, any fluoroquinolones, and at least one of the second-line injectable drugs, amikacin, capreomycin and kanamycin) or with resistance patterns beyond XDR achieve a suboptimal treatment success rate (40% and 20%, respectively) [6–8]. Given the difficulty of ensuring, in these severe cases, the minimum number of anti-TB drugs recommended by WHO to design an effective regimen, important discussions are presently taking place on both new and repurposed drugs [9, 10].

The article by Fox *et al.* [11] in this issue of the *European Respiratory Journal* (*ERJ*) highlights the role of the anti-TB drugs belonging to the (so-called) Group 5; at the time, the 2011 MDR-TB guidelines were still in force. In May of this year, in fact, new WHO guidelines were released, which modified the grouping of second-line anti-TB drugs [12, 13].

Fox *et al.* [11] focuses on the so-called repurposed drugs, such as the antibiotics approved for infections other than TB (*e.g.* linezolid, carbapenems (imipenem, meropenem and ertapenem), terizidone, thioacetazone,

Received: Nov 18 2016 | Accepted: Nov 18 2016

Conflict of interest: None declared.

clarithromycin and amoxicillin/clavulanate). They are used "off label" to treat difficult TB cases, although their efficacy/effectiveness and safety are not well known; few clinical trials and observational analytical studies are presently available, and the evidence is often anecdotal or contains methodological biases (*e.g.* missing random treatment allocation, absence of a comparable control group, *etc.*). These drugs are frequently administered when the therapeutic options are scarce in cases of complicated drug resistance patterns, and the option of the new drugs bedaquiline and delamanid has been explored.

Recently, the *ERJ* has published the results of innovative studies on drugs repurposed for MDR-TB (*e.g.* on linezolid, mefloquine, imipenem, meropenem, ertapenem and co-trimoxazole) [14–25]. Some of these observational studies were important. A group of them provided the first evidence on carbapenems in the literature [19, 20, 24]. Furthermore, the results a systematic review and meta-analysis on the observational studies on linezolid were confirmed by the first clinical trial on linezolid among XDR-TB patients, published in the *New England Journal of Medicine* [15, 16, 26].

Fox *et al.* [11] performed an important systematic review and individual patient data meta-analysis on the former Group 5 drugs. For the first time, a methodologically appropriate quantitative assessment has been made available on this heterogeneous group of drugs.

The authors selected 31 studies (9282 patients) including 24 studies in which 2191 patients were prescribed ex-Group 5 drugs. These studies mainly focused on thioacetazone, clofazimine, macrolides and amoxicillin/clavulanic acid. About half of the recruited cohort included MDR-TB patients with resistance to fluoroquinolones and/or second-line injectable agents.

The median exposure to anti-TB drugs was significantly higher than in the control group not exposed to ex-Group 5 drugs. The treatment success was 74%, almost that observed in the control group (73%). In the analysis, cases lost to follow-up were included. When thioacetazone was used, the treatment success rate improved. This finding needs to be evaluated cautiously, as the majority of data were from a single country (Latvia).

According to the study results, outcomes were less good when macrolides, clofazimine and amoxicillin/clavulanic acid were used. As it was published after the acceptance of the article by Fox *et al.* [11], the results of a promising study on clarithromycin were not considered [27].

Interestingly, as underlined by the authors, the study results showed that clofazimine seems to perform less well than reported elsewhere [28]. The findings of this study are relevant to providing further guidance on MDR-TB treatment. The study is methodologically strong, being based on individual patient data meta-analysis of a large cohort, where confounding background noise was adequately managed (*i.e.* hierarchical multivariable logistic regression analysis and propensity score base matching were used).

As frequently observed in these studies, when cases are very complicated, repurposed drugs are prescribed, such that the real effect of these drugs can be underestimated. The study by Fox *et al.* [11] has the merit of having looked comprehensively at the heterogeneous group of repurposed drugs, some of which were not even included in the last WHO treatment classification [12].

New methodological approaches to conducting TB clinical trials (*e.g.* multiarm multistage design and evaluating several regimens in one clinical trial) [29] and the recent attempt to shorten treatment durations [30, 31] are likely to provide new evidence in the coming future.

A coordinated effort of all stakeholders committed to the fight against MDR-TB is necessary to develop new drugs and to learn how better to use the existing ones. New opportunities are emerging, such as the Cape Town agreement signed in 2001 (where several stakeholders agreed to improve research and development in the TB field [32, 33]) or the recent plan of the United Nations on antimicrobial resistance (focused on a global strategy to mitigate the antimicrobial resistance burden [34]) to impact the MDR-TB epidemic.

References

1 World Health Organization. Global Tuberculosis Report 2016. WHO/HTM/TB/2016.13. Geneva, World Health Organization, 2016.
2 World Health Organization. The End-TB Strategy: Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015. Geneva, World Health Organization, 2014.
3 D'Ambrosio L, Dara M, Tadolini M, *et al.* Tuberculosis elimination: theory and practice in Europe. *Eur Respir J* 2014; 43: 1410–1420.
4 Lönnroth K, Migliori GB, Abubakar I, *et al.* Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; 45: 928–952.
5 Sotgiu G, Migliori GB. Is tuberculosis elimination a reality? *Lancet Infect Dis* 2014; 14: 364–365.
6 Falzon D, Gandhi N, Migliori GB, *et al.* Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013; 42: 156–168.
7 Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.

8 Ahuja SD, Ashkin D, Avendano M, *et al.* Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; 9: e1001300.
9 Pontali E, Sotgiu G, D'Ambrosio L, *et al.* Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. *Eur Respir J* 2016; 47: 394–402.
10 Mafukidze A, Harausz E, Furin J. An update on repurposed medications for the treatment of drug-resistant tuberculosis. *Expert Rev Clin Pharmacol* 2016; 18: 1–10.
11 Fox GJ, Benedetti A, Cox H. Group 5 drug for multidrug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2017; 49: 1600993.
12 World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis. 2016 Update WHO/HTM/TB/2016.04. Geneva, World Health Organization, 2016.
13 Caminero JA, Scardigli A. Classification of antituberculosis drugs: a new proposal based on the most recent evidence. *Eur Respir J* 2015; 46: 887–893.
14 Sotgiu G, Pontali E, Migliori GB. Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. *Eur Respir J* 2015; 45: 25–29.
15 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. *Eur Respir J* 2013; 42: 288–290.
16 Sotgiu G, Centis R, D'Ambrosio L, *et al.* Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
17 Migliori GB, Eker B, Richardson MD, *et al.* A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. *Eur Respir J* 2009; 34: 387–393.
18 De Lorenzo S, Alffenaar JW, Sotgiu G, *et al.* Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. *Eur Respir J* 2013; 41: 1386–1392.
19 Tiberi S, Sotgiu G, D'Ambrosio L, *et al.* Comparison of effectiveness and safety of imipenem/clavulanate-*versus* meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; 47: 1758–1766.
20 Tiberi S, Payen MC, Sotgiu G, *et al.* Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; 47: 1235–1243.
21 Alsaad N, Wilffert B, van Altena R, *et al.* Potential antimicrobial agents for the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2014; 43: 884–897.
22 Alsaad N, van Altena R, Pranger AD, *et al.* Evaluation of co-trimoxazole in the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2013; 42: 504–512.
23 van Rijn SP, van Altena R, Akkerman OW, *et al.* Pharmacokinetics of ertapenem in patients with multidrug-resistant tuberculosis. *Eur Respir J* 2016; 47: 1229–1234.
24 Tiberi S, D'Ambrosio L, De Lorenzo S, *et al.* Ertapenem in the treatment of multidrug-resistant tuberculosis: first clinical experience. *Eur Respir J* 2016; 47: 333–336.
25 Krieger D, Vesenbeckh S, Schönfeld N, *et al.* Mefloquine as a potential drug against multidrug-resistant tuberculosis. *Eur Respir J* 2015; 46: 1503–1505.
26 Lee M, Lee J, Carroll MW, *et al.* Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367: 1508–1518.
27 Van der Paardt AF, Akkerman OW, Gualano G, *et al.* Safety and tolerability of clarithromycin in the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2016; in press [https://doi.org/10.1183/13993003.01612-2016].
28 Padayatchi N, Gopal M, Naidoo R, *et al.* Clofazimine in the treatment of extensively drug-resistant tuberculosis with HIV coinfection in South Africa: a retrospective cohort study. *J Antimicrob Chemoth* 2014; 69: 3103–3107.
29 Phillips PP, Gillespie SH, Boeree M, *et al.* Innovative trial designs are practical solutions for improving the treatment of tuberculosis. *J Infect Dis* 2012; 205: Suppl. 2, S250–S257.
30 Sotgiu G, Tiberi S, D'Ambrosio L, *et al.* Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. *Eur Respir J* 2016; 48: 1503–1507.
31 Sotgiu G, Tiberi S, D'Ambrosio L, *et al.* WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. *Lancet* 2016; 387: 2486–2487.
32 Migliori GB, Sotgiu G. Treatment of tuberculosis: have we turned the corner? *Lancet* 2012; 380: 955–957.
33 Working Alliance for TB Drug Development. The Cape Town Declaration. www.tballiance.org/downloads/publications/CapeTownDeclaration.pdf Date last updated: February 8, 2000.
34 Laxminarayan R, Sridhar D, Blaser M, *et al.* Achieving global targets for antimicrobial resistance. *Science* 2016; 353: 874–875.