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Eur Respir J 2016; 48: 1797–1800 | DOI: 10.1183/13993003.01145-2016 | Copyright ©ERS 2016

Shorter treatment for multidrug-resistant tuberculosis: the good, the bad and the ugly

To the Editor:

We welcome the initiative by the Guideline Development Group (GDG) members to issue the 2016 update of World Health Organization (WHO) treatment guidelines for drug-resistant tuberculosis (TB) [1]. With one in two patients currently failing on treatment for multidrug-resistant (MDR)-TB, primarily as a result of the difficulties presented by cumulative drug toxicity, logistics, costs and subsequent poor adherence to therapy [2], a shorter regimen for selected patients would be a tremendous asset, even though the GDG argues that the recommendation is conditional, and the scientific evidence for the recommendation is low. Since the first reports on the efficacy of a regimen of only 9 months for MDR-TB [3, 4], two more studies have been published to support the concept of shorter regimens [5, 6] while the STREAM (Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients with MDR-TB) study is still enrolling [7]. However, shortening therapy would only apply for selected patients without prior use of or proven resistance to fluoroquinolones (group A) or second-line injectable agents (group B). At least five active drugs should be available for the intensive phase (4–6 months). Further exclusions are extrapulmonary TB, additional resistance to pyrazinamide (PZA) and pregnancy. Clofazimine [8] and linezolid [9] were regrouped as core agents in group C with ethionamide or prothionamide, while para-aminosalicylic acid was deferred to group D.

The GDG noted the lack of evidence for shortening treatment for extrapulmonary MDR-TB and did not recommend doing so, even though drug-susceptible extrapulmonary and pulmonary TB are treated with similar schedules and durations of treatment. MDR-TB treatment requires bacteriological monitoring, which is more feasible in sputum samples from pulmonary MDR-TB patients than samples from extrapulmonary MDR-TB cases.

Excluding PZA resistance is problematic. PZA susceptibility testing is difficult and not widely available, especially in low-resource settings. However, recent studies have shown excellent concordance of molecular and phenotypic susceptibility [10, 11], and testing molecular susceptibility to this important drug may become an important asset, even in low-resource settings.

We retrospectively analysed how many MDR-TB patients in the Netherlands would potentially have benefitted from the new guidelines; we therefore studied the data of all 172 consecutive patients that had started treatment since 2000. Data on patients treated between 2000 and 2009 have been published previously [8].

Five of these 172 patients had earlier MDR-TB treatment, four were pregnant, 30 had extrapulmonary MDR-TB, 28 had additional resistance to group A and/or group B drugs and 52 had PZA-resistant organisms. Four had extensively drug-resistant TB (these patients were included in our earlier report [8]), and all of these cases had a favourable outcome. As multiple exclusion criteria clustered in some patients

(table 1), nearly half (85 (49.4%) out of 172) of our patients would meet the criteria for the new shorter regimen. Interestingly, 58% of the 2000–2009 cohort, but only 36% (25 out of 69) of the 2010–2015 cohort would be eligible for shortened treatment. Of the 54 patients starting treatment between 2010 and 2013, 46 (85.2%) completed treatment successfully, one died from an unrelated cause, four interrupted their treatment and three left the Netherlands to complete their treatment elsewhere. Therefore, the high success rate at ∼85% reported earlier [8], without failure or relapse was maintained.

The evidentiary table on page 20 in the guidelines [1] is based on data from 1205 patients; 89 of those were lost to follow-up. Outcome in those without resistance to quinolones, injectables or PZA was successful in 121 (96.8%) out of 125, which is obviously excellent, but the lower limit of the confidence interval (77.3–99.6%) calls for caution.

MDR-TB treatment outcome in the Netherlands with conventional treatment of 20 months duration [8, 12] has been highly successful with very limited toxicity, and no failure or relapse. We benefitted from an extraordinary collaboration between tertiary treatment centres and public health physicians, with hardly any loss to follow-up. We have treated patients in whom treatment was extremely long, considering the fact that their lesions and their bacterial load were limited. Whether treatment duration is important in cavitary lesions and in patients with a large initial bacterial load needs to be investigated in future studies.

We believe that part of our success is due to an approach using tailored pharmacokinetic/pharmacodynamic (PK/PD) modelling. Drug susceptibility testing in MDR-TB is important [13], but merely reporting a test result below or above the European Committee on Antimicrobial Susceptibility Testing breakpoint may not provide sufficient precision. Clearly, the contribution of each individual drug depends on drug exposure relative to the drug susceptibility of the organism [14]. Molecular tests such as the MTBDRplus (version 2.0; Hain Lifescience, Nehren, Germany) to predict susceptibility to second-line drugs currently do not provide a minimum inhibitory concentration (MIC) value to allow for PK/PD calculations, while MIC values for second-line drugs have gradually changed over time. All of these considerations imply that vigilance is warranted with shortened treatment. Modern diagnostic tools should enable physicians to act promptly if treatment is stalling [15]. We believe that drug concentration monitoring has added value to fast molecular tests and drug susceptibility testing to support the shortened regimen by preventing slow response due to low drug exposure [16]. Synergy between second-line TB drugs may further benefit the short course of treatment [17].

We welcome shortened treatment and we agree that the good news of shortened treatment duration should be carefully monitored. Only four of our eligible patients were still sputum smear microscopy positive after 4 months of treatment; 81 (95%) would therefore have continued treatment for 9 months only, according to the new guideline; for these 81 patients, 9 months of treatment would remain good news during the planned 9 months of treatment, while only four would have had to extend their treatment to 12 months according to the new guidelines. However, if many more patients among the 85 starting the 9- (or 12-) month regimen would relapse because of failure to sterilise persister organisms, their treatment would become a negative experience, with a treatment duration of 9 months plus an additional 20 months. Both for low-resource settings and for programmes that currently have excellent treatment results, monitoring is therefore essential to avoid the bad and ugly effects of what is intended to be simply good.

TABLE 1 Reasons for ineligibility of 172 multidrug-resistant tuberculosis (MDR-TB) patients in the Netherlands to receive treatment of a shortened duration (9–12 months) rather than regular care (18–20 months), 2000–2015

	Previous MDR-TB drugs	Pregnancy	Extrapulmonary TB	Resistance to FLQ[#] or second-line injectable drugs[¶]	PZA resistance	Total
Previous MDR-TB drugs	5	0	0	4	3	
Pregnancy		4	2	0	0	
Extrapulmonary TB			28	2	9	
Resistance to FLQ[#] or second-line injectable drugs[¶]				22	12	
PZA resistance					28	
Patients meeting exclusion criterion	5	4	30	28	52	87

Data are presented as n. FLQ: fluoroquinolone; PZA: pyrazinamide. [#]: group A; [¶]: group B.

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Updated WHO guidelines advise 9–12 months of MDR-TB treatment; this was suitable for 85 out of 172 Dutch patients http://ow.ly/OClA303L181

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Received: June 19 2016 | Accepted after revision: Aug 22 2016 | First published online: Oct 06 2016

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

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