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Second-line injectable drugs for rifampicin-resistant tuberculosis: better the devil we know?

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In its 2020 guidelines for the treatment of rifampicin-resistant TB (RR-TB), the WHO recommends all-oral fluoroquinolone-based regimens, with bedaquiline replacing the second-line injectable drugs (SLIDs). SLIDs were used for their strong acquired resistance-preventing activity. Data from three cohorts showed acquired bedaquiline resistance ranging between 2.5% and 30.8%, with no protection from a SLID in most cases. If bedaquiline resistance is that easily acquired, it will fail to protect fluoroquinolones and other drugs from acquiring resistance. Until evidence on resistance-preventing activity shows that SLIDs can safely be replaced, we call for more prudent use of the few potent second-line TB drugs available. Studies on new treatment regimens need to prioritize the prevention of acquired resistance along with treatment success. Meanwhile, reducing the dosing of SLIDs to thrice weekly from Day 1, and their replacement for any degree of audiometry abnormalities before or during treatment will largely avoid serious ototoxicity.

Decades of TB treatment research showed that a strong regimen needs a core drug, with both high bactericidal and sterilizing activity to drive the regimen's efficacy, and a drug with acquired core-drug resistance-preventing activity.[1,2] During the 4 month intensive phase of the highly effective rifampicin-resistant TB (RR-TB) shorter treatment regimen (STR), a second-line injectable drug (SLID) is used to prevent acquired resistance to fluoroquinolones, the core drug of this regimen.[3] After a 2018 meta-analysis showed that the use of kanamycin and capreomycin predicted having an adverse outcome,[4] in its 2020 RR-TB guidelines the WHO recommends all-oral bedaquiline-containing regimens, either short or long.[5] The findings of the 2018 meta-analysis are opposite to previous meta-analyses,[6,7] did not compare regimens with regimens, and did not assess prevention of resistance acquisition.[4]

We summarize recently published data on acquired bedaquiline resistance in RR-TB cohorts, with updated data for a Pakistan cohort.[8] Second, we summarize data on the resistance-preventing activity of SLIDs.

Diacon and colleagues[9] showed a protective effect of bedaquiline on resistance acquisition. However, also in the bedaquiline arm, resistance acquisition was not rare as the background regimen was weak. Recent findings show that the widespread use of all-oral bedaquiline-containing regimens may have dire consequences. In a South African study, most treatment regimens included levofloxacin or moxifloxacin, bedaquiline and linezolid, plus either clofazimine or cycloserine, constituting a WHO-recommended all-oral regimen.[10] Of 92 patients with baseline sequencing data, 5 had a strain with *rv0678* mutations. Of the remaining 87 patients, 5 (5.7%) acquired bedaquiline resistance during treatment. All five patients had fluoroquinolone-resistant/RR-TB (Table 1) when the bedaquiline-containing regimen was started. Of those five patients, four experienced treatment failure.[10] Indeed, even though patients with initially fluoroquinolone-resistant TB were treated with regimens that included at least four likely effective drugs, as recommended by the WHO,[5] these regimens were not potent enough to prevent acquired bedaquiline resistance and a subsequent adverse treatment outcome. This confirms that emphasis on the number of active drugs, rather than ensuring complementary activity of included drugs, does not sufficiently protect against poor outcomes, including acquired resistance.[1] Another study from Germany identified bedaquiline resistance in 7 of 124 patients.[11] In at least three (2.5%; 3/120), resistance was not present before adding bedaquiline to the regimen (Table 1).

In Pakistan, bedaquiline was used either with or without SLIDs.[8] The data showed 8 of 26 (30.8%) patients to be diagnosed with bedaquiline resistance (Table 2). The vast majority of patients (80.8%; 21/26) had fluoroquinolone-resistant RR-TB when bedaquiline was added to the regimen. Linezolid was active in all eight patients with acquired bedaquiline resistance. Acquired

Table 1. Drug susceptibility results, treatment regimens and treatment outcomes in patients with acquired bedaquiline resistance

Study	Composition of BDQ-containing regimen: **Likely effective**[a] Initial resistance reported	Number of likely effective drugs[a]	Protection by FQ or SLID?[b]	BDQ mutations during treatment? [treatment month; mutation(s)]	Follow-up BDQ MIC > CC?[c]	MIC increase[c] on 7H11 agar[10] or in MGIT[11]	Outcome
Nimmo[10]	**BDQ LZD CLF Z TZ PAS** FQ	6	no	yes (6; Rv0678: C46fs, D47fs)	yes	(0.06–1.0)	failure at month 6, then died
	BDQ LZD CLF Z EMB ETO TZ PAS FQ	8	no	yes (4; Rv0678: C46fs)	yes	(0.03–1.0)	conversion at month 6, cured
	BDQ LZD TZ PAS FQ CLF ETO EMB Z	4	no	yes (6; Rv0678: D47fs)	yes	(0.06–0.5)	failure
	BDQ LZD CLF D TZ PAS	6	no	yes (6; Rv0678: E147)	no	(0.03–0.25)	failure at month 6, then died
	BDQ LZD Z TZ PAS FQ CLF ETO	5	no	yes (3; Rv0678: Q22P, D47fs)	yes	(0.03–1.0)	failure at month 6, then died
Andres[11]	**BDQ D MEM CS** CLF	4[d]	no	yes (1; Rv0678: R82P, 92insG, R94W, R156, Y157C, 193delG)	yes	(0.5–2)	no conversion at month 6, conversion after surgery
	BDQ AMK CS EMB	4[d]	SLID	yes (1; Rv0678: 138insG, 141insC)	yes	(0.75–4)	no conversion at month 6, then conversion
	BDQ CLF L ZD CS	4[d]	no	yes (2; Rv0678: 140insCT, 141insC)	yes	(0.5–2)	no conversion at month 6, then conversion

CC, critical concentration; MGIT, Mycobacteria growth indicator tube; fs, frameshift mutation; ins, insertion; del, deletion; AMK, amikacin; BDQ, bedaquiline; CLF; clofazimine; CS, cycloserine; D, delamanid; EMB, ethambutol; ETO, ethionamide; FQ, fluoroquinolone; LZD, linezolid, MEM, meropenem; PAS, para-aminosalicylic acid; TZ, terizidone; Z, pyrazinamide. SLIDs used were either amikacin or capreomycin. Amino acid changes at variant sites are specified as in the manuscripts by Nimmo *et al*. (2020)[10] and Andres *et al*. (2020).[11]

[a]Includes those drugs with data on initial susceptibility, those reported as effective or not used in previous regimens before starting BDQ.

[b]If the drug was included in the regimen when BDQ was started and also likely active.

[c]In patients initially susceptible to BDQ, acquired BDQ resistance is defined when the follow-up MIC was: (a) above the CC (on 7H11: 0.25 mg/L; in MGIT: 1 mg/L); or (b) was increased at least 4-fold but not lower than 0.125 mg/L on 7H11 or 0.5 mg/L in MGIT.

[d]Detailed molecular and phenotypic drug susceptibility testing informed the constitution of the regimen.[11]

bedaquiline resistance was significantly more frequent when SLIDs did not protect bedaquiline [53.8% (7/13) versus 7.7% (1/13); OR 9.6; 95% CI 1.3–70.5] and in patients previously treated with a SLID-containing second-line regimen [58.3% (7/12) versus 7.1% (1/14); OR 12.3; 95% CI 1.6–92.0]. Two of 8 patients with acquired bedaquiline resistance were cured.[8] Patients with acquired bedaquiline resistance more likely had a poor treatment outcome [75.0% (6/8) versus 16.7% (3/18); OR 11.5; 95% CI 1.8–74.2].

Bedaquiline may fail as a replacement for the SLID in patients diagnosed with fluoroquinolone-susceptible RR-TB, particularly when using molecular tests with lower sensitivity for fluoroquinolone-resistant minority populations. The bedaquiline bactericidal activity takes 1 week to develop.[12] Undetected, yet frequently present, fluoroquinolone-resistant mutants[13] will thus not be eradicated in this first week, but with 99% of the susceptible bacilli killed by that time,[14] they may now surpass the 1% threshold to qualify as a fluoroquinolone-resistant strain. By the time bedaquiline becomes the drug exerting the highest resistance selection pressure,[12] fluoroquinolone-resistant bacilli will have multiplied abundantly as the now dominant strain. When bedaquiline is not protected by a fluoroquinolone, bedaquiline resistance may be acquired and fluoroquinolone and bedaquiline co-resistant bacilli may next become the dominant strain. Moreover, bedaquiline susceptibility testing is not available in most high TB-burden countries. Primary bedaquiline resistance, found in up to 5% of patients,[11,15] may also foster acquired fluoroquinolone resistance, leaving patients with RR-TB resistant to fluoroquinolones and bedaquiline and a grim prognosis.[1] Acquired resistance to core drugs compromises TB control. Acquired rifampicin resistance occurred in about 1 per 1000 initially susceptible patients.[16] Even at this low rate, it took only a decade of widespread use until 2% of new patients had primary RR-TB, reaching over 15% in some countries.[17] The proportion of patients with acquired bedaquiline resistance varied in the relatively small cohorts reported above and approaches to RR-TB treatment differed across settings. Still,

Table 2. Drug susceptibility results, treatment regimens and treatment outcomes in patients with and without acquired bedaquiline resistance in Pakistan

Composition of BDQ-containing regimen: **Likely effective**[a] Initial resistance reported *Used previously (but without DST results)*[b]	Number of likely effective drugs[a]	Protection by FQ or SLID?[c]	BDQ mutations during treatment [treatment month; mutation(s)]	Follow-up BDQ MIC >CC?[d]	MIC increase[d] on 7H11[e]	BDQ ADR	Outcome
BDQ LZD CLF *CS PAS* MXF CM ETO Z	3	no	yes (7; Rv0678: 137insG)	no	(0.03–0.25)	yes	cured
BDQ LVX LZD ETO CLF *PAS AMC CS* Z	5	FQ	yes (5; Rv0678: 140insC)	yes	(0.03 to >0.5)	yes	cured
BDQ LZD CLF *CS* LVX ETO INH Z	3	no	no	no	(0.03–0.25)	yes	died
BDQ LZD D ETO CLF LVX INH Z	5	no	yes (1; Rv0678: 192insG)	yes	(0.03 to >0.5)	yes	failure
BDQ MXF CM LZD CLF *CS PAS* ETO EMB Z	5	FQ, SLID	yes (6; Rv0678: V20G; PepQ: A87G)	no	(0.06–0.25)	yes	failure
BDQ LZD ETO CLF Z *CS PAS* MXF AMK EMB	5	no	yes (4; Rv0678: A99V, 140insC)	yes	(0.12 to >0.5)	yes	failure
BDQ LZD CLF *AMC CS PAS* MXF ETO CM Z	3	no	yes (5; Rv0678: 193delG; PepQ: V92G)	no	(0.03–0.12)	yes	failure
BDQ LZD CLF *CS* LVX ETO EMB INH Z	3	no	yes (3; Rv0678: 137insG)	no	(0.03–0.12)	yes	failure
BDQ AMK ETO CS PAS Z LVX	6	SLID	no	no	(0.03–0.06)	no	cured
BDQ LZD CLF *PAS* MXF CM ETO Z	3	no	no	no	(≤0.008 to 0.016)	no	cured
BDQ LZD CLF *CS PAS* LVX ETO EMB Z	3	no	yes (9, PepQ: I193T)	no	(0.12–0.06)	no	cured
BDQ CM ETO CLF Z MXF EMB	5	SLID	yes (1; PepQ: A86P)	no	(0.06–0.06)	no	cured
BDQ CM LZD ETO D CLF Z *CS PAS AMC CLR* MXF	7	SLID	no	no	(0.016–0.06)	no	cured
BDQ CM LZD ETO CLF CS LVX EMB Z	6	SLID	no	no	(≤0.008 to 0.06)	no	cured
BDQ LZD CLF PAS *CS AMC* MXF ETO INH Z	4	no	no	no	(0.06–0.03)	no	cured
BDQ LZD D CLF AMC MXF ETO EMB INH Z	4[f]	no	no	no	(0.03–0.06)	no	cured
BDQ AMK ETO CLF MXF	4	SLID	no	no	(0.06–0.06)	no	cured
BDQ AMK ETO CS PAS Z MXF	6	SLID	no	no	(0.06–0.06)	no	cured
BDQ AMK LZD CLF PAS *CS* MXF ETO Z	5	SLID	no	no	(0.06–0.12)	no	cured
BDQ LZD ETO CLF PAS Z *CS* LVX CM	6	no	yes (2; Rv0678: L35V; PepQ: V92G, P97V)	no	(≤0.008 to 0.016)	no	cured
BDQ CM LZD ETO *CS* MXF Z	4	SLID	no	no	(0.016–0.03)	no	cured
BDQ MXF AMK LZD ETO *CS* Z	5	FQ, SLID	no	no	(0.03–0.03)	no	cured
BDQ LZD CLF *ETO CS* MXF CM Z	3	no	no	no	(0.03–0.06)	no	cured
BDQ CM LZD CLF PAS AMC MXF Z	5[f]	SLID	no	no	(0.03–0.03)	no	failure
BDQ MXF CM LZD CLF D ETO CS PAS AMC CLR	9[f]	FQ, SLID	yes (4; PepQ: V92G)	no	(0.25–0.03)	no	failure
BDQ MXF AMK ETO *CS PAS* EMB	4	FQ, SLID	no	no	(0.03–0.06)	no	died

CC, critical concentration; ADR, acquired drug resistance; DST drug susceptibility testing; AMK, amikacin; AMC, amoxicillin/clavulanic acid; BDQ, bedaquiline; CLF, clofazimine; CLR, clarithromycin; CM, capreomycin; CS, cycloserine; D, delamanid; EMB, ethambutol; ETO, ethionamide; FQ, fluoroquinolone; INH, isoniazid; LZD, linezolid; LVX, levofloxacin; MXF, moxifloxacin; PAS, p-aminosalicylic acid; Z, pyrazinamide.

[a]Includes those with data on initial susceptibility, those reported as effective or not used in previous regimens before starting BDQ. When phenotypic DST (performed on different media, with moxifloxacin, levofloxacin and ofloxacin) showed initial resistance or when WGS showed a mutation conferring resistance we considered the strain as initially FQ resistant. FQ was prescribed using the normal dose (400 mg for MFX).

[b]Drugs used in a previous RR-TB treatment regimen, and for which no initial DST results were reported.

[c]If the drug was included in the regimen when BDQ was started and also likely active.

[d]In patients initially susceptible to BDQ, ADR is defined when the follow-up MIC was: (a) above the CC (on 7H11: 0.25 mg/L; in MGIT: 1 mg/L); or (b) was increased at least 4-fold but not lower than 0.125 mg/L on 7H11 or 0.5 mg/L in MGIT.

[e]Concentrations tested were 0.008, 0.016, 0.03, 0.06, 0.12 and 0.25 mg/L.

[f]AMC and CLR not counted as 'likely active' TB drugs.

even at a rate of a few percent, acquired bedaquiline resistance will rapidly render the drug useless as the core drug. A more prudent and likely more effective strategy would be the replacement by bedaquiline, not of the injectable drug, but of the fluoroquinolone, in the case of (high-level) fluoroquinolone resistance, or just the addition of bedaquiline to the unmodified STR, i.e. in the case of unknown or low-level fluoroquinolone resistance.[1]

For the WHO-recommended all-oral STR, the 'data vacuum' on acquired bedaquiline resistance-preventing activity contrasts with exhaustive evidence on the effect of the SLID-containing STR.[18] In the STR, kanamycin is administered during the initial 4 months.[3] Acquired resistance was identified in none of 859 patients with initially fluoroquinolone-susceptible TB and treated with a gatifloxacin-based/SLID-containing STR.[19] When 2 instead of 4 months of kanamycin was tested, acquired fluoroquinolone resistance was significantly more frequent.[20] In a multi-country RR-TB study, initial resistance to SLIDs was the strongest predictor of the acquisition of fluoroquinolone resistance.[21] Findings from the Pakistan second-line cohort also showed a protective effect of SLIDs against the acquisition of bedaquiline resistance (Table 2).[8]

A strong argument for not using SLIDs is the risk of irreversible ototoxicity. Hearing loss is severe in about 6%[22] and is predicted by the cumulative dose of SLIDs (including streptomycin) and pre-existing hearing loss. The proportion of patients experiencing severe hearing loss decreases progressively since: (a) the STR uses 4 months of a SLID instead of the clearly excessive 8 months in the previously recommended long regimen;[7] (b) the pre-treatment cumulative dose has been reduced since the phasing out of the streptomycin-strengthened retreatment regimen; (c) thrice-weekly standard dose (15 mg/kg, reduced for elderly patients) of the most powerful SLID, amikacin (C_{max}/WT MIC = 22 for amikacin, but only 5 for kanamycin and capreomycin),[23] for the entire intensive phase will considerably reduce the total amount of drug taken and thus the risk of ototoxicity,[24,25] most likely without reducing efficacy;[26,27] and (d) early detection and replacement of the SLID by linezolid for any hearing loss was effective in preventing severe hearing loss in Niger.[28] Linezolid is now a first-choice drug for all RR-TB patients. However, it causes severe adverse events more frequently than SLIDs.[29] Moreover, recent data on linezolid's failing acquired resistance-prevention activity,[10] confirmed in our Pakistan cohort where only SLIDs were significantly protective, mean that systematic replacement of the SLID by linezolid is likely to be a serious mistake.

Studies assessing the safety and efficacy of intermittent standard doses of SLIDs are needed.[24] To assure adherence despite the painful injections, staff must convey the reason why they are indispensable and provide mental and practical support for the administration of SLIDs.[30]

Until evidence on resistance-preventing activity shows that SLIDs can be safely replaced by another drug, or that an equally potent and safe third-line core drug is available for immediate use in patients with TB resistant to rifampicin, fluoroquinolones and bedaquiline, we call for responsible use of the few potent second-line TB drugs available.

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None to declare.

Author contributions

All authors contributed to the design. S.T. collected the data. S.T., T.D. and A.V.D. summarized the data. A.V.D and T.D. wrote the first draft. All authors contributed to the interpretation of the findings, critically revised subsequent versions and approved the final version.

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