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Review Paper

Resistance to Newer and Repurposed Anti-Tuberculosis Drugs in MDR/RR-TB: Mechanisms, Detection and Clinical Strategies

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ABSTRACT

Background: Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) required shorter, fully oral treatment with Bedaquiline, nitroimidazoles delamanid and pretomanid, repurposed linezolid and clofazimine. Resistance is a growing problem for these agents threatening these gains. Objective: To synthesize evidence on resistance mechanisms, diagnostics, clinical consequences and management for bedaquiline, linezolid, pretomanid, delamanid and clofazimine.Main content: Resistance is mainly due to de-repression of the efflux pump MmpS5-MmpL5 by Rv0678, also with lesser contribution from atpE and pepQ, and well documented cross-resistance. The linezolid resistance is linked to rrl/rplC. Pretomanid and delamanid share an F420-dependent activation pathway (ddn, fbiA-D), so there is a concern for nitroimidazole cross-resistance. Detection is based on phenotypic drug susceptibility testing (DST) or targeted sequencing or whole genome sequencing (WGS) interpreted using the WHO mutation catalogue, but there remains some genotype-phenotype discordance. Resistance that occurs during BPaL/BpaLM is associated with baseline resistance, functional monotherapy, lack of activity of the companion drug and pharmacokinetically heterogeneity, which has the effect of prolonged culture conversion, therapeutic failure and restricted choices for future treatments.Conclusion: Baseline testing, drug dosing based on pharmacokinetics, pharmacovigilance and expanded rapid diagnostics are needed to preserve these drugs

INTRODUCTION

Multidrug resistant (MDR) tuberculosis (TB) is still an important challenge in TB control worldwide, and is caused by drug-resistant Mycobacterium tuberculosis. The first new class of anti-TB drugs to be discovered in decades is

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Bedaquiline, which targets mycobacterial ATP synthase [1]. In combination with delamanid, pretomanid, linezolid and clofazimine, it allowed for the transition from long injectable-based treatment to shorter fully oral treatment regimens, which now form the basis of WHO recommended BPaL and BPaLM treatment regimens with a duration of 6 months [2].

This progress is threatened by resistance to the same drugs. The pooled prevalence of bedaquiline resistance in drug-resistant TB cases is estimated to be not negligible [3] based on a meta-analysis. Resistance-associated variants were seen in treatment-naïve populations and acquired bedaquiline resistance was reported soon after the introduction [4]. The addition of cross-resistance among Bedaquiline and clofazimine due to the efflux mechanism further reduces treatment choices [5]. Linezolid is associated with resistance and dose-limiting toxicity [6]. Delamanid and pretomanid share an activation pathway and could potentially be compromised both [7].

These drugs, which form the backbone of virtually all WHO-recommended second-line treatment regimens, limit choices for replacement more than resistance to an older second-line medication that has a number of alternatives. Bedaquiline and clofazimine resistance often occur together due to a shared efflux with one another, and both of the nitroimidazole have an identical pathway for bioactivation, meaning that a single genetic event can reduce the effectiveness of more than one drug at a time. This review collates the evidence on resistance mechanisms, detection, clinical and pharmacokinetic consequences and prevention strategies and where evidence is limited or unconfirmed, specifically identifies this.

2. Newer Drugs, Targets and Evolution of Therapy

Traditionally, MDR-TB treatment has been long and arduous (18-24 months), highly toxic and had relatively low success. The diarylquinoline Bedaquiline inhibits the c-subunit (atpE) of mycobacterial F1F0-ATP synthase, which results in ATP depletion of replicating and dormant bacilli. The oxazolidinone, linezolid, binds 23S rRNA at the peptidyl transferase center and is the mechanism underlying the activity of BPaL but is limited by myelosuppression and neuropathy [8]. Pretomanid and delamanid are nitroimidazoles, which must be bioactivated by the F420-dependent nitroreductase system in order to have a bactericidal/sterilizing effect, and delamanid also inhibits mycolic acid synthesis [9]. Clofazimine is a repurposed riminophenazine that produces reactive oxygen species and interacts with the respiratory chain, and has resistance profile similar to bedaquiline with significant overlap due to common efflux. Moxifloxacin is the anchor drug of BPaLM; the trials of the investigational inhaled spectinamides have been suggested as alternatives to linezolid [10].

BPaL (bedaquiline-pretomanid-linezolid) was found to be effective in highly resistant TB in a shorter duration in the Nix-TB trial. Within BPaL, ZeNix optimized the dosing of linezolid to reduce its toxicity, and TB-PRACTECAL expanded its evaluation of BPaLM to RR-TB. The trials led to WHO's "consolidated guidance" to use BPaL/BPaLM for suitable patients [11], making this limited group of "core" agents more dependent on – and more at risk from – resistance.

Table 1. Newer/repurposed anti-TB drugs, targets and resistance genes

Drug	Target/Mechanism	Principal Resistance Genes	Refs
Bedaquiline	ATP synthase c-subunit	*atpE*, *Rv0678*, *pepQ*	[12,13]
Clofazimine	Respiratory chain/ROS	*Rv0678*, *MmpL5/MmpS5*	[14]
Linezolid	23S rRNA peptidyl transferase	*rrl*, *rplC*	[15,16]
Pretomanid/Delamanid	F420-dependent nitroreduction	*ddn*, *fbiA-D*	[7,17]

The common theme for all five drugs is that there are few loci that yield resistance to a drug, either through direct mutations in the drug target or shared mutations in an activation pathway or a shared efflux system; resistance does not occur through diffuse, unpredictable genomic variation, making in-principle targeted molecular diagnostics feasible, although in practice they are not always sensitive.

3. Molecular Mechanisms of Resistance

There are two mechanisms by which Bedaquiline resistance is developed: target-based and efflux-mediated. The most prominent pathway is loss of function mutations of the transcriptional repressor, Rv0678, that normally regulates the expression of the MmpS5-MmpL5 efflux system [18]. Rv0678 encodes a MarR family regulator, missense mutations, insertions and deletions eliminate DNAbinding, de-repress efflux and increase bedaquiline/clofazimine extrusion. The studies of clinical cohorts or in vitro selection confirm that the main resistance locus for Rv0678.The clinical cohort and in vitro selection studies confirm Rv0678 as the dominant resistance associated locus [19,20]. Rv0678 variants are seen, even when there is no evidence of previous exposure, which indicates low frequency variation or transmission; southern Africa surveillance indicates phylogenetic evidence of onward transmission [21].

High level resistance from direct mutations in atpE is due to changes in the drug binding pocket and less frequently reported than Rv0678 variants [13]. Low level resistance to bedaquiline/clofazimine, associated with mutations in the gene encoding a putative peptidase, pepQ, is of particular interest for the occurrence of borderline phenotypes [22]. The structural characterization of this efflux complex MmpS5-MmpL5 helps to understand the effect of altered expression of this pump, in this case by derepression of the regulator Rv0678, which lowers the accumulation of drugs inside cells.

Point mutations in rrl (23S rRNA) that change the binding site for the antibiotic and rplC, have been consistently associated with linezolid resistance, and together they are responsible for most phenotypically confirmed resistance, but quantitative mapping of specific rplC and rrl mutations is not complete [15]. There was a significant, although not 100% overlap between molecular testing and evaluation of phenotypically resistant isolates using nanopore-based methods [16].

Resistance to pretomanid occurs through mutations in two possible targets, namely, ddn or the F420 biosynthesis genes fbiA, fbiB, fbiC and fbiD; as with delamanid the activation is

analogously mediated. This is a shared F420-dependence that provides the mechanism for predicted cross-resistance with pretomanid and laminitide. More broadly, the efflux proteins MmpS5-MmpL5, which have been implicated in azole resistance as well, clearly show that the genes are not drug-specific, but rather share a transport pathway that is co-selected across agents. The relative proportion of exposure to Rv0678 or atpE/pepQ varies between the different cohorts, as this is the most commonly detected bedaquiline-resistance determinant in multi-country analyses reflecting the strains and exposure history.

4. Cross-Resistance

Rv0678-mediated efflux upregulation is responsible for the upregulation of both bedaquiline extrusion and clofazimine extrusion, which explains why mutations that confer resistance to either drug often result in resistance to both; this has been documented in genotype/phenotype studies, in vitro selection and clinical cohorts with acquired resistance to clofazimine after bedaquiline treatment [23,24]. Primary resistance to both agents has been found even within treatment-naïve isolates by primary resistance surveys [25].

Shared activation pathway leads to theoretical, and in the selection studies demonstrated, cross-resistance of pretomanid and delamanid that may have direct implications for sequencing BPaL/BPaLM (via activation-pathway mutations that affect pretomanid may affect delamanid, and vice versa); clinical-cohort quantification is currently limited. Longitudinal data from patients treated with concomitant (cART) or sequential therapy (sART) of bedaquiline and delamanid, respectively, illustrates the practical implications of cross-resistance in treatment sequencing, particularly because of limited drug availability to build short regimens [26].

5. Detection and Diagnosis

Phenotypic DST is still the standard but takes viable culture and weeks to be completed, with multilaboratory studies validating the critical concentrations for bedaquiline, which has been the source of previous breakpoint inconsistencies, and WHO technical guidance for newer agents [27,28]. WHO guidance on deployment priorities for national programs.Genotypic and targeted next-generation sequencing (NGS) assays that cover bedaquiline, linezolid, delamanid and pretomanid resistance genes have a shorter turnaround time and can predict resistance to multiple drugs in a single assay [29]. Genotype-based prediction, including newer agents, has been greatly extended by the compendium of the CRyPTIC Consortium which links genomic information from more than 12,000 isolates with the quantitative resistance information [30].

In spite of these developments, genotype-phenotype discordance still exists for bedaquiline, linezolid and the nitroimidazoles, and there is still incomplete understanding of what impact individual variants has on the functioning of those drugs, especially in the case of Rv0678 mutations with uncertain significance. A low-frequency population resistant to the drug at the start of treatment may be clinically relevant as a precursor to treatment-emergent resistance as a variant present at a low allelic fraction at treatment start can grow under drug pressure to become the dominant, phenotypically resistant population later in treatment, which a single timepoint sequencing detection threshold cannot reliably detect. The WHO mutation catalogue offers a standardized, evidence-based interpretation framework for genotypic results for these drugs, complementing global molecular DST harmonization efforts [31], but its evidence base is ongoing and practical limits of sequencing

availability in high burden settings and culture-dependent turnaround are present [32].

Table 2. Comparison of diagnostic approaches for newer-drug resistance

Method	Turnaround	Key Advantage	Key Limitation	Refs
Phenotypic DST	Weeks	Reference standard; captures unknown mechanisms	Slow; breakpoint standardization challenges	[27,28]
Targeted NGS	Days	Multi-gene, multi-drug panel from one assay	Requires sequencing infrastructure	[29,33]
Whole-genome sequencing	Days	Genome-wide; supports catalogue refinement	Cost, bioinformatics expertise, culture dependence	[30,31]

6. Treatment-Emergent Resistance

Baseline resistance to bedaquiline, linezolid or pretomanid is generally rare in treatment-naïve populations, and has been linked to worse outcomes if it is not identified prior to the start of treatment. In four pretomanid-containing trials, both baseline and acquired resistance to these three drugs had an impact on outcome, further highlighting the importance of pre-therapy susceptibility testing [34]. Acquired resistance has been reported both in bedaquiline containing regimens and systematic reviews described the frequency and risk factors for acquired resistance, while cross-sectional/longitudinal analysis of patients in South Africa have characterised the genetic and epidemiological features of patients with acquired resistance during treatment [35, 36]. One of the main features that are shared is de facto monotherapy where the companion drugs are already resistant and bedaquiline is the only drug that is working, thus speeding up the selection of the resistant mutants. Acquired-resistance risk is heightened when companion-drug activity is inadequate due to undetected baseline resistance or a lack of choice, such as is seen in cohorts from China and South Africa [37]. Most treatment-outcome studies do not explicitly isolate the contribution of adherence in newer-drug resistance emergence, but show that poor adherence is associated with a higher likelihood of poor outcomes and amplification of resistance in cohorts of MDR-TB patients, suggesting that adherence support is a component of any broader resistance-prevention approach that includes biological risk factors. There is a dose-limiting toxicity issue with Linezolid between adequate bactericidal exposure and minimizing myelosuppression/neuropathy; ZeNix and hollow-fiber modeling found that dosing was important to maximize the sterilizing effect while minimizing toxicity and emergence of resistance. In addition, the sequence of treatments within treatment episodes is important: longitudinal analyses of concomitant/sequential exposure to bedaquiline and delamanid indicate that exposure to one drug before the other drug in the same treatment episode affects the risk of resistance, suggesting that such analyses are needed to consider a patient's cumulative treatment history [26].

7. Clinical Consequences

A cohort in China and South Africa found reduced susceptibility to bedaquiline during treatment to be associated with delayed sputum culture conversion and poor treatment outcomes such as failure to

achieve durable conversion [38,36]. The addition of bedaquiline, pretomanid/delamanid and linezolid to almost all current short regimens can leave few options if resistance to any of these drugs, or cross-resistance to the other nitroimidazole, occurs [39]. There is evidence of this from cohort data illustrating acquisition of clofazimine resistance after treatment with bedaquiline, as exposure to one drug can render a second, mechanistically related drug ineffective before it is even given.

Phylogenetic clustering of bedaquiline/clofazimine-resistance variants at the population level suggests that resistance may have been transmitted between people, in addition to being selected in patients admitted to hospital for treatment with the drug, and may have implications for surveillance and public-health action [21]. This dimension of transmission is programmatic, meaning that it implies that resistance prevalence within a specific context is not attributable entirely to the practices of the treatment providers in that context and that there is a need for molecular surveillance to identify acquired compared to transmitted resistance to allow for appropriate targeting. Extremely drug-resistant strains are capable of acquiring the ability to resist multiple drugs as was reported for an isolate from Uganda that was resistant to bedaquiline, linezolid, and clofazimine [40] – a set of drugs that when combined could effectively cure the patient of whom they were used by a whole genome sequencing case report.

8. Pharmacokinetics and Drug Exposure

The drug Bedaquiline has a long halflife; it is well distributed in tissues, metabolizes to an active metabolite (M2) through CYP3A4; the potential of interaction is clinically significant in the context of MDR-TB or comorbid HIV treatment [41]. Sub-therapeutic exposure, due to inter-patient pharmacokinetic difference, drug interaction or the dosing strategy, has been suggested as a potential factor in selection of resistance [42]. Due to the pharmacokinetic variability of linezolid and its close therapeutic window, hollow-fiber dose-optimization modelling and clinical assessment of alternative doses in BPaL-based regimens was driven. As a result, the high lipophilicity of clofazimine results in slow absorption, high tissue levels and a very long elimination half-life which helps to guide dosing for adequate early exposure to avoid significant accumulation-related toxicity [43].

Population pharmacokinetic analysis of bedaquiline has characterized inter-individual exposure variability, and led to the development of dosing strategies that limit the exposure in the intensive and continuation phase of treatment, thus making exposure a modifiable risk factor that can be managed by dose individualization [44]. While it is not yet possible to establish large-scale therapeutic drug monitoring (TDM) outcome trials for these agents, pharmacokinetic (PK) reviews on exposure concerns for these agents specifically mention TDM and exposure optimisation as strategies that should be evaluated further to reduce the risk of resistance, especially in patients with comorbidities, drug interactions, and extremes of body weight which are associated with atypical exposures. Available evidence, taken together, is consistent with the hypothesis that sub-optimal exposure levels may be conducive to selection of resistance, although quantitative models linking the specific levels of exposure to clinical emergence of resistance have not yet been established.

9. Prevention and Management

Baseline susceptibility testing is recommended for the selection of bedaquiline, linezolid and (where possible) the nitroimidazoles to prevent functional monotherapy and guide to identification of patients requiring individualised treatment. Well-

designed drug regimens should be based on baseline DST and local resistance epidemiology with sufficient likely effective companion drugs to prevent the development of resistance by reducing selective pressure. Active pharmacovigilance, including for linezolid-associated myelosuppression and neuropathy, ensures sufficient exposure without interruption and a dose interruption, which could exacerbate the functional-monotherapy situation pharmacovigilance aims to avoid, is itself a risk. Population-level and phylogenetic surveillance enables early detection of transmission clusters and program-level responses as opposed to individual responses. Baseline resistance testing (and, if applicable, serial resistance testing) to guide regimen construction and pharmacokinetic parameters (dose selection, interaction management, exposure monitoring if available) support individualized regimen construction, which is supported by genotype-phenotype characterization of sequential isolates. None of these measures is effective on its own; the more that are implemented the more effective, and weaknesses in any one measure (e.g. testing capacity, without adherence support; dosing optimization without surveillance) can result in a vulnerable weak link in the prevention chain.

10. EVIDENCE GAPS AND FUTURE DIRECTIONS

Many variants of Rv0678 are not fully functionally characterized, leading to genotype-phenotype discordance; little clinical-cohort (versus in vitro) evidence of relationship between exposure and resistance to pretomanid-delamanid; and a plausible but not yet prospectively confirmed exposure-resistance relationship. Multiple potentially relevant publications were found in this review that lacked bibliographic verification, reflecting a rapidly changing literature where sometimes preprints or conference abstracts precede peer-reviewed publications and data for implementation of targeted NGS in high-burden, resource-limited programs is generally limited compared to the pace at which assays are developed.

Continued development of rapid, near-point-of-care molecular assays that include resistance loci for all newer agents; scaling WGS-based surveillance, with continued expansion of compendium efforts like CRyPTIC; continuing refinement of the WHO mutation catalogue as genotype-phenotype data continue to be generated in different settings; and pharmacokinetically guided dosing, especially for bedaquiline and linezolid. Enlarging the newer-drug armamentarium to include more compounds and regimens is ongoing, with spectinamides being one of the candidates for substitution of linezolid [45]. The documented differences in availability of newer drugs provide further evidence that resistance-prevention strategies need to be matched with access to all the recommended TB drugs and diagnostics as well to access to formulations suitable for children, and age-specific considerations for TB management and prevention of resistance.

11. DISCUSSION AND CONCLUSION

There is no theoretical risk of resistance of newer and reused anti-TB medicines, it is a current and emerging issue. The key features of bedaquiline-clofazimine cross-resistance, on one hand, and the overlapping resistance mechanism for F420-dependent pathway of pretomanid and delamanid, demonstrate that this armamentarium, although mechanistic different from previous agents, is not immune to the same resistance pathways that have undermined first- and second-line regimens historically. In BPaL/BPaLM-type therapy, fewer drugs are used in combination, increasing the impact of individual resistance events.

There remain uncertainties that are still critical: for variants of Rv0678 which are rare or new, molecular testing cannot currently fully replace phenotypic testing; and the pharmacokinetic contribution to the emergence of resistance, although plausible, is yet to be definitively quantified in prospective studies. There is a further tension between regimen simplification and resistance risk: regimen simplicity requires standardization, which improves tolerability and shortens regimen duration but on its own lowering individualized tailoring to a patient's resistance profile, which has been repeatedly shown to be associated with acquired resistance in independent cohorts, both for undetected baseline resistance and for potentially inadequate companion-drug activity, representing functional monotherapy. The ability to rapidly and equitably build up baseline resistance testing capacity, along with diagnostic innovation, mutational catalogue refinement, pharmacokinetically informed dosage, and pharmacovigilance and molecular surveillance will be key to reconciling the programmatic benefits of standardization with individualized, resistance-informed design, so that the therapeutic advances of the last 10 years are not threatened by the resistance challenges of the next 10. None of these levers are stand-alone, and in fact, it will be their cumulative use over time and across levels of resource, that will safeguard the future of the newer-drug era of MDR/RR-TB treatment.

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