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Pretomanid for tuberculosis treatment: an update for clinical purposes

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ABSTRACT

Coronavirus disease (COVID-19) pandemic determined a 10 years-set back in tuberculosis (TB) control programs. Recent advances in available therapies may help recover the time lost. While Linezolid (LZD) and Bedaquiline (BDQ), previously Group D second line drugs (SLDs) for TB, have been relocated to Group A, other drugs are currently being studied in regimens for drug resistant TB (DR-TB). Among these, Pretomanid (PA), a recently introduced antimycobacterial drug derived from nitroimidazole with both solid bactericidal and bacteriostatic effect, and with an excellent effectiveness and tolerability profile, is in the spotlight. Following promising data obtained from recently published and ongoing randomized controlled trials (RCTs), the World Health Organization (WHO) determined to include PA in its guidelines for the treatment of rifampicin-resistant (RR), multi drug resistant (MDR) and pre-extensively drug resistant TB (pre-XDR-TB) with BDQ, LZD and Moxifloxacine (MFX) in a 6-month regimen. Although further studies on the subject are needed, PA may also represent a treatment option for drug-susceptible TB (DS-TB), latent TB infection (LTBI) and non tuberculous mycobacteria (NTM). This narrative review aims to examine current implementation options and future possibilities for PA in the never-ending fight against TB.

1. Introduction

Coronavirus disease (COVID-19) pandemic heavily impacted on the diagnosis and management of tuberculosis (TB) with an estimated global decrease of TB case detection of 18%, and the first increase year-over-year of TB-related deaths since 2005 reported in 2021 (Dheda et al., 2022). Moreover, the economical effects of the COVID-19 pandemic are expected to increase the catastrophic costs for TB treatment in high-burden, limited resources settings (Dheda et al., 2022). If immediate action is not undertaken a 10-years delay in TB control programs has been estimated (Dheda et al., 2022).

TB represents a global health crisis being one of the first causes of death from a single infectious pathogen worldwide; moreover the spread of drug resistant strains (DR-TB) is fueling the TB pandemic (Global, 2021).

These strains are defined as follows: rifampicin-resistant TB (RR-TB), multi-drug resistant TB (MDR-TB) with resistances to rifampicin (R) and isoniazid (H), pre-extensively drug resistant TB (pre-XDR-TB) with resistances to R, H and a fluoroquinolone (FLQ) among levofloxacin (LFX) or moxifloxacin (MFX), and extensively drug resistant TB (XDR-TB) with resistances to R, H, LFX or MFX and either bedaquiline (BDQ) or linezolid (LZD) (Li et al., 2021; Rapid, 2022).

First-line treatment for drug-susceptible pulmonary tuberculosis (DS-TB) requires four drugs administered for six months, with a reported success rate of 86%, while treatment of DR-TB requires longer, more expensive regimens hampered by a greater pill burden (Gotham et al., 2017).

In 2017, the European Center for Disease Prevention and Control (ECDC) reported a success rate of 58.7% for RR/MDR-TB cases and only 43% for XDR-TB at 24 months of follow-up after treatment completion (European center for disease prevention and control, 2017).

Hence the need for shorter, more effective, fully oral regimens with a lighter pill burden in order to increase treatment adherence and ultimately treatment success (van de Berg et al., 2021).

Pretomanid (PA), previously known as PA-824, is a new antimycobacterial oral drug approved in 2019 by the US Food and Drug

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Administration (FDA) (FDA Drug Approval Package, 2019).

Currently, the use of PA is approved in the BDQ-PA-LZD-MFX (BPaLM) and BDQ-PA-LZD (BPaL) combined regimens to treat patients at least 14 years old with pulmonary RR, MDR or pre-XDR-TB (Lyons, 2021; Rapid, 2022).

In this narrative review, we give an overview of the current use and future perspective of PA for clinical practice.

2. Methods

We performed a MEDLINE/PubMed search on May 1st, 2022. The search string was as follows: ((*PRETOMANID) AND (PA-824)) OR (PA-824)*.

3. Results

According to PRISMA 2020 flow diagram (Page at al., 2020), of the total 338 papers identified (334 from MEDLINE/PubMed and 4 from clinicaltrials.gov), as shown in Fig. 1, 9 were excluded by language screening (language other than English), 145 were excluded by title screening (not pertinent to our narrative review), and 99 were excluded by abstract screening. The remaining 85 papers were screened by full text and discussed by the Authors, who jointly made the final decision about which papers to consider for inclusion. The pertinent references of the selected 85 papers were evaluated and, if considered relevant, eventually included in the manuscript (Fig. 1).

Data of ongoing PA clinical trials were retrieved from clinicaltrials.gov/.

Moreover, we attached in supplementary files (Table S1) the full list of papers included in this review.

This narrative review was ultimately organized in the following major chapters: i) PA chemical structure; ii) pharmacokinetics, pharmacodynamics and patent of PA; iii) trial; iv) adverse effects, drug interactions and PA administration in special populations; vi) drug resistance; vii) related cost; viii) future perspective.

3.1. Chemical structure

PA is an oral bicyclic nitroimidazooxazine anti-mycobacterial drug which includes the nitroimidazole pyran A/B ring, an ether link and an hydrophobic side chain. The chemical name is (6S)-2-Nitro-6- {[4-(trifluoromethoxy)phenyl]methoxy} −6,7-dihydro- 5H-imidazo[2,1-b] [1,3]oxazine (Fig. 2). The molecular formula is C14H12F3N3O5, and the molecular weight is 359.26 uma. (FDA Drug Approval Package, 2019; Cherian et al., 2011; Pstragowski et al., 2017).

3.2. Pharmacokinetics

PA needs phase I and II biotransformation by several metabolic pathways. The elimination half-time is estimated at 16–20 h. The mean Tmax is 4–5 h and the steady state is achieved in 5–6 days. The drug diffuses into the body with a Vd/F of 92–180 L and is modestly bound to

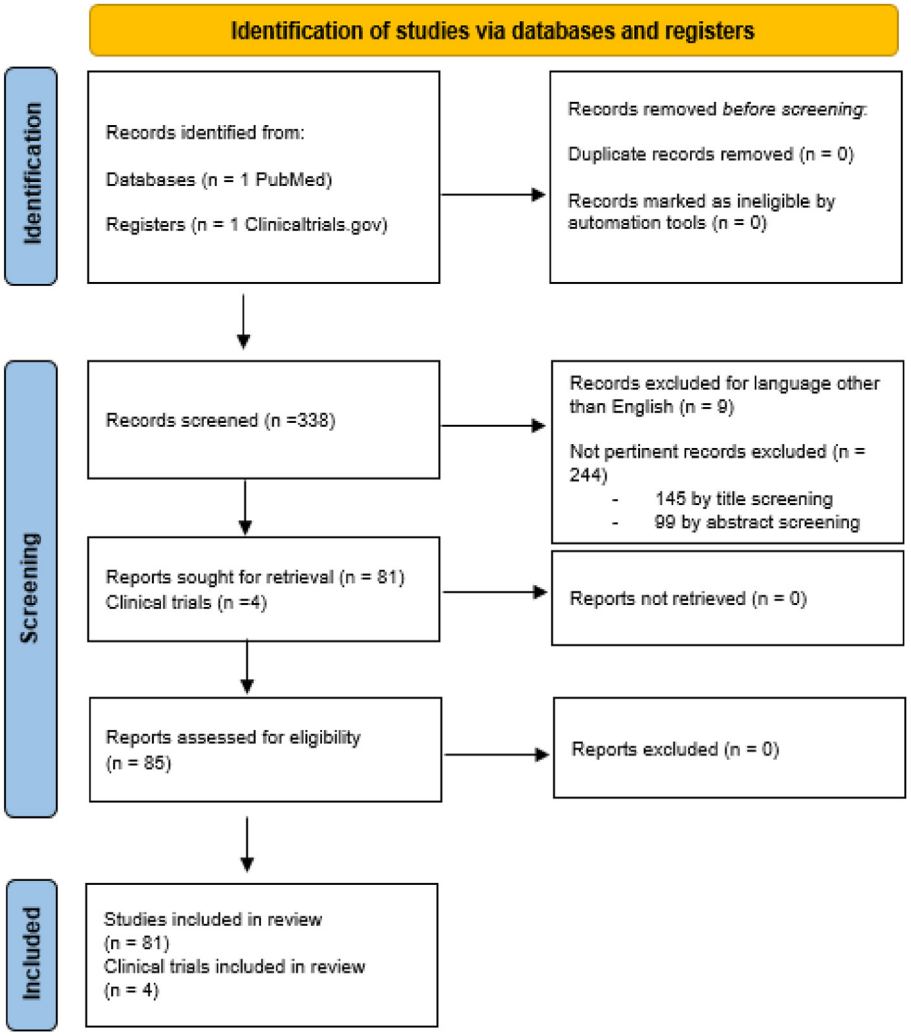

Fig. 1. PRISMA flow diagram adapted for our narrative review.

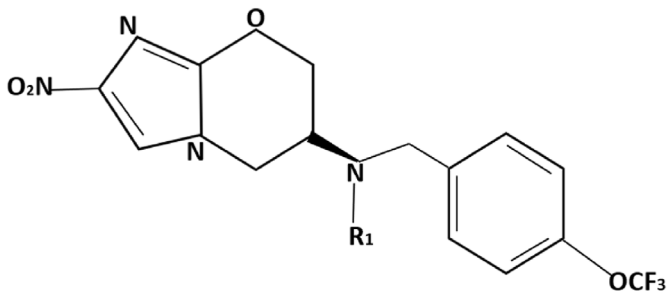

Fig. 2. Pretomanid chemical structure.

albumin (86.3–86.5%). A single daily dose posology is possible due to the good tissue absorption and to the long half-life of this drug. PA crosses the blood-brain barrier due to its lipophilic nature (Bahuguna and Rawat, 2020; Ginsberg et al., 2009a,b; Wang et al., 2015; Stancil et al., 2021; Diacon et al., 2012a,b).

The intake of the drug with food, especially a high-fat and high-calorie meal, enhances the solubility of the tablets and the gastrointestinal absorption of PA (Winter et al., 2013).

PA is metabolized by cytochrome CYP3A for about 20% of its intake (Pstragowski et al., 2017; Mitnick et al., 2009) and about 53% of the drug's dose is excreted in urine and 38% in feces (Wang et al., 2015).

3.3. Pharmacodynamics

PA is a prodrug and needs activation by *Mycobacterium tuberculosis* (Mtb) deazaflavin dependent-nitroreductase (ddn) which transforms PA into three primary active metabolites. The drug is clinically active against replicating and non-replicating bacilli through two main mechanisms of action (Pstragowski et al., 2017; Singh et al., 2008; Malo et al., 2021): 1) in aerobic conditions PA inhibits protein and lipid synthesis, which are essential components of the MTb cell, by a dose-dependent ability to decrease the availability of keto mycolic acids by an inadequate oxidative transformation of precursor hydroxymycolates; 2) in anaerobic state, PA generates des-nitro metabolites and the release of nitric oxide (NO). NO inhibits cytochrome *c* oxidase that leads to a significant reduction of the ATP concentration in cells (Li et al., 2021; Stancil et al., 2021; Villemagne et al., 2012; D'Ambrosio et al., 2015). This activity under anaerobic condition explains PA efficacy on non-replicating mycobacteria (Stancil et al., 2021; Singh et al., 2008; Manjunatha et al., 2009) comparable to R and LZD efficacy on inhibiting the growth of dormant phenotype Mtb (Diacon et al., 2012a,b; Ahmad et al., 2011; Wong et al., 2013; Fu and Tai, 2009). In vitro, the compound minimum inhibitory concentration (MIC) was estimated in between 0.015 and 0.25 μg/ml for drug-susceptible Mtb and among 0.03 and 0.53 μg/ml for drug-resistant strains (Pstragowski et al., 2017; Ginsberg et al., 2009a,b). In animal studies, PA showed a time dependent activity during the intensive phase of treatment as well as in the continuation period and a CFU count reduction by 0.1 log10 units/day over 24 days. The lowest bactericidal dose was 100 mg/kg/day and the minimal effective dose was 12.5 mg/kg/day (Mitnick et al., 2009; Conradie et al., 202; Tyagi et al., 2005). In a human comparative study, early bactericidal activity (EBA), defined as a decrease in log(10) colony forming units (CFU) of MTb per 1 ml of sputum after 14 days of treatment, no difference of response was found between PA at a dosage of 200 mg and 1200 mg establishing 200 mg as the minimum effective dosage for pulmonary TB (PTB) (Ahmad et al., 2011).

3.4. Patent

The patent for PA as an anti–mycobaterial agent was released on the January 28, 2021 with International Publication Number: WO2021/016012A1. Patent description is available at https://patents.google.com/patent/WO2021016012A1/en.

3.5. Trials

The newly released World Health Organization (WHO) guidelines, which included PA in regimens for the treatment of RR-TB, MDR-TB and pre-XDR-TB, were based on the following trials (World Health Organization, 2022).

3.5.1. NC001, NC002, STAND (PaMZ)

Between 2012 and 2014, 2 phase II trials (NC001 and NC002) confirmed the excellent EBA of PA combined with MFX and pyrazinamide (Z) emerged in preclinical studies (Diacon et al., 2012a,b; Dawson et al., 2015). This regimen was found to be non-inferior to the standard of care, with the eradication of 99% of Mtb after 2 and 8 weeks of treatment, even for MDR-TB cases. Notably, NCOO2 was the first trial to study a regimen both for the treatment of DS-TB and MDR-TB and at the same time to investigate potential interaction with antiretroviral drugs to treat patients with Human Immunodeficiency Virus (HIV) co-infection. These results paved the way for the development of a partially randomized, open-label, non-inferiority Phase 3 clinical trial (STAND--Shortening Treatments by Advancing Novel Drugs) studying the same regimen on 234 adults with DS-TB or RR-TB randomized to either 200 mg PA, 400 mg MFX and 1500 mg Z daily for 6 months (6Pa 200MZ) or 4 months (4Pa 200MZ); 100 mg PA for 4 months in the same combination daily (4Pa 100MZ) versus the standard of care (H, R, Z, E daily for 8 weeks, followed by H, R daily for 18 weeks: 2HRZE/4HR). However, 8 months in the trial, the recruitment was paused after three hepatotoxicity associated deaths were reported in the experimental arm. Further examination did not find correlation with drug induced liver injury (DILI) and the trial resumed. Final data showed higher rates of negative outcomes for the PaMZ regimen (treatment failure, relapse, adverse events) than the standard of care but, due to the small sample size, the trial was considered underpowered and results were deemed inconclusive (Tweed et al., 2021).

3.5.2. Simplici-TB trial (BPaMZ)

Following promising preclinical data on improved bactericidal activity, prevention of BDQ resistance and diminished time for relapse-prevention in drug-susceptible isolates with the addition of PA to BDQ-containing regimens several trials were commenced (Xu et al., 2019).

Simplici-TB, an open-label, partially randomized trial, is evaluating the efficacy, tolerability, and safety of BPaMZ regimen for the treatment of DS-TB with BDQ 200 mg daily for 8 weeks then 100 mg daily for 9 weeks, together with PA 200 mg + MFX 400 mg + Z 1500 mg daily for 17 weeks (total treatment duration 4 months) versus the standard of care (2HRZE+4HR), and for DR-TB with BDQ 200 mg daily for 8 weeks then 100 mg daily for 18 weeks, together with PA 200 mg + MFX 400 mg + Z 1500 mg daily for 26 weeks (total treatment duration 6 months). This trial is currently ongoing, the estimated completion date was February 25, 2022, results were not available at the time of this review (https://clinicaltrials.gov/ct2/show/NCT03338621).

3.5.3. Nix-TB (BPaL)

In 2015 NIX-TB, an open-label, single arm phase III trial, for the study of a regimen including BDQ, LZD and PA for the treatment of XDR-TB and treatment intolerant/non-responsive-TB in South African patients as young as 14 with or without HIV-coinfection (with a $CD4^+$ cell count of 50 or above) was initiated. 71 patients with XDR-TB and 38 patients with MDR-TB were included in this study and orally administered BDQ 400 mg for 2 weeks followed by 200 mg thrice-weekly for 24 weeks, PA 200 mg daily and either LZD 600 mg twice daily or LZD 1200 mg once daily for 26 weeks, or 39 weeks for those culture-positives at week 16. A favourable outcome was reported in 89% of XDR-TB, 92% for MDR-TB for a composite positive outcome of 90%. Notably, culture-conversion was obtained in 100% cases in 4 months, while 65% of patients were culture-negative by week 8. Seven total deaths were reported, 6 during the course of treatment,1 after relapse of disease. Unfortunately, 81% of

patients reported peripheral neuropathy and half of the patients were diagnosed with haematological disturbances, common side effects of LZD, highlighting the need for LZD better dose-finding (van de Berg et al., 2021; Conradie et al., 2020; Nedelman et al., 2020; Silva et al., 2018; Oelofse et al., 2021).

3.5.4. ZeNIX

In 2017, ZeNIX trial (phase 3 partially-blinded, randomized trial) followed its predecessor's path to resolve the issue of LZD toxicity, with either a halved duration of therapy or daily dosage of LZD, and to assess effectiveness of such reduced dosage and posology. Preliminary results, presented at the International AIDS Society (IAS) Conference in July 2021, showed that while effectiveness was preserved, as favourable outcomes were reported in 93.2% of patients on 1200 mg of daily LZD for 26 weeks, in 88.9% of patients on 1200 mg of LZD for 9 weeks, in 90.9% of patients on 600 mg of LZD for 26 weeks, in 84.1% of patients on 600 mg of LZD for 9 weeks fewer adverse events were reported. Further analysis of raw data is pending (https://theprogramme.ias2021.org/Abstract/Abstract/2405).

3.5.5. TB practecal

PA implementation in regimens for MDR-TB is being studied in another multi-centre, open label, multi-arm, randomized, controlled, phase II-III trial named TB PRACTECAL conducted by *Medecins sans frontieres* (MSF). Patients have been randomized in one of three experimental arms, each studying a different combination regimen of BDQ, PA, LZD and MFX or clofazimine (CFZ) with a total duration of 24 weeks. This trial's estimated date of completion is December 2022, no results were available at the time of this review (https://clinicaltrials.gov/ct2/show/study/NCT02589782).

3.6. Adverse effects

Real-life data are lacking but most commonly adverse effects related to PA administration reported in trials were: gastrointestinal (GI) symptoms (28,4%), hepatic disorders (25,5%) with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation (19,2%), skin or subcutaneous tissue disorders (16,6%), headache (11,0%) as shown in Fig. 3 (Nedelman et al., 2020).

QTc prolongation was not reported in studies evaluating adverse events during PA monotherapy and is not to be expected at labelled dosing. However, further studies are needed on this matter and, given the concomitant administration of drugs with demonstrated effect on QTc length (CFZ, BDQ, LFX, MFX), periodic monitoring of QTc with electrocardiogram (ECG) is recommended (Li et al., 2021).

Reversible increases of serum creatinine levels have been consistently reported in literature (Diacon et al., 2010; Olaru et al., 2015). Quite curiously these alterations are considered unreflective of renal function and probably due to selective inhibition of creatinine tubular secretion as a cosmetic side effect (Li et al., 2021; Ginsberg et al., 2009a,b; Diacon et al., 2010; Olaru et al., 2015; Ginsberg et al., 2009, 2009).

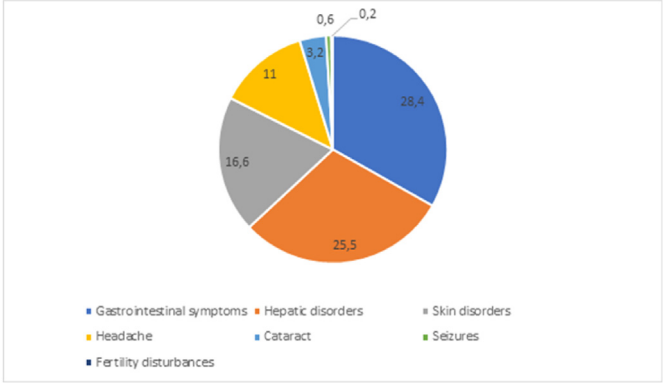

Fig. 3. Most common adverse events reported during PA administration in combination regimens (Nedelman et al., 2020).

Transient liver enzyme elevation was also commonly reported in preclinical studies and confirmed in patients receiving PA-containing regimens (LiverTox, 2012; Gils et al., 2022).

While testicular toxicity was noted in male rats administered PA, no effect on male human fertility was reported and sex hormone levels were consistently in range among male trial participants (World Health Organization, 2022; Black and Buchwald, 2021). An ongoing trial will further assess the effect of PA on male fertility (https://clinicaltrials.gov/ct2/show/NCT04179500).

3.7. Drug-drug interactions (DDIs)

The simultaneous intake of some drugs decreases plasma concentration of PA. For example, the area under the curve (AUC) reduction in PA concentration is 66% when coadministered with R, 35% when coadministered with efavirenz and 17% when coadministered with ritonavir (Salinger et al., 2019; Gopalan et al., 2016).

The effect of ritonavir on PA concentration is not clinically significant, therefore these drugs can be administered together in case of necessity (Ignatius and Dooley, 2019). Instead, efavirenz causes the induction of CYP3A which contributes for an estimated 20% to PA metabolism (Dooley et al., 2014). In patients on antiretroviral treatment (ART) the association of PA and efavirenz should be avoided because of the significant reduction in PA exposure caused by efavirenz (Dooley et al., 2014). Darunavir increases PA half-life and reduces its AUC and Cmax (Wang et al., 2018). By contrast PA does not affect the exposure of efavirenz or protease inhibitors like lopinavir or darunavir (Dooley et al., 2014). Initial concerns of a potential interaction between R and PA causing a decrease of AUC in PA concentration (Salinger et al., 2019) were dissipated after an interim analysis determined unlikely an impairment of efficacy if PA was administered with food (Ignatius et al., 2021). Even though H inhibits CYP3A enzymes, there is no evidence of a significant effect on PA kinetics (Ignatius et al., 2021). Conflicting data on an antagonistic effect of PA on the bactericidal activity of BDQ have been reported in literature (Muliaditan and Della Pasqua, 2021). In preclinical studies comparing different combinations of antitubercular drugs, PA added to BDQ and Z containing regimens did not increase EBA but showed reduced rates of relapse (Stancil et al., 2021).

PA does not enhance or inhibit CYP3A activity (Wang et al., 2018). No effects were found on midazolam plasma concentration in patients on treatment with PA (Winter et al., 2013). In vitro studies showed that PA inhibits the OAT3 drug transporter thus leading to an increased risk of adverse events related to the drugs substrate of this transporter. For instance, methotrexate, an OAT3 substrate, may need dosage adjustment when coadministered with PA (Tyagi et al., 2005).

PA does not alters the activity of cell-wall transporters such as breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug and toxin extrusion 1 and 2 (MATE1, MATE2), organic anion transporter 1 and B1 (OAT1, OAT1B1), organic anion transporting polypeptide 1B3 (OATP1B3), organic cation transporter 1 and 2 (OCT1, OCT2) or p-glycoprotein (P-gp) (FDA Drug Approval Package, 2019).

3.8. Special populations

No differences based on sex, body weight, race, PTB severity or HIV status has shown to modify PA pharmacokinetics (FDA Drug Approval Package, 2019).

3.9. Pregnancy and breast-feeding

In animal studies, maternal “no observed adverse effect level” (NOAEL), defined as the greater drug concentration at which no adverse effect is observed, was 10 mg/kg (rat model); embryo-fetal NOAEL was

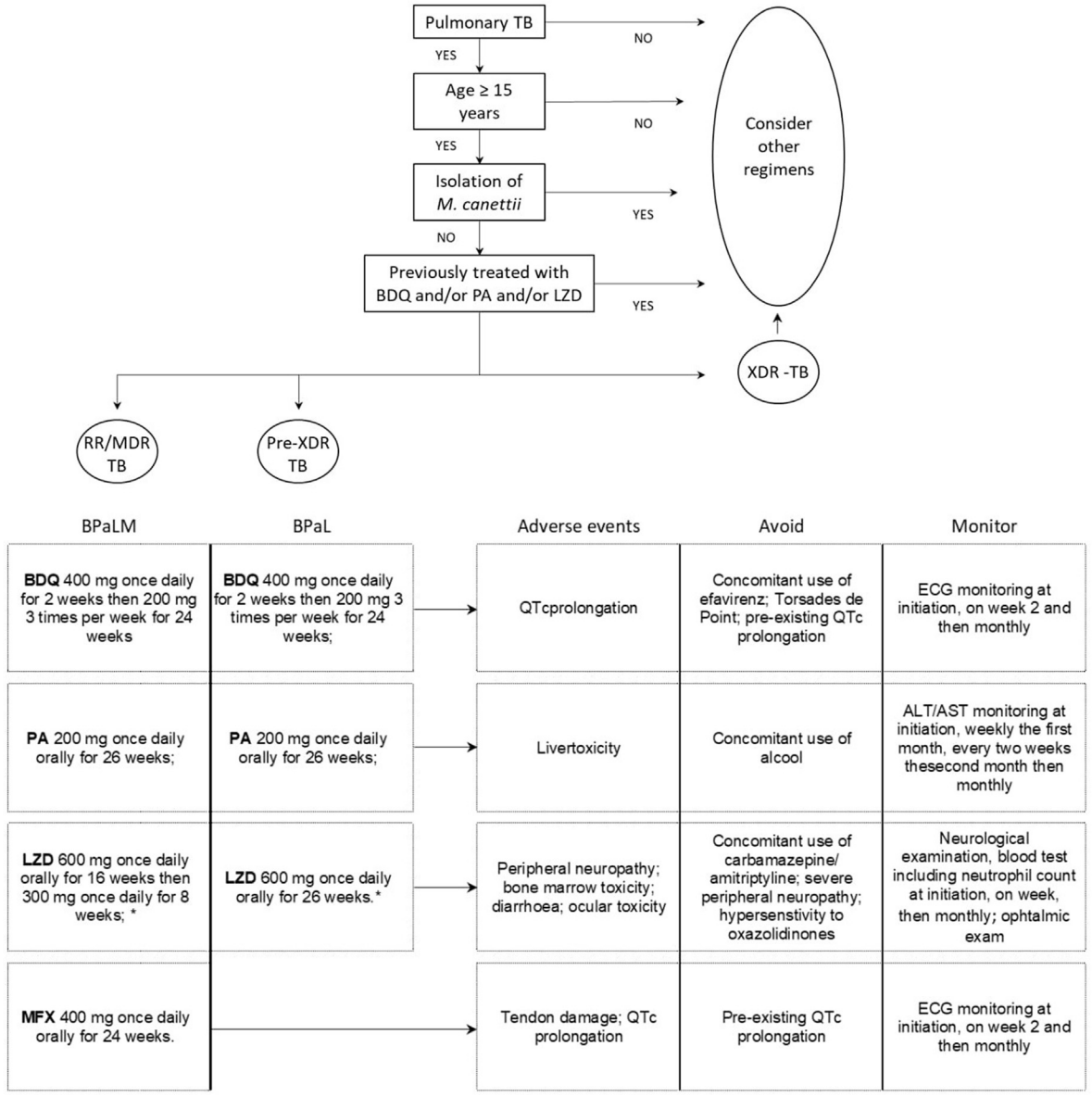

Fig. 4. Therapeutic algorithm for PA-containing regimens.
*For LZD dose finding is currently ongoing and therapeutic drug monitoring may be needed.

30–60 mg/kg (rat-rabbit model) (Stancil et al., 2021). A higher concentration of PA was found in milk (1.6 μg/mL) compared to plasma (1.1 μg/mL) (Stancil et al., 2021). To date, no data on PA administration during lactation in humans are available; other drugs should be considered in such circumstances. However, if PA is essential for the mother's treatment and cannot be substituted, both breastfeeding and PA administration should be continued (FDA Drug Approval Package, 2019; Stancil et al., 2021, Drugs and Lactation Database, 2020).

3.10. Children

Currently there is no data on PA effect and pharmacokinetic in children even though a prototype dispersible pediatric formulation is under evaluation (Garcia-Prats et al., 2018).

3.11. TB-HIV coinfection

PA, in the BPaL regimen, has shown to be safe and effective in HIV-positive people on ART as well as in HIV-negative people. We recommend that careful assessment of ART, with a switch to antiretroviral treatment without potential DDIs with PA, should be carried out to avoid PA lack of efficacy (Mulder et al., 2022).

3.12. Resistance to PA

Single nucleotide polymorphism (SNPs) mutations, an insertion or a deletion in genes target of the drug or enzymes involved in the drug metabolism can be responsible for PA resistance. Five genes causing 83% of mutations are considered accountable for cross drug resistance to PA and Delamanid (DLM): ddn (29%), fgd1 (7%), fbiA (19%), fbiB (2%), fbiC (26%) (Stancil et al., 2021; Gómez-González et al., 2021). fbiA, fbiB, fbiC, and fbiD are implicated in the biosynthesis of F420, a two-electron transfer cofactor involved in redox reactions and methane pathway (Stancil et al., 2021).

The bacterial ddn encodes for a 151 amino acids F420-dependent nitroreductase that is essential for the activation of the prodrug. A loss of function mutation in fbiD (Rv2983) results in ddn inability to mediate the NAP reduction (Stancil et al., 2021). Ddn mutations can occur

spontaneously, frequently (within a range of 10-5/10-7), thus rapidly leading to the inactivation of the nitroreductase. Surveillance for ddn polymorphisms should be always conducted (Lee et al., 2020; Kadura et al., 2020) and PA should always be administered in combined regimens in order to prevent the onset of resistances (Stancil et al., 2021; Haver et al., 2015). However, at the moment no standardized rapid method for the detection of PA-resistance is available, with whole genome sequencing as the sole test capable of identification which is not always readily available (Rifat et al., 2020). Furthermore, Rv2983 mutants showed phenotypic sensitivity to the use of malachite green as a selective decontaminant for common solid-media culture, such as Lowenstein-Jensen, possibly hampering the isolation of PA-resistant strains (Rifat et al., 2020).

3.13. Cost analysis of PA

The economic aspect of PA is as relevant as are its chemical properties and clinical applications. DR-TB treatment is extremely expensive, moreover, out-of-pocket fees and loss of productivity often represent a catastrophic cost for patients (Mulder et al., 2022) thus affecting adherence to therapy and ultimately treatment outcomes. Ongoing trials in high-burden RR/MDR-TB and XDR-TB settings are showing that BPaL regimen can be two-to-five times cheaper than conventional treatment (Mulder et al., 2022; Gomez et al., 2021). The reduced cost of BPaL derives from a decreased procurement price established by the Global Drug Facility (GDF), from a shorter therapy, from a reduction of the total number of drugs involved, but also from a reduced use of health services such as outpatient consultations for directly-observed-therapy (DOT), home visits and safety monitoring blood tests (Mulder et al., 2022). The estimated prices of drugs used in XDR-TB treatment were USD $8-$17/month for BDQ, $5-$16/month for DLM, $11-$34/month for PA, $4-$9/month for LZD (Mulder et al., 2022). The cost of PA-containing three-drug regimens was expected to be $53-$276 while for DLM based four drug regimens (DLM, LZD, BDQ, CFZ, high-dose H - or ethionamide, either with or without Z) is $238-$507 (in the current Global Drug Facility list price, a PA treatment is estimated to cost US$ 364) (Gomez et al., 2021).

3.14. Future challenges for implementation of PA in the treatment of TB

Current indications of PA use are shown in Fig. 4. The use of PA in settings other than the treatment of DR-TB has been evaluated. As previously said, in STAND and Simplici-TB trial, PA was tested against Mtb drug-susceptible strains (Tweed et al., 2021; Xu et al., 2019). In STAND trial, PA-containing regimens administered to DS-TB have shown a superior bactericidal effect compared to standard of care (McKenna and Furin, 2019) even though higher rates of adverse events were reported, possibly due to the concomitant administration of companion drugs with known high rates of adverse events (Riccardi et al., 2020). In a Phase II dose ranging randomized trial, a dose of 100 mg–200 mg PA daily appeared safe and effective against DS-TB (Tweed et al., 2019). BloadPaZ and B200PaZ are encouraging regimens for the treatment of patients with DS-TB. PA based regimens could then decrease treatment duration and pill burden for DS-TB (Tweed et al., 2019). Another motive to implement alternative regimens for DS-TB is the poor performance of the standard of care (2HRZE4HR) when the relatively frequent H-monoresistance is present (Tweed et al., 2019).

Furthermore, given its dual activity on both replicating and non-replicating MTb, PA represents an interesting option for new regimens for latent tuberculosis infection (LTBI) of both DS and DR-TB. Studies in animal models showed limited activity of PA monotherapy in LTBI while further data is needed to assess its usage in combination therapy in order to reduce treatment length and side effects (Dutta and Karakousis, 2014; Somasundaram et al., 2013).

Given the expected use on a large scale of PA, the development of readily available methods for drug-resistance detection through molecular and phenotypic tests is urgently needed (Rifat et al., 2020).

PA could turn into an ally in the challenging treatment of non tuberculous mycobacteria (NTM) species. However, *M. avium*, *M. intracellulare*, *M. abscessus* and *M. fortuitum* are innately resistant to PA. No effectiveness was found against *M. leprae*. The activity against *M. ulcerans* ($\leq$4 to $\geq$16 μg/mL) appears to be lower. It is unclear if the drug is active against *M. kansasii* (Stancil et al., 2021). The different resistant pattern of NTM against PA may lie in the presence of alternative forms of ddn sequences, essentials for the activation of the prodrug (Zhang et al., 2020).

Alternative drug formulations to oral PA tablets were also tested, such as a dry powder formulation for aerosol inhalation with reportedly similar pharmacokinetics behaviors (Sung et al., 2009). Sung et al. showed higher stability of this formulation and a better pharmacokinetic profile than oral or intravenous administration. Topical administration may permit PA dosage reduction and further decrease treatment duration and systemic side effects (Villemagne et al., 2012; Sung et al., 2009).

4. Conclusions

The implementation of recently approved combinations of antitubercular drugs for a shorter, safer and overall more effective treatment for DR-TB may contribute to reduce the estimated 10-years delay in TB control programs due to the COVID-19 pandemic (Dheda et al., 2022), although the precise effect of the current Ukrainian crisis, which is expected to increase the percentage of patients living with TB without proper care (Sotgiu et al., 2022), has yet to be assessed.

In this landscape, attempts to reduce treatment duration also for DS-TB and LTBI are fundamental. Given its optimal safety and effectiveness profile, PA, among other drugs, holds the potential to be one of the main actors for future positive developments in TB control and eradication.

CRediT authorship contribution statement

Sara Occhineri: Investigation, Data curation, Writing – original draft, Writing – review & editing. **Tommaso Matucci:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Laura Rindi:** Validation, Supervision. **Giusy Tiseo:** Validation, Supervision. **Marco Falcone:** Validation, Supervision. **Niccolò Riccardi:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing, Validation, Supervision, Project administration. **Giorgio Besozzi:** Conceptualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crphar.2022.100128.

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