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Systematic review

Pretomanid for tuberculosis: a systematic review

Tinne Gils [1, *], Lutgarde Lynen [1], Bouke C. de Jong [2], Armand Van Deun [3], Tom Decroo [1, 4]

[1] Unit of HIV and Coinfections, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[2] Unit of Mycobacteriology, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium
[3] Independent consultant, Leuven, Belgium
[4] Research Foundation Flanders, Brussels, Belgium

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ABSTRACT

Background: Outcomes of treatment of tuberculosis patients with regimens including pretomanid have not yet been systematically reviewed.
Objectives: To appraise existing evidence on efficacy and safety of pretomanid in tuberculosis.
Data Sources: Pubmed, clinicaltrials.gov. and Cochrane library.
Study eligibility criteria: Quantitative studies presenting original data on clinical efficacy or safety of pretomanid.
Participants: Patients with tuberculosis.
Interventions: Treatment with pretomanid or pretomanid-containing regimens in minimum one study group.
Methods: Two authors independently extracted data and assessed risk of bias. Data on efficacy (early bactericidal activity, bactericidal activity, end-of-treatment outcomes and acquired resistance) and safety were summarized in tables. Mean differences in efficacy outcomes between regimens across studies were calculated.
Results: Eight studies were included; four randomized controlled trials on 2-week early bactericidal activity in rifampicin-susceptible tuberculosis, three trials with randomized rifampicin-susceptible tuberculosis arms and a single rifampicin-resistant tuberculosis arm (two on 8-week bactericidal activity, one on end-of-treatment outcomes), one single-arm trial with end-of-treatment outcomes in highly resistant tuberculosis. Activity of pretomanid–moxifloxacin–pyrazinamide was superior to standard treatment on daily change in colony-forming units at days 0–2, 0–56 and 7–56 and time to culture conversion in rifampicin-susceptible tuberculosis (hazard ratio: 1.7; 95% CI 1.1–2.7), but not at end of treatment in one study. This study was stopped due to serious hepatotoxic adverse events, including three deaths, in 4% (95% CI 2–8) patients on pretomanid–moxifloxacin–pyrazinamide and none in controls. In patients with uncomplicated rifampicin-resistant tuberculosis on pretomanid-moxifloxacin-pyrazinamide treatment, 91% (95% CI 59–100) had favourable end-of-treatment outcomes. In patients with highly resistant tuberculosis, 90% (95% CI 83–95) on pretomanid–bedaquiline–linezolid had favourable outcomes six months after treatment, but linezolid-related toxicity was frequent. No acquired resistance to pretomanid was reported.
Conclusions: Evidence suggests an important role for pretomanid in rifampicin-resistant and highly resistant tuberculosis. Trials comparing pretomanid to existing core and companion drugs are needed to further define that role. **Tinne Gils, Clin Microbiol Infect 2022;28:31**

Introduction

Tuberculosis (TB) was the leading cause of death by a single infectious agent in 2019 [1]. TB treatment regimens contain an active core drug with high bactericidal and high sterilizing activity to drive its efficacy [2]. For rifampicin-resistant (Rr) TB treatment

* Corresponding author. Tinne Gils, Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000, Antwerp, Belgium.
E-mail address: tgils@itg.be (T. Gils).

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regimens fluoroquinolones and bedaquiline (Bdq) act as core drugs. High early bactericidal activity (EBA) is important to prevent resistance against the core drugs. Reported acquired Bdq resistance during all-oral treatment shows that constituting robust Rr-TB treatment regimens is still challenging [3–6]. Since 2019, pretomanid (Pa) can be used under operational research conditions with Bdq and linezolid (Lzd) for Rr-TB with fluoroquinolone resistance [4,7]. Pa is an oral nitroimidazole with in vitro and in vivo activity against *Mycobacterium tuberculosis* (MTB) [8–10]. Pa kills active MTB through inhibition of mycolic acid biosynthesis, blocking cell wall production. In anaerobic or hypoxic conditions, Pa acts against non-replicating bacilli [11,12]. In mice, Pa contributed to bactericidal activity and relapse prevention when combined with Bdq-Lzd or Bdq-moxifloxacin (Mfx)-pyrazinamide (Z) and prevented acquired Bdq resistance in the former [13]. Bioavailability of Pa at 50–1500 mg in humans was good and increased after a high-calory, high-fat meal compared to the fasting state [14,15]. With a half-life of 16–20 hr, Pa can be given once daily. CYP3A4 accounted for ≈20% of Pa metabolism in vitro [16]. However, rifampicin is unlikely to reduce Pa's efficacy when given with food [17]. In healthy subjects receiving Pa no serious adverse events (SAE) occurred [18,19]. We summarized efficacy and safety-related outcomes of Pa-containing treatment regimens in TB patients.

Material and methods

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Synthesis without meta-analysis in systematic reviews for reporting [20,21]. We searched Medline using Pubmed with search terms “pretomanid” or “PA-824” for peer-reviewed publications, without language restrictions, until December 2020. An automatic search with the same terms was used until March 2021. We hand-searched published data on Pa on clinicaltrials.gov and the Cochrane library of clinical trials. Quantitative studies reporting original data on primary endpoints in more than one participant diagnosed with TB and receiving Pa as a single drug or as part of a treatment regimen were included. Two authors independently screened titles and abstracts and full articles and assessed selected articles for risk of bias with the Cochrane tool for randomized trials and an adapted Newcastle-Ottawa tool for non-randomized studies [22,23]. We extracted data on study and participant characteristics and safety- and efficacy-related outcomes, including acquired resistance to study drugs. Due to content heterogeneity between the included studies regarding intervention (composition and dosage of included regimens and duration of administration) and outcomes, we did not conduct a meta-analysis. We have summarized study and participant baseline characteristics and safety data for all studies in tables. We tabulated efficacy-related results of individual studies grouped per treatment duration and regimen. Study arms showing treatment regimen data (at least three drugs) and arms that differed only for a single drug (one drug replacing another one, or one drug was added) were compared head to head. For these comparisons only Pa at 200 mg was considered as single drug. When not reported, we calculated mean differences in efficacy outcomes between regimens and controls within a study and between regimens across studies (two-sample t-test). We tabulated statistically significant differences ($p < 0.05$) in efficacy outcomes. A forest plot was constructed to present end-of-treatment outcomes. We compared safety outcomes for regimens with the same treatment duration (z-test). We used 2020 World Health Organization (WHO) definitions for multidrug-resistant TB (MDr-TB: TB with resistance to R and H; pre-extensively-resistant TB (pre-XDr-TB: Rr/MDr-TB with fluoroquinolone-resistant and extensively resistant TB (XDr-TB: pre-XDr-TB with resistance to Bdq or Lzd [24]. EBA was the ability of the drug to kill mycobacteria in the first two weeks of administering treatment, measured by quantification of viable colony-forming units (CFU) of MTB in overnight sputum collection (EBA_{CFU}) or prolongation of time to positivity (TTP) of MTB in automated liquid culture systems (EBA_{TTP}). Bactericidal activity was a change in CFU and TTP of MTB and time to culture and smear conversion after 56 days of treatment. Treatment efficacy outcome definitions were based on WHO definitions and shown in the table legend [25]. Tabulated events include those not considered treatment related unless specified. Safety data were retrieved from the article or clinicaltrials.gov. Pa was dosed at 200 mg daily unless specified. Posology and treatment duration of other drugs are specified in Table 1 and when they formed the only difference between regimens within a study. Analyses were done with Stata (StataCorp. 2019. Stata Statistical Software*: Release 16*. College Station, TX: StataCorp LLC). We did not register a review protocol online.

Results

Study characteristics

The search identified 285 studies. Seven studies met inclusion criteria (Fig. 1). Tweed et al. (2021) was included in March 2021 [26].

Risk of bias of the included studies

Randomized studies were classified as having moderate to high risk of bias, because none applied double blinding to the complete cohort (please see supplementary material). Dawson et al. [31] and Tweed et al. [26,32] were considered at high risk of bias due to the open-label design and the presence of a non-randomized arm. One single-arm trial provided lower quality of evidence compared to other included studies [33].

Participants baseline characteristics

Table 2 shows participant baseline resistance profiles and HIV-status.

Except Tweed et al. [26,32], all studies reported baseline minimum inhibitory concentrations (MIC) for Pa. In Diacon et al. [29] and Dawson et al. [31] none had MIC indicative of Bdq resistance. In Conradie et al. the baseline MIC for Bdq and Lzd was above the recommended critical concentration (1 μg/mL) in 5% (3/57) (two had a MIC for Bdq of 2 μg/mL, and one of 4 μg/mL in liquid medium at baseline) [33].

Treatment efficacy

Early bactericidal activity

Four studies focused on EBA in Pa (Table 3) or Pa-containing regimens (Table 4, supplementary material).

In Diacon et al. [27,28] respectively 4% (3/69, two on Pa, one on Pa 1200 mg) and 1% (1/69, on Pa 50 mg) interrupted treatment after adverse events, 1% (1/69, on Pa 1000 mg) withdrew consent [27,28].

In Diacon et al. [29], 8% (7/85) on Pa-Mfx-Z stopped following adverse events (20% (3/15), and 7% (1/15) in each other experimental arm. Pa-Mfx-Z had superior day 0–2 EBA_{CFU} to HRZE. In Diacon et al. [30], 7% (1/15) interrupted on Pa-Bdq-Cfz and 7% (1/15) on Cfz following consent withdrawal, 7% (1/15) on HRZE after patient's request, 7% (1/15) on Bdq-Z-Cfz due to non-compliance and 7% (1/15) on Pa-Bdq-Z following adverse events [30].

Table 1
Characteristics of studies including tuberculosis patients on pretomanid-containing regimens

Study, year, country, ref. no.	Design	Population	Study size	Regimens used and arms [a]	Time on treatment	Primary end-point (definition)
Diacon 2010, South Africa [27]	RCT	Adults, treatment-naive, pulmonary sputum smear-positive Rs-TB Excl. HIV-positive on ART or CD4≤ 300 cells/μL	69	Arm 1: Pa Arm 2: Pa600 Arm 3: Pa1000 Arm 4: Pa1200 Control: HRZE	2 weeks	Early bactericidal activity (Mean rate of change in $\log_{10}$ CFU/day/mL sputum over days 0–14 on treatment)
Diacon 2012, South Africa [28]	RCT	Adults, treatment-naive, pulmonary sputum smear-positive Rs and Hs-TB Excl. HIV-positive with CD4≤ 300 cells/μL	69	Arm 1: Pa50 Arm 2: Pa100 Arm 3: Pa150 Arm 4: Pa Control: HRZE	2 weeks	Early bactericidal activity (Mean rate of change in $\log_{10}$ CFU/day/mL sputum over days 0–14 on treatment)
Diacon 2012, South Africa [29]	RCT	Adults, treatment-naive, pulmonary Rs-TB Excl. HIV-positive on ART or CD4≤ 300 cells/μL	85	Arm 1: Bdq [b] Arm 2: Bdq-Z [c] Arm 3: Pa-Z Arm 4: Pa-Bdq [c] Arm 5: Pa-Mfx-Z Control: HRZE	2 weeks	Early bactericidal activity (Mean rate of change in $\log_{10}$ CFU/day/mL sputum over days 0–14 on treatment)
Diacon 2015, South Africa [30]	RCT	Adults, treatment-naive, pulmonary sputum smear-positive Rs and Hs-TB Excl. HIV-positive with CD4≤ 300 cells/μL	105	Arm 1: Cfz Arm 2: Z Arm 3: Bdq[d]-Z-Cfz Arm 4: Pa-Bdq[d]-Z Arm 5: Pa-Bdq[d]-Cfz Arm 6: Pa-Bdq[d]-Z-Cfz Control: HRZE	2 weeks	Early bactericidal activity (Mean rate of change in $\log_{10}$ CFU/day/mL sputum)
Dawson 2015, South Africa, Tanzania [31]	RCT with single Rr-TB arm	Adults, treatment-naïve, pulmonary sputum smear-positive Rs-TB Adults, Rr-TB [f] Excl. HIV-positive with CD4≤200 cells/μL	207	Arm 1: Pa100-Mfx-Z Arm 2: Pa-Mfx-Z Control: HRZE Arm 3: Pa-Mfx-Z	8 weeks	Bactericidal activity (Mean rate of change in $\log_{10}$ CFU/week/mL sputum over days 0–56 on treatment)
Tweed 2019, South Africa, Tanzania, Uganda [32]	RCT with single Rr-TB arm	Adults, treatment-naive pulmonary sputum smear-positive Rs-TB Adults, Rr-TB [f] Excl. HIV-positive with CD4≤100 cells/μL	240	Arm 1: Pa-Bdq-Z Arm 2: Pa-Bdq[e]-Z Control: HRZE Arm 3: Pa-Bdq[e]-Mfx-Z	8 weeks	Bactericidal activity (Daily percentage change in time to sputum positivity in liquid medium over days 0–56 on treatment)
Conradie 2020, South Africa [33] [g]	Single arm study	Aged >14 years, pre-XDr-TB, Non-responsive MDr-TB Excl. HIV-positive with CD4≤50 cells/μL	109	Pa-Bdq-Lzd	6–9 months	Efficacy (Incidence of combined bacteriological failure or relapse or clinical failure 6 months after treatment end)
Tweed 2021, Kenya, Malaysia, South Africa, Tanzania, Thailand, The Philippines, Uganda, Ukraine [26] [h]	RCT with single Rr-TB arm	Adults, treatment-naïve, pulmonary sputum smear-positive Rs- and Hs-TB Adults, Rr-TB[f] Excl. HIV-positive with CD4≤100 cells/μL	284	Arm 1: 4Pa100-Mfx-Z Arm 2: 4Pa-Mfx-Z Arm 3: 6Pa-Mfx-Z Control: HRZE Arm 4: 6Pa-Mfx-Z	4–6 months	Efficacy (Incidence of combined bacteriological failure or relapse or clinical failure at 12 months after randomization)

ART, anti-retroviral treatment; Bdq, bedaquiline; CD4, CD4 T-lymphocytes count; CFU, colony-forming units; Cfz, clofazimine; Cs, cycloserine; E, ethambutol; Eto, ethionamide; FQ, fluoroquinolone; H, isoniazid; Hh, high-dose isoniazid; Hs-TB, isoniazid-susceptible tuberculosis; Lzd, linezolid; MDr-TB, multidrug-resistant tuberculosis; Mfx, moxifloxacin; Pa, pretomanid; Pto, prothionamid; qd, per day; R, rifampicin; Rs, rifampicin-susceptible tuberculosis; RCT, randomized controlled trial; Rr-TB, rifampicin-resistant tuberculosis; Rs-TB, rifampicin-susceptible tuberculosis; SLI, second-line injectable; TB, tuberculosis; Z, pyrazinamide; pre-XDr-TB, pre-extensively resistant tuberculosis.

[a] Dosage unless specified otherwise: Bdq 400 mg qd for 2 weeks and 200 mg three times a week after that, Cfz 300 mg qd for 3 days and 100 mg qd after that, Lzd 1200 mg qd, Mfx 400 mg qd, Pa 200 mg qd, Z 25 mg/kg or 1500 mg qd.

[b] Bdq dose: 400 mg qd, except 700 mg on day 1, 500 mg on day 2 + Z placebo.

[c] Bdq dose: 400mg qd, except 700 mg on day 1, 500 mg on day 2.

[d] Bdq dose: 200mg qd, except 400 mg on day 1, 300 mg on day 2.

[e] Bdq 200 mg qd.

[f] Group not randomized.

[g] Non-responsive MDr-TB: TB resistant to H, R and not responding to treatment, or treatment discontinued due to side-effects. Pre-XDr-TB: TB with resistance to R, H, FQ and at least one second-line injectable (XDr-TB in previous WHO guidelines).

[h] Numbers 4 and 6 before the regimen refer to the total number of months of administration of that regimen.

Bactericidal activity after 8 weeks of treatment

Results related to 8-week bactericidal activity are presented in Table 5 and Table 6 [26,31,32].

In Dawson et al. (2015), 1/207 (<1%) rifampicin-susceptible TB (Rs-TB) patient on Pa-Mfx-Z was excluded from the efficacy analysis [31]. Tweed et al. (2019) excluded 3% (2/59) of patients on Pa-Bdq-Z, 5% (3/60) on Pa-Bdq200-Z, 3% (2/61) on HRZE, and 37% (22/60) on Pa-Bdq-Mfx-Z due to pyrazinamide resistance, and 2% (1/60) on Pa-Bdq200-Z had no data [32].

Treatment efficacy at end of treatment

Two studies reported final treatment outcomes (Fig. 2, Table 7).

In Conradie et al. (2020), outcomes were similar regardless of resistance profile or HIV status [33]. Tweed et al. (2021) [26] was interrupted due to safety concerns, remaining underpowered for its primary outcome. Per protocol analysis showed 73% (38/52) favourable outcomes in patients on 4Pa100-Mfx-Z, 81% (46/57) on 4Pa-Mfx-Z, 91% (43/47) on 6Pa-Mfx-Z and 98% (52/53) of controls (2HRZE/4HR). The absolute difference in unfavourable outcomes with the control group in 12-month modified intention-to-treat analysis was 25.0% (95% CI -12.4%–37.6%) for 4Pa100-Mfx-Z, 17.4% (95% CI -6.5%–28.3%) for 4Pa-Mfx-Z, and 6.6% (95% CI −2.2%–15.4%) for 6Pa-Mfx-Z. All ten Rr-TB patients reached a favourable outcome in per protocol analysis. Among HIV-positive participants, 33% (14/43) in experimental arms versus 13% (2/15) of controls experienced unfavourable outcomes. Two years after randomization, the difference in unfavourable outcomes between the 6Pa-Mfx-Z and control arms was 7.6% (95% CI −7.7–22.9%) in modified intention-to-treat and 4.8% (95% CI 6.5–16.0%) in per protocol analysis. Seven additional patients died of non-TB-related causes during two-year follow-up (1 in the 4Pa-Mfx-Z, 6Pa-Mfx-Z and Rr-Tb arm, 2 in the 4Pa100-Mfx-Z and control arm [26].

Acquired resistance to study drugs

In Diacon et al. 6% (4/65) of patients who finished treatment had MIC for Pa increased from 0.1 μg/mL at baseline to >0.4 μg/mL [28]. In Dawson et al., 0.5% (1/206) who finished treatment) had MIC of Pa increased from <0.025 at baseline to 0.1 μg/mL, while the MIC for Mfx did not increase [31]. In Conradie et al. (2020), genome sequencing was performed for patients with relapse. One patient relapsed with the same strain as the baseline one and acquired Bdq resistance (*Rv0678* mutations). The MIC of Bdq was 4 μg/mL in the relapse isolate compared to 0.5 μg/mL at baseline. The second patient had no baseline result, but a relapse strain susceptible to Bdq, Pa and Lzd [33]. Acquired resistance to Pa was not reported.

Comparison of efficacy

Table 8 shows statistically significant differences in efficacy outcomes between relevant regimens.

Safety

Studies administering Pa for two weeks reported no treatment-related SAE [27–30] (Table 9). Adverse events during two weeks of Pa-administration resulted in treatment interruptions in all treatment groups in Diacon et al. [29] and one patient on Pa-Bdq-Z in Diacon et al. [30]. In Dawson et al. [31], more SAE occurred on Pa-Mfx-Z (7/62, 11%) compared to Pa100-Mfx-Z (1/60, 2%) (p 0.032) and HRZE (1/59, 2%) (p 0.034). In Tweed et al. [32], discontinuation following adverse events happened in Pa-Bdq-Z (10%, 6/59), Pa-Bdq200-Z (8%, 5/60) and HRZE (3%, 2/61). Tweed et al. [26] reported three deaths in experimental arms attributed to the regimen: 2% (1/65) on 4Pa100-Mfx-Z and 3% (2/71) on 4Pa-Mfx-Z. More grade 3–5 events were reported on Pa-Bdq-Lzd in highly resistant TB (62/109, 57%) compared to 6Pa-Mfx-Z in Rr-TB (3/13, 23%) (p0.021) [26,33].

Hepatotoxicity

Liver-enzyme increases during two weeks of treatment with Pa-containing regimens led to withdrawal of 7% (1/15) on each experimental regimen in Diacon et al. (2012), and 7% (1/15) on Pa-Bdq-Z in Diacon et al. (2015) [29,30]. In Dawson et al. [31], increased liver enzymes led to treatment interruptions in 13% (8/60) on Pa100-Mfx-Z, 13% (8/62) of Rs-TB and 8% (2/26) of Rr-TB patients on Pa-Mfx-Z, and 10% (6/59) on HRZE. Three serious hepatic adverse events were reported (3% (2/62) on Pa-Z-Mfx, 2% (1/59) on HRZE) [31]. In Tweed et al. [32], liver-enzyme elevations led to withdrawal of 8% (5/59) of patients on Pa-Bdq-Z, 5% (3/60) on Pa-Bdq200-Z, 3% (2/61) on HRZE and 3% (2/60) of Rr-TB patients on Pa-Bdq-Mfx-Z and were more common in Pa-Bdq-Z than in HRZE [32]. Hepatic SAE occurred in 3% (2/59) patients on Pa-Bdq-Z, 3% (2/60) on HRZE and 3% (2/61) of Rr-TB patients [32]. Three hepatotoxic lethal adverse events were attributed to delayed recognition of medication-induced liver failure in Tweed et al. [26], leading to its halt at eight months enrolment. Hepatic adverse events happened in experimental arms (36% (24/67) on 6Pa-Mfx-Z, 24% (17/71) on 4Pa-Mfx-Z, 29% (19/65) on 4Pa100-Mfx-Z) and 31% (21/68) of controls. Liver-related SAE were significantly higher in Rs-TB patients on 4Pa-Mfx-Z (6%, 4/71) and 6Pa-Mfx-Z (6%, 4/67) compared to HRZE (0%) (p 0.047, 0.041). Eleven percent (23/203) and 7% (14/203) of Rs-TB patients taking Pa and 6% (4/68) and 3% (2/68) on HRZE had peak ALT of 5–10 × or >10 × the upper-limit of normal, respectively [26]. In Conradie et al. [33], liver-enzyme increases caused 7% (8/109) to temporarily interrupt treatment.

Cardiotoxicity

One patient on Pa-Mfx-Z for two weeks was withdrawn following QT-prolongation (QTcF: 510 ms, QTbF: 517 ms) [29]. One patient on Pa 100 mg had an atrioventricular block [27,28]. In Diacon et al. [30], non-significant QTcB or QTcF changes of ≥60 ms from baseline were reported in 13% (2/15) and 27% (4/15) of patients on Pa-Bdq-Cfz. Dawson et al. [31] reported increases of ≥60 ms in QTcB and QTcF in 5% (3/15) and 3% (2/15) on Pa100-Mfx-Z and QTcF in Pa-Mfx-Z; 7% (4/15) Rs-TB and 8% (2/15) of Rr-TB patients. QTcF increase from baseline was significantly higher in Pa-Mfx-Z in Rs-TB (18 ms (95% CI 15–20)) when compared to other arms (Pa100-Mfx-Z: 11 ms (95% CI 8–14), HRZE: 7 ms (95% CI 3–10), Pa-Mfx-Z (Rr-TB: 11 ms (95% CI 6–17)) [31]. Cardiac arrhythmia was a SAE (2%, 1/62) in Pa-Z-Mfx [31]. In Tweed et al. [32], 5% (3/60) of Rs-TB patients on Pa-Bdq-Z and 2% (1/61) on HRZE had QTcB/F changes of ≥60 ms from baseline. Conradie et al. [33] and Tweed et al. [26] reported no QTcB/F changes of ≥60 ms from baseline. In Tweed et al. [26], the mean QTcF change from baseline was higher for 6Pa-Mfx-Z (18 ms (95% CI 15–22)) and 4Pa-Mfx-Z (18 ms (95% CI 14–22)) than HRZE (9 ms (95% CI 5–13).

Other adverse events

Gastro-intestinal, dermatological, musculoskeletal adverse events and hyperuricemia were commonly reported in included studies. In Conradie et al. [33], 81% (88/109) of patients experienced Lzd-related peripheral neuropathy and 48% (52/109) myelosuppression, leading to Lzd interruption (66% (72/109)) or dose reduction (85% (93/109)).

Summary of results

0–14 days EBA of Pa (alone or in drug combinations) varied between 0.063–0.233 on EBA_{CFU} and 2.621–18.482 on EBA_{TTP} [27–30]. Eight-week bactericidal activity measured on daily change in CFU in Pa combinations ranged between 0.11 (95% Bayesian credibility interval (BCI) 0.10–0.12) in Pa-Bdq200-Z and 0.16 (95%

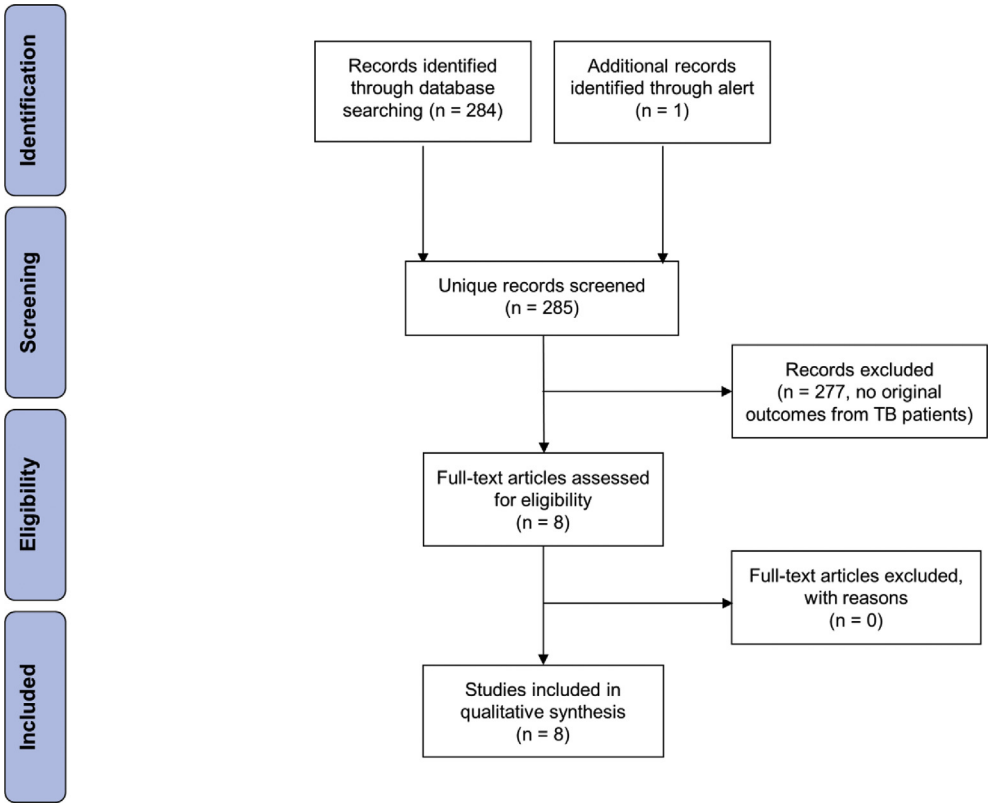

Fig. 1. Selection process for studies presenting original outcome data of tuberculosis patients receiving pretomanid. TB, tuberculosis.

BCI 0.13–0.18) in Pa-Mfx-Z [30,32]. Pa-Mxf-Z had the highest 8-week bactericidal activity overall and Pa-Bdq200-Z in Tweed et al. [31,32]. Favourable outcomes were reported in 67%–87% of Rs-TB and 90–92% of Rr-TB patients treated with Pa [26,33]. After maximum eight weeks on Pa, 27–95% of patients experienced adverse events, 7–77% treatment-related, and 0–11% SAE [27–30]. Among patients receiving Pa at least four months, 87–100% experienced adverse events and 5–17% SAE [26,33].

Pa-Z had superior EBA_{TTP} to Pa, Bdq-Z superior EBA_{TTP} and 0–14 day EBA_{CFU} to Bdq and Pa-Bdq inferior EBA_{TTP} to Pa-Z. Pa-Mfx-Z but not Pa-Bdq-Z had superior EBA_{CFU} and EBA_{TTP} to Pa-Z [27–30]. Pa-Mfx-Z showed superior 0–2 day EBA_{CFU} and 8-week bactericidal activity but more SAE after eight weeks (p 0.034) and liver-enzyme increases after six months administration (p 0.024) compared to HRZE [26,29,31]. Pa-Bdq (200)-Z had superior 8-week bactericidal activity to HRZE but inferior to Pa-Mfx-Z [31,32]. While treatment outcomes were not different among Rr-TB regimens, Pa-Bdq-Lzd caused significantly more grade 3–4 adverse events compared to 6Pa-Mfx-Z [26,33].

Discussion

We summarized efficacy- and safety-related outcomes of TB-patients treated with Pa alone, or with a Pa-containing regimen. Included studies demonstrated strong and consistent EBA of Pa. In Rs-TB, EBA of Pa and Bdq improved when adding Z, confirming data from animal studies [35]. Pa-Z had earlier and stronger EBA_{TPP} compared to Bdq-Z (29). Mfx, but not Bdq, added significant EBA to Pa-Z [29]. Pa-Mfx-Z compared to HRZE was superior on 0–2 day EBA_{CFU} and 0–56 day bactericidal activity but not at end of treatment in Tweed et al. and limited by hepatotoxicity [26]. Pa-Bdq-Z had superior 8-week bactericidal activity to HRZE, but no final outcomes were available [32].

In Rr-TB, Pa-containing regimens were not compared to other regimens. Pa-Mfx-Z in Rr-TB showed comparable 8-week bactericidal activity to HRZE in Rs-TB and 10/11 Rr-TB patients had a favourable outcome in Tweed et al. [26,31]. Rr-TB patients on Pa-Bdq-Mfx-Z in Tweed et al. [32] had faster culture conversion compared to Rs-TB patients on HRZE. High conversion rates in pyrazinamide-resistant compared to pyrazinamide-susceptible TB patients on Pa-Bdq-Mfx-Z demonstrate the essential contribution of Z to the regimen, raisings concern about its applicability in settings with a high prevalence of pyrazinamide-resistant [32,36].

Pa-Bdq-Lzd showed excellent end-of-treatment outcomes in MDr-TB and XDr-TB patients previously unexposed to Bdq [33]. Unpublished results 24 months post-treatment indicate sustained favourable outcomes (88% intention-to-treat, 91% modified intention-to-treat) with improved Lzd-related neuropathy [37]. One patient was successfully treated without SAE with Pa-Bdq-Lzd with Lzd (600 mg/day) at extended dosing intervals [38]. In Conradie et al. [33], Lzd-toxicity led to regimen interruptions in 66% of patients, increasing the risk of Bdq resistance due to its six-month half-life, which in turn may favour acquired Pa resistance [29,39]. While clinical Pa resistance has not yet been documented, one of two evaluated relapses developed Bdq resistance in Conradie et al. [33].

No increase of the MIC of Pa was recorded above its provisionally set critical MIC (1 μg/mL) [40]. Spontaneous mutations have been observed in vitro in genes involved in Pa activation, leading to MIC increases of $\geq 8\times$ from baseline [41]. Resistance to delamanid, also a nitroimidazole, develops through mutations in the same genes and cross-resistance between Pa and delamanid is possible but undocumented [42]. Determining the frequency of acquired resistance to Pa after unsuccessful treatment will require large cohorts.

Table 2
Baseline resistance profile and HIV-status of tuberculosis patients in studies including pretomanid-containing regimens

Study	Regimen	*N*	DST method	Resistance						HIV positive
				R	H	Z	E	FQ	SLI	
Diacon 2010 [27] [a]	All	65	MGIT	0	NR	NR	NR	NR	NR	10 (15%)
Diacon 2012 [28]	All	69	MGIT	0	0	NR	NR	NR	NR	6 (9%)
	Pa50	15		0	0	NR	NR	NR	NR	0
	Pa100	15		0	0	NR	NR	NR	NR	2 (13%)
	Pa150	15		0	0	NR	NR	NR	NR	1 (7%)
	Pa	16		0	0	NR	NR	NR	NR	2 (13%)
	HRZE	8		0	0	NR	NR	NR	NR	1 (13%)
Diacon 2012 [29] [a]	All	85	MGIT, MIC	0	NR	NR	NR	0	NR	6 (7%)
Diacon 2015 [30]	All	105	MGIT	0	3 (3%)	2 (2%)	NR	NR	NR	11 (11%)
	Pa-Bdq-Z	15		0	NR	0	NR	NR	NR	1 (7%)
	Pa-Bdq-Cfz	15		0	NR	0	NR	NR	NR	3 (20%)
	Pa-Bdq-Z-Cfz	15		0	NR	1 (7%)	NR	NR	NR	1 (7%)
	Bdq-Z-Cfz	15		0	NR	1 (7%)	NR	NR	NR	0
	Z	15		0	NR	0	NR	NR	NR	2 (13%)
	Cfz	15		0	NR	0	NR	NR	NR	1 (7%)
	HRZE	15		0	0	0	NR	NR	NR	3 (20%)
Dawson 2015 [31]	All	207	LPA, MGIT	26 (13%)	26 (13%)	20	NR	5	NR	40 (19%)
	Pa100-Mfx-Z	60		0	0	0	NR	1 (2%)	NR	12 (20%)
	Pa-Mfx-Z	62		0	0	2 (3%)	NR	2 (3%)	NR	8 (13%)
	HRZE	59		0	0	1 (2%)	NR	1 (2%)	NR	13 (22%)
	Pa-Mfx-Z	26		26 (100%)	26 (100%)	17 (65%)	NR	1 (4%)	NR	7 (28%)
Tweed 2019 [32]	All	240	LPA, MGIT, Xpert	60 (25%)	53 (22%)	29 (12%)	19 (8%)	NR	NR	53 (22%)
	Pa-Bdq-Z	59		0	0	2 (3%)	2 (4%)	NR	NR	8 (14%)
	Pa-Bdq200-Z	60		0	0	3 (5%)	4 (7%)	NR	NR	10 (17%)
	HRZE	61		0	0	2 (3%)	2 (3%)	NR	NR	10 (16%)
	Pa-Bdq-Mfx-Z	60		60 (100%)	53 (88%)	22 (37%)	11 (22%)	NR	NR	25 (42%)
Conradie 2020 [33] [b]	Pa-Bdq-Lzd	109	MGIT, WGS	109 (100%)	109 (100%)	NR	NR	71 (65%)	71 (65%)	56 (51%)
Tweed 2021 [26]	All	245	LPA, MGIT, WGS Xpert	11 (5%)	5 (2%)	0	NR	0	NR	64 (26%)
	4Pa100-Mfx-Z	57		0	0	0	0	0	NR	13 (23%)
	4Pa-Mfx-Z	61		0	0	0	0	0	NR	13 (21%)
	6Pa-Mfx-Z	56		0	0	0	0	0	NR	17 (30%)
	HRZE	60		0	0	0	0	0	NR	15 (25%)
	6Pa-Mfx-Z	11		11 (100%)	5 (45%)	NR	NR	0	NR	6 (55%)

Bdq, bedaquiline; Cfz, clofazimine; DST, drug susceptibility testing; E, ethambutol; FQ, fluoroquinolone; H, isoniazid; LPA, line probe assay; MIC, minimum inhibitory concentration; Mfx, moxifloxacin; MGIT, mycobacteria growth indicator tube; NR, not reported; Lzd, linezolid; Pa, pretomanid (200 mg daily unless followed by daily dose); R, rifampicin; SLI, second-line injectable; WGS, whole genome sequencing; Z, pyrazinamide.

[a] HIV-status stratified by regimen not reported.

[b] 34% (38) were classified as having multidrug-resistant tuberculosis, 17% (19) not responding to treatment and 17% (19) for which treatment was stopped due to side effects.

Table 3
Early bactericidal activity against *Mycobacterium tuberculosis* of pretomanid

Study	Regimen	*N*[a]	0–14 days	0–2 days	2–14 days
Daily rate of change in CFU: Mean log_{10} CFU/mL sputum (SD) or (95% CI)					
Diacon 2010 [27]	Pa	12	0.106 (0.049)	0.109 (0.487)	0.106 (0.063)
	Pa600	12	0.107 (0.053)	0.096 (0.226) [b]	0.113 (0.079)
	Pa1000	14	0.091 (0.083)	0.025 (0.340) [b]	0.095 (0.062)
	Pa1200	11	0.088 (0.084)	-0.035 (0.420) [b]	0.113 (0.099)
	HRZE (control)	7	0.148 (0.055)	0.403 (0.290)	0.112 (0.050)
Diacon 2012 [28]	Pa50	12	0.063 (0.058) [b]	0.093 (0.211) [b]	0.059 (0.060) [b]
	Pa100	15	0.091 (0.073) [b]	0.111 (0.332) [b]	0.088 (0.085)
	Pa150	14	0.078 (0.074) [b]	-0.009 (0.290) [b]	0.096 (0.098)
	Pa	14	0.112 (0.070) [b]	0.160 (0.255) [b]	0.104 (0.083)
	HRZE (control)	8	0.177 (0.042)	0.470 (0.316)	0.128 (0.070)
Prolongation of time to positivity: Mean hours/day (SD)					
Diacon 2010 [27]	Pa	12	3.818 (2.327)[b]	1.115 (15.256) [b]	3.833 (2.954)
	Pa600	13	4.776 (2.879)[b]	5.788 (12.173) [b]	5.090 (2.768)
	Pa1000	11	4.865 (3.461)[b]	2.795 (9.230) [b]	4.069 (1.916) [b]
	Pa1200	12	4.440 (2.169)[b]	1.400 (7.659) [b]	4.868 (3.224)
	HRZE (control)	8	9.741 (5.249)	24.125 (12.794)	7.344 (4.660)
Diacon 2012 [28]	Pa50	13	2.621 (2.534) [b]	1.483 (8.153) [b]	2.958 (2.652) [b]
	Pa100	14	4.969 (3.644) [b]	-1.345 (8.586) [b]	5.744 (3.973)
	Pa150	15	4.633 (3.687) [b]	4.867 (12.755) [b]	4.594 (5.035) [b]
	Pa	13	4.640 (3.447) [b]	3.096 (8.202) [b]	5.391 (3.608) [b]
	HRZE (control)	8	13.364 (3.979)	37.016 (5.639)	9.422 (4.367)

CFU, colony-forming units; CI, confidence interval; E, ethambutol; H, isoniazid; Pa, pretomanid (200 mg daily unless followed by daily dose); R, rifampicin; SD, standard deviation; Z, pyrazinamide.

[a] *N* is the number of participants included for analysis until the latest timepoint.

[b] Measurement statistically different to the control group in post hoc analysis of mean differences ($p < 0.05$).

Table 4
Early bactericidal activity against *Mycobacterium tuberculosis* of pretomanid-containing regimens

Study	Regimen	N[a]	0–14 days	0–2 days	0–7 days
Daily rate of change in CFU: Mean log_{10}CFU/mL sputum (SD) or (95% CI)					
Diacon [29] [d]	Pa-Bdq	14	0.114 (0.050)	0.114 (0.149)[c]	0.114 (0.089)
	Pa-Z	14	0.154 (0.040)[c]	0.170 (0.082)[c]	0.155 (0.040)[c]
	Pa-Mfx-Z	12	0.233 (0.128)[c,d,e]	0.315 (0.133)[b,c,d,e,f]	0.225 (0.091)[c,d,e]
	Bdq	14	0.061 (0.068)[b]	−0.022 (0.121)[b]	0.043 (0.074)[b]
	Bdq-Z	15	0.131 (0.102)	0.079 (0.167)	0.106 (0.119)
	HRZE (control)	10	0.140 (0.094)	0.177 (0.188)	0.162 (0.124)
Diacon [30]	Pa-Bdq-Z	12	0.17 (0.08–0.26)	0.20 (0.06–0.33)	NR
	Pa-Bdq-Cfz	15	0.08 (0.01–0.15)	0.06 (-0.05–0.16)	NR
	Pa-Bdq-Z-Cfz	13	0.12 (0.04–0.19)	0.16 (0.04–0.28)	NR
	Bdq-Z-Cfz	13	0.12 (0.04–0.21)	0.13 (0.01–0.26)	NR
	Z	15	0.04 (-0.03–0.10)	0.08 (-0.03–0.21)	NR
	Cfz	14	-0.02 (-0.09–0.05) [b]	0.02 (-0.09–0.13)	NR
	HRZE (control)	15	0.15 (0.07–0.23)	0.14 (0.04–0.25)	NR
Prolongation of time to positivity: Mean hours/day (SD)					
Diacon [29]	Pa-Bdq	15	5.855 (2.785)	3.941 (9.156)[b]	3.948 (3.968)[b]
	Pa-Z	14	8.805 (3.468)	10.243 (5.982)[b]	10.243 (5.982)[b,c,d]
	Pa-Mfx-Z	13	18.482 (22.582) [c]	21.018 (11.506)[c,d,e,f]	19.396 (13.024)[c,d,e,f]
	Bdq	14	5.414 (3.523) [b]	2.043 (5.945)[b]	4.625 (3.600)[b]
	Bdq-Z	15	9.970 (6.987)	12.393 (10.475)[b]	11.115 (8.299)[b,c,d]
	HRZE (control)	10	11.841 (3.932)	25.492 (12.360)	19.557 (7.160)
Daily percentage change in time to positivity: Mean % (95% CI)					
Diacon [30]	Pa-Bdq-Z	14	7.0 (5.1–9.4)	13.2 (9.0–17.9)	NR
	Pa-Bdq-Cfz	15	4.3 (2.9–5.7)	6.0 (4.2–7.8)[b]	NR
	Pa-Bdq-Z-Cfz	13	6.3 (4.2–8.6)	10.6 (8.0–13.3)	NR
	Bdq-Z-Cfz	13	4.9 (3.3–6.8)	9.1 (6.5–12.2)	NR
	Z	15	2.0 (0.8–3.4) [b]	4.7 (2.4–7.5)[b]	NR
	Cfz	14	-0.3 (-1.5–1.0) [b]	2.1 (−0.5–5.0)[b]	NR
	HRZE (control)	15	6.3 (4.8–7.6)	12.9 (8.9–17.9)	NR

Bdq, bedaquiline; CFU, colony-forming units; Cfz, clofazimine; CI, confidence interval; E, ethambutol; H, isoniazid; Mfx, moxifloxacin; Pa, pretomanid (200 mg daily unless followed by daily dose); R, rifampicin; Z, pyrazinamide.
[a] N is the number of participants included for analysis until the latest timepoint.
[b] Measurement statistically different to the control group in post-hoc analysis of mean differences (95% CI).
[c] Reported by authors as superior to Bdq
[d] Reported by authors as superior to Pa-Bdq.
[e] Reported by authors as superior to Bdq-Z.
[f] Reported by authors as superior to Pa-Z.

Table 5
Bactericidal activity against *Mycobacterium tuberculosis* by changes in CFU or TTP in studies including pretomanid-containing regimens

Study	Regimen	*N*	0–56 days	7–56 days	*N*	0–56 days	7–56 days
		Daily rate of change in CFU: Mean log10 CFU/mL sputum (95% BCI)			Daily rate of change mean log10 TTP: Mean hr (95% BCI)		
Dawson 2015 [31]	Pa100-Mfx-Z	56	0.13 (0.11–0.16)	0.12 (0.09–0.14)	55	0.02 (0.02–0.03)	0.02 (−0.01–0.02)
	Pa-Mfx-Z	54	0.16 (0.13–0.18)[a]	0.15 (0.12–0.17) [a]	57	0.02 (0.02–0.03)	0.02 (0.01–0.02)
	HRZE (control)	54	0.11 (0.09–0.13)	0.10 (0.08–0.13)	58	0.02 (0.01–0.02)	0.01 (0.01–0.02)
	Pa-Mfx-Z (Rr-TB)	9	0.12 (0.07–0.17)	0.10 (0.05–0.17)	9	0.02 (-0.01–0.03)	0.01 (−0.01–0.03)
					Daily percentage change in TTP: Mean % change (95% CI)		
Tweed 2019 [32]	Pa-Bdq-Z	57	0.12 (0.11–0.14)	NR	57	4.9 (4.3–5.5) [a]	NR
	Pa-Bdq200-Z	56	0.11 (0.10–0.12)	NR	56	5.2 (4.6–5.8) [a]	NR
	HRZE (control)	59	0.12 (0.11–0.13)	NR	59	4.0 (3.7–4.4)	NR

BCI, Bayesian credibility interval; Bdq, bedaquiline; Bdq200, Bdq dosed 200 mg daily; CFU, colony-forming units; CI, confidence interval; H, isoniazid; IQR, interquartile range; Lzd, linezolid; Mfx, moxifloxacin; NLME, non-linear mixed–effects modelling; NR, not reported; Pa, pretomanid (200 mg daily unless followed by daily dose); R, rifampicin; Rr-TB, rifampicin-resistant tuberculosis; TTP time-to-positivity; Z, pyrazinamide.
[a] Reported by authors as superior to HRZE.

It remains unclear whether Pa can act as a regimen's core drug, with high bactericidal and sterilizing activity, or protect other drugs against acquired resistance. Pa contributed significantly to the sterilizing activity of Bdq-Mfx-Z and Pa-Bdq-Lzd in mice. Pa assisted to redue treatment duration and contributed to avoiding selection of Bdq-resistant mutants [13]. The EBA of Pa as a single drug was similar to Bdq in included studies, but lower than 2-week EBA reported for R, H, and fluoroquinolones [43]. Data from Conradie et al. [33] do not allow to conclude on Pa's capacity as core drug due to its limited follow-up time and the presence of Bdq. Sterilizing activity in Pa-Bdq-Lzd could depend entirely on Pa. Remaining Bdq deposits could delay relapse, and follow-up time is insufficient to evaluate Pa's capacity to prevent it. However, the case of acquired Bdq and not Pa resistance suggests that Bdq rather than Pa was driving efficacy of Pa-Bdq-Lzd after the initial 5–6 days [33]. The high efficacy of Pa-Bdq-Lzd for patients with fluoroquinolone-resistant Rr-TB might be at stake due to the widespread use of Bdq for non-complicated Rr-TB. The use of Pa-Bdq-Lzd is restricted to Rr-TB patients without past exposure to Bdq or Lzd, thus excluded for those previously treated with the recommended Rr-TB regimen [4].

Table 6
Bactericidal activity against Mycobacterium tuberculosis by culture conversion in studies including pretomanid-containing regimens

Study	Regimen	Days to culture conversion: median (IQR)		Culture negative at day 56: % (95% CI)				Culture negative status: HR (95% CI)			
		N		***N***	Liquid	***N***	Solid	***N***	Liquid	***N***	Solid
Dawson 2015 [31]	Pa100-Mfx-Z	35	42 (35–an)	35	66 (48–81)	35	83 (66–93)		NR		NR
	Pa-Mfx-Z	35	49 (41–56) [a]	35	71 (54–85)[a]	35	94 (81–99)		1.7 (1.1–2.7) [a]		1.5 (1.1–2.2) [a]
	HRZE (control)	32	56 (43–an)	37	38 (22–55)	32	88 (71–96)		1 (Ref)		1 (Ref)
	Pa-Mfx-Z (Rr-TB)	8	56 (45–an)	8	50 (16–84)	8	63 (24–93)		NR		NR
Tweed 2019 [32]	Pa-Bdq-Z	57	49 (35–an)	57	67 (54–81)	57	89 (80–98)	34	1.8 (1.1–2.9)[a]	46	1.3 (0.9–1.8)
	Pa-Bdq200-Z	56	49 (35–56)	56	76 (64–88)[a]	56	84 (74–94)	37	2.0 (1.3–3.2)[a]	43	1.1 (0.8–1.6)
	HRZE (control)	59	56 (49–an)	59	51 (37–65)	59	86 (76–95)	25	1 (Ref)	45	1 (Ref)
	Pa-Bdq-Mfx-Z (Rr-TB)	60		60	92 (82–97)[a]	60	98 (91–100) [a]	38	3.3 (2.1–5.2)[a]		2.3 (1.5–3.4) [a]
	Of whom Zs-TB	38	41 (35–56)	38	96 (89–100)	38	100 (100–100)		NR		NR
	Of whom Zr-TB	22	49 (34–56)	22	80 (62–97)	22	95 (85–100)		NR		NR
Tweed 2021 [26]	4Pa100-Mfx-Z		NR	54	61 (47–74)		NR		NR		NR
	4Pa-Mfx-Z		NR	58	62 (48–74)		NR		NR		NR
	6Pa-Mfx-Z		NR	53	66 (52–78)		NR		NR		NR
	HRZE (control)		NR	57	54 (41–68)		NR		NR		NR

Bdq, bedaquiline; Bdq200, Bdq dosed 200 mg daily; Cfz, clofazimine; E, ethambutol; H, isoniazid; HR, hazard ratio; IQR, interquartile range; Mfx, moxifloxacin; NR, not reported; Pa, pretomanid (200 mg daily unless followed by daily dose); R, rifampicin; Rr-TB, rifampicin-resistant tuberculosis; Rs-TB, rifampicin-susceptible tuberculosis; Z, pyrazinamide; Zs-TB, pyrazinamide-susceptible tuberculosis; Zr-TB, pyrazinamide-resistant tuberculosis.
[a] Reported by authors as superior to HRZE.

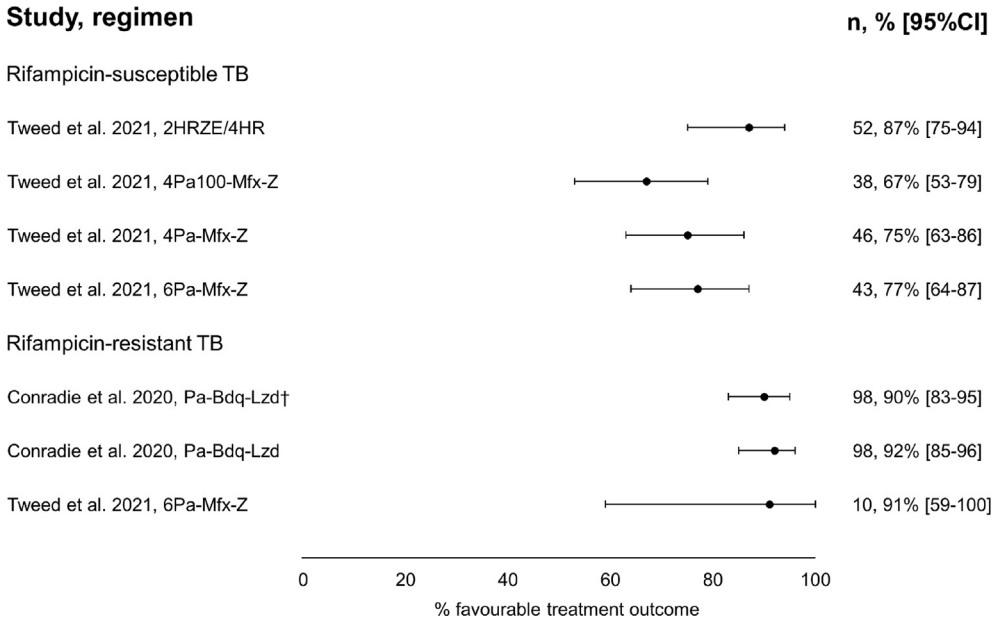

Fig. 2. Favourable treatment outcomes in studies including tuberculosis patients receiving pretomanid. Results from modified intention-to-treat analysis, unless indicated with † = intention-to treat. Favourable outcome in Conradie et al, 2020: Clinical disease resolved, culture negative at 6 months after treatment. Favourable outcome in Tweed et al, 2021: culture negative at 12 months after randomisation with minimum two negative cultures after the positive one. Bdq, bedaquiline; CI, confidence interval; E, ethambutol; H, isoniazid; Lzd, linezolid; Mfx, moxifloxacin; Pa, pretomanid; R, rifampicin; TB, tuberculosis; Z, pyrazinamide.

The onset of Pa's EBA was faster compared to Bdq, so Pa-based regimens could be superior to Bdq-based regimens for the prevention of acquired resistance [29]. TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s); ClinicalTrials.gov Identifier: NCT02589782) was stopped early as the superiority of Pa-Bdq-Mfx-Lzd compared with control was shown [44]. Pa with Lzd might prevent acquired resistance to Bdq and Mfx in this regimen. However, Bdq resistance also developed when Bdq was combined with Pa and Lzd in Conradie et al. [33]. Delamanid was also not yet compared to Pa in clinical trials. While in vitro potency of delamanid was superior to Pa in MDr-TB and pre-XDr-TB, delamanid added to an optimized background regimen failed to show superior efficacy to placebo in a phase III study [45,46].

The safety profile of Pa requires further investigation. Serious Pa-induced hepatotoxicity was especially common when combined with Mfx and Z, two drugs associated with liver toxicity [47]. No evidence exists of cross-sensitivity of Pa with other TB-drugs [48]. In Conradie et al. [33], hepatotoxicity led to treatment interruptions but was reversible. Hepatotoxicity could thus be induced by Z rather than Pa and prevented by avoiding the combination. Significant cardiotoxicity associated with Pa was

Table 7
Unfavourable outcomes in studies including tuberculosis patients receiving pretomanid

Study	Regimen	*N*	Unfavourable outcome		Death	Failure	Relapse	Lost to follow-up	Withdrawal/other
			n	% (95% CI)	*n*	*n*	*n*	*n*	*n*
Conradie 2020 [33] [a]	6–9 Pa-Bdq-Lzd	109	11	10 (5–17)	7	0	2[b]	1	1
	Of whom MDr-TB	38	3	8 (2–21)	1	0	1	1	0
	Of whom pre-XDr-TB	71	8	11 (5–21)	6	0	1	0	1
Tweed 2021 [26][c]	4Pa100-Mfx-Z	57	19	33 (21–47)	2	9	2	1	5
	4Pa-Mfx-Z	61	15	25 (14–37)	2	6	1	0	6
	6Pa-Mfx-Z	56	13	23 (13–36)	2	1	1	0	9
	HRZE (control)	60	8	13 (6–25)	0	0	0	0	8
	6Pa-Mfx-Z (Rr-TB)	11	1	9 (0–41)	0	0	0	0	1

Analysis excluded late screening failures, lost-to-follow-up/withdrawn with negative culture, accidental death, pregnancy, missing month 12 sample, re-infection with new TB-strain. Only those with assessable status included. LTFU reported only during treatment, deaths include during follow-up if TB related. Bdq, bedaquiline; E, ethambutol; Eto, ethionamide; H, isoniazid; Lzd, linezolid; MDr-TB, multidrug-resistant tuberculosis; Mfx, moxifloxacin; Pa, pretomanid; R, rifampicin; RCT, randomized controlled trial; Rr-TB, rifampicin-resistant tuberculosis; TB, tuberculosis; Z, pyrazinamide; pre-XDr-TB, pre-extensively drug-resistant tuberculosis.

[a] Intention-to-treat analysis. Unfavourable outcome: clinical or bacteriological failure or relapse.

[b] One patient relapsed with the same strain, showing acquired resistance to BDQ. For the other patient, no baseline isolate was available.

[c] Modified intention-to-treat analysis. Unfavourable outcome: bacteriological or clinical failure (not accidental death) or lost-to-follow-up/withdrawn before end of treatment. Unfavourable outcomes classified as withdrawals/other included adverse events (7%, 18/245), protocol non-adherence (3%, 6/245), physician decision (2%, 4/245) and clinical deterioration during follow-up (0.4%, 1/245).

Table 8
Comparison of efficacy between regimens from studies including pretomanid

Arm 1	Arm 2	Outcome measure	Outcome 1 (95% CI)	Outcome 2 (95% CI)	p-value	p-value source	Reference
Pa	Cfz	CFU 0–14 days	0.11 (0.07–0.15)	-0.02 (-0.09–0.05)	0.002	own analysis	[28,30]
Pa	Pa-Z	TTP 0–2 days	3.10 (−1.86–8.05)	10.24 (6.93–13.56)	0.013	own analysis	[28,29]
		TTP 0–14 days	4.64 (2.80–6.48)	8.81 (6.80–10.81)	0.003	own analysis	[28,29]
		TTP 2–14 days	5.39 (3.21–7.57)	8.42 (6.41–10.44)	0.036	own analysis	[28,29]
Bdq	Bdq-Z	CFU 0–14 days	0.06 (0.02–0.10)	0.13 (0.08–0.19)	0.040	own analysis	[29]
		TTP 0–2 days	2.04 (-1.25–5.34)	12.39 (6.59–18.19)	0.002	own analysis	[29]
		TTP 0–7 days	4.63 (2.55–6.70)	11.12 (6.52–15.71)	0.012	own analysis	[29]
		TTP 0–14 days	5.41 (3.38–7.45)	9.97 (6.10–13.84)	0.028	own analysis	[29]
Pa-Z	Pa-Bdq	TTP 0–2 days	10.24 (6.93–13.56)	3.94 (-1.13–9.01)	0.034	own analysis	[29]
		TTP 0–7 days	10.24 (6.93–13.56)	3.95 (1.75–6.15)	0.002	own analysis	[29]
		TTP 0–14 days	8.81 (6.80–10.81)	5.86 (4.31–7.40)	0.017	own analysis	[29]
Pa-Z	Pa-Mfx-Z	CFU 0–2 days	0.17 (0.13–0.22)	0.32 (0.24–0.39)	0.001	own analysis	[29]
		CFU 0–7 days	0.16 (0.13–0.18)	0.23 (0.17–0.28)	0.016	own analysis	[29]
		CFU 0–14 days	0.15 (0.13–0.18)	0.23 (0.16–0.31)	0.037	own analysis	[29]
		TTP 0–2 days	10.24 (6.93–13.56)	21.02 (14.65–27.39)	0.003	own analysis	[29]
		TTP 0–7 days	10.24 (6.93–13.56)	19.40 (11.88–26.92)	0.021	own analysis	[29]
Pa-Mfx-Z	HRZE	CFU 0–2 days	0.32 (0.24–0.39)	0.18 (0.04–0.31)	0.042	own analysis	[29]
		CFU 0–56 days	0.16 (0.13–0.18)	0.11 (0.09–0.13)	0.005	own analysis	[31]
		CFU 7–56 days	0.15 (0.12–0.17)	0.10 (0.08–0.13)	0.016	own analysis	[31]
		HR culture conversion liquid medium	1.7 (1.1–2.7)	1	NR	Dawson 2015	[31]
		HR culture conversion solid medium	1.5 (1.1–2.2)	1	NR	Dawson 2015	[31]
Pa-Bdq-Z	HRZE	TTP 0–56 days	4.87 (4.31–5.47)	4.04 (3.67–4.42)	0.019	Tweed 2019	[32]
		HR culture conversion liquid medium	2.0 (1.3–3.2)	1	<0.001	Tweed 2019	[32]
Pa-Bdq200-Z	HRZE	TTP 0–56 days	5.17 (4.61–5.77)	4.04 (3.67–4.42)	0.002	Tweed 2019	[32]
		HR culture conversion liquid medium	1.8 (1.1–2.9)	1	0.016	Tweed 2019	[32]
Pa-Mfx-Z	Pa-Bdq-Z	CFU 0–56 days	0.16 (0.13–0.18)	0.12 (0.11–0.14)	0.011	own analysis	[31,32]
Pa-Mfx-Z	Pa-Bdq200-Z	CFU 0–56 days	0.16 (0.13–0.18)	0.11 (0.10–0.12)	0.000	own analysis	[31,32]

The two-sample t-test was used for own analysis. Bdq, bedaquiline; CFU, bactericidal efficacy measured as daily rate of change in mean $\log_{10}$ colony-forming units; CI, confidence interval; E, ethambutol; H, isoniazid; HR, hazard ratio; Mfx, moxifloxacin; Pa, pretomanid; R, rifampicin; TTP, bactericidal efficacy measured as daily rate change in mean $\log_{10}$ or percentage change in time-to-positivity; Z, pyrazinamide.

uncommon and Pa-Mfx-Z-related QtcF changes were not clinically significant in Tweed et al. [26,31]. Cardiotoxicity is common during Mfx use [47]. Pa has caused testicular atrophy and impaired fertility in male rats and its reproductive risk in humans is being investigated (ClinicalTrials.gov Identifier: NCT04179500) [7].

A major limitation of this systematic review is the absence of a meta-analysis. However, pooled outcome estimates from different drug combinations and dosages would not have clarified the individual contribution of Pa. Moreover, we compared head-to-head outcomes between arms differing only for a single drug. Longer studies are necessary to position and rank Pa between existing core and companion drugs.

Existing evidence is encouraging for the use of Pa in TB treatment: Pa demonstrated early and sustained bactericidal activity in Rs-TB and Rr-TB. Hepatotoxicity could limit its use in Rs-TB. For Rr-TB, limited data indicate that Pa could act as a core drug. Comparative trials are needed to further define its efficacy and safety.

Table 9
Adverse events in studies including tuberculosis patients receiving pretomanid

Study	Regimens	*N*	Any adverse event	Treatment-related adverse events	Liver-enzyme increases	ECG findings[a]	Grade 3–5 adverse events	Serious adverse events	Discontinuation following adverse events	Death following adverse events
Diacon 2010 [27]	Pa	15	6 (40%)	1 (7%)	0	0	NR	1 (7%)	2 (13%)	0
	Pa600	15	4 (27%)	2 (13%)	0	0	NR	0	0	0
	Pa1000	16	5 (31%)	5 (31%)	0	1 (6%)	NR	0	0	0
	Pa1200	15	7 (47%)	5 (33%)	1 (7%)	0	NR	0	1 (7%)	0
	HRZE (control)	8	3 (38%)	2 (25%)	0	0	NR	1 (13%)	0	0
Diacon 2012 [28]	Pa50	15	10 (68%)	13–20%	0	1 (7%)	NR	1 (7%)	1 (7%)	0
	Pa100	15	5 (33%)	13–20%	0	1 (7%)	NR	0	0	0
	Pa150	15	5 (33%)	13–20%	0	3 (20%)	NR	0	0	0
	Pa	16	7 (44%)	13–20%	1 (6%)	3 (19%)	NR	1 (6%)	0	0
	HRZE (control)	8	4 (50%)	Nr	0	0	NR	0	0	0
Diacon 2012 [29]	Pa-Bdq	15	10 (67%)	5 (33%)	1 (7%)	0	NR	1 (7%)	1 (7%)	0
	Pa-Z	15	7 (47%)	3 (20%)	1 (7%)	0	NR	0	1 (7%)	0
	Pa-Mfx-Z	15	9 (60%)	6 (40%)	1 (7%)	1 (7%)	NR	1 (7%)	3 (20%)	0
	Bdq	15	7 (47%)	2 (20%)	1 (7%)	0	NR	0	‘1 (7%)	0
	Bdq-Z	15	6 (40%)	2 (13%)	1 (7%)	0	NR	0	1 (7%)	0
	HRZE (control)	10	5 (50%)	3 (30%)	0	0	NR	0	0	0
Diacon 2015 [30]	Pa-Bdq-Z	15	9 (60%)	4 (27%)	1 (7%)	0	1 (7%)	0	1 (7%)	0
	Pa-Bdq-Cfz	15	8 (53%)	7 (47%)	0 [d]	4 (27%)	0 [d]	0	0	0
	Pa-Bdq-Z-Cfz	15	11 (73%)	11 (73%)	1 (7%)	5 (33%)	0	0	0	0
	Bdq-Z-Cfz	15	10 (67%)	4 (27%)	1 (7%)	2 (13%)	1 (7%)	0	0	0
	Z	15	10 (67%)	5 (33%)	1 (7%)	0	0	0	0	0
	Cfz	15	9 (60%)	6 (40%)	1 (7%)	0	3 (20%)	1 (7%)	0	0
	HRZE (control)	15	8 (53%)	7 (47%)	0	1 (7%)	0	0	0	0
Dawson 2015 [31]	Pa100-Mfx-Z	60	52 (87%)	NR	10 (17%)	1 (2%)	18 (30%)	1 (2%)	8 (13%)	0
	Pa-Mfx-Z	62	57 (92%)	NR	11 (18%)	6 (10%)	23 (37%)	7 (11%)	12 (19%)	0
	HRZE (control)	59	50 (85%)	NR	7 (12%)	3 (5%)	15 (25%)	1 (2%)	7 (12%)	0
	Pa-Mfx-Z (Rr-TB)	26	23 (88%)	NR	3 (12%)	2 (8%)	6 (23%)	0	3 (12%)	0
Tweed 2019 [32]	Pa-Bdq-Z	59	50 (85%)	38 (64%)	6 (10%)	0	19 (32%)	4 (7%)	6 (10%)	1 (2%)
	Pa-Bdq200-Z	60	45 (75%)	29 (48%)	4 (7%)	3 (5%)	17 (28%)	3 (5%)	5 (8%)	1 (2%)
	HRZE (control)	61	44 (72%)	29 (48%)	3 (5%)	1 (2%)	14 (23%)	4 (7%)	2 (3%)	1 (2%)
	Pa-Bdq-Mfx-Z (Rr-TB)	60	57 (95%)	46 (77%)	3 (5%)	0	13 (22%)	4 (7%)	2 (3%)	0
Conradie 2020 [33]	Pa-Bdq-Lzd	109	109 (100%)	NR	17 (16%)	0	62 (57%)	19 (17%)	8 (7%)[b]	6 (6%)
Tweed 2021 [26] [c]	4Pa100-Mfx-Z	65	61 (94%)	NR	9 (14%)	NR	25 (39%)	3 (5%)	6 (9%)	4 (6%)
	4Pa-Mfx-Z	71	62 (87%)	NR	12 (17%)	NR	21 (30%)	8 (11%)	6 (9%)	3 (4%)
	6Pa-Mfx-Z	67	63 (94%)	NR	14 (21%)	NR	22 (33%)	8 (12%)	11 (16%)	3 (5%)
	HRZE (control)	68	62 (91%)	NR	5 (7%)	NR	19 (28%)	3 (4%)	4 (6%)	2 (3%)
	6Pa-Mfx-Z (Rr-TB)	13	12 (92%)	NR	1 (8%)	NR	3 (23%)	3 (23%)	0	1 (8%)

Bdq, bedaquiline; Cfz, clofazimine; ECG, electrocardiogram; Lzd, linezolid; Mfx, moxifloxacin; NR, not reported; Pa, pretomanid (200 mg daily unless followed by daily dose); Rr-TB, rifampicin-resistant tuberculosis; Rs-TB, rifampicin-susceptible tuberculosis; Z, pyrazinamide.

[a] ECG findings are reported if: QTcB or QTcF greater than 500 ms, increase of >60 milliseconds from baseline, atrioventricular block or if reported as cardiotoxicity. When not specified, events include those considered unrelated to treatment.

[b] Excludes deaths. In all cases of treatment interruption, treatment was resumed and finalized. One patient interrupted for more than 35 days.

[c] Three hepatotoxicity-induced deaths during treatment (4Pa100-Mfx-Z ($n = 1$), 4Pa-Mfx-Z ($n = 2$)) were considered treatment related.

Transparency declaration

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Author contributions

T.G. and T.D. were responsible for conception and performed literature search, article selection, critical appraisal, and data extraction. T.G. wrote the first draft. All authors revised the manuscript and read and approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.08.007.

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