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Review

Bedaquiline: Current status and future perspectives

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ABSTRACT

The development of drug-resistant tuberculosis (TB) is a major threat worldwide. Based on World Health Organization (WHO) reports, it is estimated that more than 500 000 new cases of drug-resistant TB occur annually. In addition, there are alarming reports of increasing multidrug-resistant TB (MDR-TB) and the emergence of extensively drug-resistant TB (XDR-TB) from different countries of the world. Therefore, new options for TB therapy are required. Bedaquiline (BDQ), a novel anti-TB drug, has significant minimum inhibitory concentrations (MICs) both against drug-susceptible and drug-resistant TB. Moreover, BDQ was recently approved for therapy of MDR-TB. The current narrative review summarises the available data on BDQ resistance, describes its antimicrobial properties, and provides new perspectives on clinical use of this novel anti-TB agent.

Contents

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1. Introduction

Tuberculosis (TB), an ancient infectious disease caused by *Mycobacterium tuberculosis* and other closely related species, with an incidence of approximately 500 000 TB cases and an estimated two million to three million deaths worldwide annually, is ranked as the second leading cause of death worldwide among infectious diseases [1–3]. Although overall TB rates are on the decline, the prevalence of multidrug-resistant TB (MDR-TB) and, more recently, extensively drug-resistant TB (XDR-TB) is increasing and spreading at an alarming rate, which should be held in consideration [2,4].

According to epidemiological results, TB is more deadly than other infectious diseases such as acquired immune deficiency syndrome (AIDS) and malaria. Despite a 22% global decline in TB deaths between 2000 and 2015, it is still one of the top 10 causes of death worldwide [5]. Also, on the eve of the first turning point in 2020, the World Health Organization (WHO) still reports TB to have the highest mortality rate of any infectious disease worldwide, even surpassing HIV/AIDS and causing 1–5 million deaths in 2018 [6]. According to WHO reports, the prevalence of MDR-TB varies from 0% to 65% in different countries [7]. In fact, the prevalence of TB mortality varies from <5% in some countries to >20% in the African Region [8]. Approximately two-thirds of MDR-TB cases are currently reported in China, India and Russia. Of the approximately half a million people who developed MDR-TB in 2018, only the equivalent of one in three cases were enrolled in treatment [6]. In 2016, there were approximately 10.4 million new cases of TB worldwide, of which 1.7 million died from TB, and approximately 600 000 recent cases of MDR-TB have appeared worldwide, leading to 240 000 deaths in 2017 [8]. According to recent WHO reports, Europe and seven countries with heavy burdens (Kenya, Lesotho, Myanmar, Russia, South Africa, Tanzania and Zimbabwe) are reaching a turning point in 2020. The incidence and mortality are also declining relatively rapidly in the WHO African Region [6]. Therefore, efforts in the discovery of novel and more effective anti-TB agents are urgently required. Bedaquiline (BDQ), previously known as TMC207, R207910 or compound J, is a new last-line anti-TB drug belonging to the diarylquinoline group. It was first discovered by Andries et al. in 2005 [9]. They investigated different chemical compounds in order to select prototypes and to examine their inhibitory effect on multiple-cycle growth of *Mycobacterium smegmatis* by whole-cell assay. From these prototypes, Andries et al. indicated BDQ as the lead compound among a series of diarylquinolines with laboratory effects on several mycobacteria, especially *M. tuberculosis* [10,11]. This new anti-TB drug with a novel mechanism of action is the first drug in a new class approved to treat MDR-TB and XDR-TB since the approval of rifampicin in 1971 in the USA [2]. The US Food and Drug Administration (FDA) granted BDQ accelerated approval based on phase 2 data and a reduction in the time to sputum smear and culture conversion among MDR-TB patients treated with BDQ, which highlighted an advantage of this drug in addition to its key role in the treatment of MDR-TB. However, considering limited data obtained from phase two trials, final approval remains contingent on confirmatory phase three trials. Following promising findings, BDQ under the trade name Sirturo®, is now the first new FDA-approved anti-TB drug in Europe and the USA for use in MDR-TB therapy [12,13]. Despite the outstanding advantages of BDQ as a very promising anti-TB drug, there is a black box warning relating to the drug's effectiveness and safety [1,14,15].

2. Antimicrobial properties of bedaquiline

2.1. Structure of bedaquiline (Fig. 1)

BDQ falls into the class of compounds known as diarylquinolines, which belongs to a novel category of anti-TB drugs. BDQ contains a quinolinic central heterocyclic nucleus with alcohol and amine side chains that are responsible for its anti-TB activity [16,17]. The structural formula of BDQ shows two major components: (i) a hydrophobic part containing $—N(CH_3)_2$, which has a vital role in binding to the ATP synthase; and (ii) an H_2-bonding acceptor/donor that provides stability. However, the anti-TB activity of BDQ is attributed to the diarylquinoline ring, the side chain with the *N*,*N*-dimethyl amino terminus, the hydroxyl group and the naphthalene moiety. According to previous reports, the molecular weight of BDQ is approximately 555.51 Da with a molecular formula of $C_{32}H_{31}BrN_2O_2{\cdot}C_4H_4O_4$ [18–20]. It is chemically compounded with fumaric acid (1:1) as BDQ fumarate. BDQ as an enantiopure compound harbouring two adjacent chiral centres was purified from a mixture of four isomers using high-performance liquid chromatography (HPLC). Some inactive ingredients including croscarmellose sodium, lactose monohydrate, polysorbate 20, microcrystalline cellulose, hypromellose 2910 (15 mPa s), colloidal silicon dioxide, corn starch, magnesium stearate, purified water are reported in the drug BDQ [9,21,22]. Regarding the structural complexity of BDQ, and in order to improve the anti-TB effect of this drug as well as its pharmacokinetic/pharmacodynamic properties, extensive research projects have focused on reducing the complexity of the structure while maintaining its anti-TB activity. Although these research activities led to the identification of new related compounds, none of these has progressed to clinical evaluation. Therefore, there is still a need for identification of BDQ analogues to deliver potential new leads [23,24] .

2.2. Mechanism of action of bedaquiline

Although it is well established that BDQ is closely related to the fluoroquinolones, unlike the fluoroquinolones it displays no inhibitory effects on DNA gyrase and its mechanism of action differs. BDQ is the only FDA-approved anti-TB drug that targets adenosine triphosphate (ATP) by inhibiting the proton pumping mechanism [25]. ATP is produced by ATP synthase and is a vital

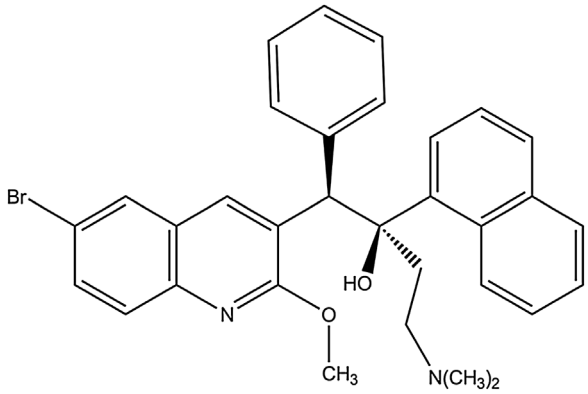

Fig. 1. Structure of bedaquiline as the free base form.

molecule for all eukaryotic and prokaryotic cells, including mycobacteria in the extracellular or intracellular form, replicating or non-replicating, and active or dormant. ATP synthase, a ubiquitous key enzyme located in the inner membrane of mycobacterial mitochondria, is able to generate energy to fuel the catabolic and anabolic reactions of growing mycobacterial cells [9,18,23,26]. This complex enzyme is composed of two sectors, cytoplasmic sector F_1 (five subunits a3, b3, g, d and ε) and membrane sector F_0 (three subunits a, b2 and c10-15). The c subunits of F_0 are arranged in the form of disks and function as an ion-conducting pathway, and F_1 contains three catalytic sites that combine one ADP with a phosphate (Pi) to form ATP. Evidence showed that the proton motive force through F_0 reinvigorates the rotation of the cylindrical ring of subunits c and results in coupled rotation of the catalytic b subunit of F1 domain resulting in ATP synthesis [9,23,27]. It is well documented that BDQ can bind to the oligomeric/proteolipidic subunit c in the F_0 domain of the ATP synthase complex and prevent its function. BDQ has been also shown to be able to inhibit mycobacterial F-ATP synthase via targeting the enzyme's ε subunit in addition to binding to its c subunit [9,23]. The inhibitory effect of BDQ on ATP synthase is specific for mycobacteria. It should be noted that the ATP synthase complex in humans possesses 20 000-fold lower sensitivity to BDQ compared with *M. tuberculosis*, indicating unlikely target-based toxicity and interaction with human ATP synthase [23,28].

2.3. Spectrum of activity of bedaquiline

Different studies on BDQ indicated that it has potent antimycobacterial activity against *M. tuberculosis* and the majority of nontuberculous mycobacteria (NTM), both rapidly and slowly growing [29]. BDQ showed a selective effect against a wide variety of dormant and actively replicating mycobacteria as well as non-pathogenic organisms such as *M. smegmatis* [18,30,31]. Some mycobacterial species such as *Mycobacterium xenopi*, *Mycobacterium shimoidei* and *Mycobacterium novocastrense* are naturally resistant to BDQ, with minimum inhibitory concentrations (MICs) of >8 mg/L. However *M. smegmatis* mutant strains and some of TB strains have developed resistance to BDQ. Interestingly, an *Mycobacterium flavescens* strain in which alanine 63 in AtpE was replaced by methionine that was completely resistant to BDQ was also reported [24,32,33]. In a 2005 study by Andries et al., the activity of BDQ against *M. tuberculosis* isolates compared with rifampicin and isoniazid was assessed. The authors indicated that BDQ had greater potency than either rifampicin or isoniazid [9,10]. In a study by Chahine et al., it was demonstrated that the average MIC of BDQ against MDR isolates of *M. tuberculosis* was 0.03 mg/L. Overall, it can be inferred that BDQ is a narrow-spectrum antibiotic whose activity that appears to be limited to mycobacteria [18].

3. Bedaquiline resistance

A major problem in patients with TB is the prolonged duration of therapy and multiple anti-TB regimens that may lead to acquired drug resistance and its dissemination among mycobacteria [12,29]. Further treatment may potentially reduce antibiotic-susceptible isolates, allowing highly resistant isolates to become predominant. Increasing resistance to anti-TB agents and emerging MDR and XDR-TB strains is a major health threat in numerous regions globally and should be considered. Since the introduction of BDQ for the treatment of MDR-TB, resistance to this antibiotic emerged [34,35]. At the end of 2015, 50 countries described having received BDQ for treatment of more than 2500 patients. Based on WHO reports, at the end of 2017, 68 countries described having introduced or begun using BDQ for the treatment of MDR/XDR-TB. Although BDQ is a recommended drug for increasing treatment efficacy of MDR-TB, inadequate or improper use of BDQ may lead to the rapid emergence of resistant strains [34]. The WHO has also suggested that the emergence of resistance to BDQ may be caused by improper use of this antibiotic, which should be carefully monitored [36].

The WHO clearly emphasised the improvement of precise and reproducible drug susceptibility testing for BDQ and proposed that if there is no specific drug susceptibility testing, serial MIC determinations should be applied for monitoring BDQ resistance. Several studies around the world have shown controversies in the definition of BDQ resistance. Unfortunately, up to now, standardised drug susceptibility testing for BDQ has not been developed and agreed upon [13,34,36]. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, MIC breakpoints for BDQ are defined as follows: susceptible, ≤0.25 mg/L; and resistant, >0.25 mg/L [29,37].

3.1. Mechanisms of resistance to bedaquiline

Published data regarding antibiotic resistance in TB have described two main mechanisms: (i) primary or transmitted drug resistance; and (ii) secondary or acquired drug resistance [33,38]. Several investigators strongly emphasise that resistance mechanisms are mainly linked to chromosomal mutations [39,40]. To date, known molecular mechanisms underpinning resistance to BDQ are divided in three categories [10,37]. The first mechanism is related to mutations in the *atpE* gene that encodes a transmembrane protein of F_1/F_0-ATP synthase and was previously reported by Andries et al. [10]. The likelihood of resistance mutations to BDQ is 5×10^{-7} at 4-fold the MIC and 5×10^{-8} at 8-fold the MIC. By sequencing the *atpE* gene in in vitro-selected *M. tuberculosis* isolates upon exposure to BDQ, six distinct amino acid substitutions and mutations in the subunit c forming the C ring in the ATP synthase were revealed, including replacement of Asp28 → Gly, Asp28 → Ala, Leu59 → Val, Glu61 → Asp, Ala63 → Pro and Ile66 → Met, which prevent BDQ from binding to its target, the c subunit, thus maintaining H^+ transfer and ATP synthesis. These mutations are able to increase the MIC of BDQ by 10–133-fold. Mutations causing the substitution Ala63 → Pro resulted in a 133-fold increase in the MIC (4 mg/L) compared with wild-type *M. tuberculosis* H37Rv. The mutations Glu61 → Asp, Ile66 → Met and Asp28 → Gly resulted in a 16- to 33-fold increase in MIC, from 0.5 to 1 mg/L, compared with wild-type H37Rv. In *M. tuberculosis* mutant strains, mutations causing the substitution Leu59 → Val caused a small rise in the MIC (8-fold).

The amino acid substitution Asp28 → Ala in *Mycobacterium fortuitum* mutants harbouring this mutation led to a 400-fold increase in MIC, whereas it was caused a 32-fold increase in *Mycobacterium abscessus* mutants. *M. abscessus* with the specific point mutation Ala63 → Pro and *M. smegmatis* with the specific

point mutation Ile66 → Met showed a 64- to 133-fold increase in the MIC. Recently, two new substitutions (D28N and A63V) were found to be associated with increased BDQ MICs in clinical isolates [23,38]. In a recent study by Huitric et al. to identify point mutations in the *atpE* gene, 53 in vitro mutants were investigated [41]. They discovered five single point mutations (A28V, A63P, I66M, A28P and G61A) in the *atpE* gene in only 28% (15/53) of the BDQ-resistant isolates and no mutation was detected in *atpE* or even in the F0, F1 operons in the remaining 72% (38/53). This finding strongly highlighted the possible existence of other resistance mechanisms against BDQ that need to be explored. Additionally, no resistant mutants were reported when exposed to 3 mg/L.

It is noteworthy that some of NTM are inherently resistant to BDQ. This has been associated with replacement of the methionine residue with an alanine amino acid in the 63rd position in subunit c. The second mechanism is related to mutations in Rv0678 modulating expression of the MmpS5–MmpL5 efflux pump. These mutations are identified in isolates upon in vitro exposure to BDQ or clofazimine (CFZ) and in some of isolates of patients treated with the BDQ [2], which resulted in a high 2- to 8-fold increase in the BDQ MIC and a 2- to 4-fold increase in the CFZ MIC. Drug efflux as a significant mechanism both in intrinsic and acquired BDQ resistance has recently attracted much interest among microbiologists, pharmacologists and clinicians. Interestingly, a study performed by Gupta et al. assessing the effect of verapamil on efflux inhibition demonstrated an 8- to 16-fold decrease in their BDQ and CFZ MICs in the presence of verapamil [42].

Although efflux pumps contribute to BDQ and CFZ resistance by reducing the transmembrane potential, it was showed that addition of efflux pump inhibitors such as verapamil caused in a 2- to 16-fold decrease in the MIC of BDQ and CFZ [43]. However in another study conducted in South Africa, all 12 isolates with a ≥4-fold increase in BDQ MIC had mutations in Rv0678, a transcriptional repressor of the MmpS5–MmpL5 efflux pump [35]. Hartkoorn et al. also showed the role of *Rv0678* gene mutations in BDQ and CFZ cross-resistance, potentially restricting therapeutic choices [44]. Although the majority of *Rv0678* mutants were reported in patients treated with BDQ-containing regimens, recently some of researchers also reported these mutant strains in patients without prior exposure to BDQ or CFZ [45].

Interestingly, Villellas et al. demonstrated a high frequency of *Rv0678* resistance-associated variants (RAVs) among MDR-TB isolates (23/347; 6.6%) [12]. Surprisingly, none of the patients except for seven subjects had a history of exposure to either BDQ or CFZ. The occurrence of *Rv0678* RAVs in MDR-TB strains was 9-fold higher compared with non-MDR-TB isolates (0.7%) [12]. In a study by Andries et al., a high prevalence of mutations in *Rv0678* was also reported (6.6%), suggesting the important role of this gene in increasing the MICs of BDQ [10]. In another report, it was noted that mutation in *Rv0678* was detected in five MDR-TB isolates and this mutation persisted despite restriction in its use for over 1 year [46]. In a recent study, investigation of MDR-TB patient who received BDQ for 6 months indicated that mutation in position 2 (GTG → GCG) in *Rv0678* that leads to impair function is responsible for the high-level resistance observed [47]. Recent published studies described mutations in the *Rv0678* regulator gene (2 T > C leading to M1A) related to BDQ and CFZ resistance in a patient with MDR-TB [39,48].

Another mechanism contributing to the development of resistance to CFZ and BDQ is non-target mutations in *pep*Q (*Rv2535c*, a putative Xaa-Pro aminopeptidase). Point mutation in *pep*Q is believed to be a potential cause of BDQ or CFZ resistance in *M. tuberculosis* isolates. These mutations were selected in mice by treatment with BDQ. The *pep*Q mutations were associated with low-level resistance to BDQ and cross-resistance to CFZ. Mutation in *pepQ* led to a slight increase of ~4-fold in BDQ and CFZ MICs. These mutations act by reduction of the antibiotic effectiveness in vivo but did not result in complete resistance. Accordingly, one intriguing study in a murine TB model showed that a *pep*Q mutant was virulent and less susceptible to BDQ and CFZ [39]. The results obtained from this study explained that resistance mediated by *pep*Q mutation may be related to higher antibiotic efflux, but this is not linked to overexpression of *mmpL5* and *mmpS5*. This comprehensive report also demonstrated that *pep*Q dysfunction is adequate for decreased susceptibility both in vitro and in vivo [39,49].

3.2. Epidemiology of bedaquiline resistance

Since the recent administration of BDQ as an option for MDR-TB, several thousands of people had received this drug around the world [50]. Like other drugs, BDQ-resistant strains emerged pretty quickly and increased concern about its future role in anti-TB regimens. *M. tuberculosis* isolates acquire resistance to BDQ by spontaneous chromosomal mutation in *atpE* (BDQ target), *Rv0678* (transcriptional repressor of the MmpS5–MmpL5 efflux pump), *Rv0677c*, *pepQ* (encoding an Xaa-Pro aminopeptidase) genes and mutations in the intergenic region between *Rv0678* (efflux pump MmpL5) and *Rv0677c* (efflux pump MmpS5) that result in suppression of ATP synthase inactivity [50,51].

Until now, a few patients with BDQ resistance have been described. In 2014, the first case of a MDR-TB patient with a BDQ-resistant isolate was reported. After 24 months of treatment and relapse, isolates with cross-resistance to BDQ and CFZ (*Rv0678* mutation) were observed in a Tibetan patient [52]. Therefore, it is recommended that if a previous anti-TB regimen with CFZ was used, susceptibility to BDQ should be ensured before starting a BDQ-containing regimen [53].

In 2019, the emergence of low-level BDQ-resistant strain in a 50-year-old patient with XDR-TB was reported. The baseline isolate was susceptible to BDQ by MGIT (Mycobacterium Growth Indicator Tube), but the colorimetric resazurin microtitre assay (REMA) showed increased MICs up to 8-fold compared with the baseline isolate at weeks 22, 32, 42 and 64 of treatment [54]. In a retrospective study conducted by Ghajavand et al., MICs and possible mutations related to resistance were examined in 24 *M. tuberculosis* strains from patients previously receiving a BDQ-containing regimen. The BDQ MIC was ≥0.25 mg/L in 15 isolates. Moreover, one pre-XDR isolate and four (one MDR, one pre-XDR and two XDR) isolates had MICs of 4 mg/L and 8 mg/L, respectively. Whole-genome sequencing revealed that two isolates harboured non-synonymous mutations in *mmpl5* (efflux pump) and one isolate showed *rv1979c* M245L mutation [50].

In Pakistan, Ghodousi et al. evaluated 70 *M. tuberculosis* strains from 30 patients previously administered BDQ-containing regimens. The baseline strains were susceptible to BDQ, but five patients acquired resistance to BDQ and an increase in MICs (range, 0.125 to >0.5 mg/L) during treatment. In addition, they examined specific mutations in *Rv0678* contributing to elevated BDQ MICs in cases failing therapy [55]. In 2016 in Russia, Zimenkov et al. studied 85 isolates from 27 patients with decreased susceptibility to BDQ (MIC ≥ 0.06 mg/L). They documented numerous cases with strains with increased MICs of BDQ before treatment and high MICs of BDQ associated with *mmpR* gene mutation [56]. Like other drugs, the occurrence of BDQ resistance is frightening because it may prompt the fast failure of this novel antibiotic. As a consequence, detection of BDQ resistance mechanisms and an increase of standardised antibiotic susceptibility testing will help to direct treatment and diminish the risk of resistance.

4. Synergy

4.1. Synergism of bedaquiline with delamanid

There are concerns about possible additive cardiac toxicity for BDQ plus delamanid (DLM) combination therapy [57]. It has recently been reported that these drugs have a good effect on MDR/XDR-TB patients particularly when four active antibiotics cannot be involved in a regimen [57–60].

The first case of XDR-TB treated with co-administration of DLM/BDQ with CFZ was reported in 2016 [61]. DLM, a bicyclic nitroimidazooxazole agent, prevents the synthesis of mycolic acids in mycobacteria [62,63]. The patient was resistant to second-line drug treatment, so there were no resources currently available for this patient and combination therapy was started. The recommended regimen was interrupted after eight doses of BDQ with DLM administration because there were ongoing concerns regarding QTc prolongation. The patient was closely monitored and an electrocardiogram (ECG) was repeated biweekly [61]. A QTc interval >500 ms is considered a risk factor for severe arrhythmia, and if this sign is seen in patients, clinicians should interrupt treatment and consider the patients carefully [64]. Nearly 1 month later, BDQ was restarted and revealed a negative sputum smear and culture alongside correction in electrolytes, serum albumin and ECG QT wave interval at 2-months follow-up [61].

Furthermore, in 2016 Lachâtre et al. reported favourable clinical, microbiological (smear and culture) and radiological responses in a 20-year-old man with pulmonary TB who had received BDQ plus DLM at 6-month follow-up. The combination of two drugs had no side effects such as QT interval prolongation [65]. In another study, five patients living in Russia, India and the Netherlands received BDQ with DLM in combination. The patients had either drug treatment failures or relapsed during their treatment and were resistant to at least five anti-TB drugs. Continuation of the suggested regimen showed the sputum and cultures of four patients converted to negative after 18–435 days and 28–218 days, respectively, however one patient died from respiratory failure. For three patients the QTcF intervals remained normal and only two patients had brief abnormalities in their heart performance that quickly normalised [64].

Although DLM and BDQ combination appears to be helpful in severe, almost untreatable, XDR-TB cases, some concerns about potential cardiac side effects (QT interval prolongation) remain contested [66]. Recently, a retrospective cohort study was performed in Armenia, India and South Africa to assess the efficacy and safety of DLM and BDQ combination therapy for MDR-TB. All laboratory tests related to drug safety such as haemoglobin/electrolyte measurement and ECG monitoring were carried out regularly and suggested that using combination therapy with BDQ and DLM had no additive or synergistic QTcF-prolonging effect. Moreover, efficacy assessment of the combination determined by negative sputum culture showed that all patients in this study had a documented negative culture at 6 months [67].

At the present time, we can consider BDQ and DLM combination as a novel anti-TB treatment for MDR and XDR strains that needs close monitoring and adequate management of patients during their co-administration to consider potential cardiological side effects [59,61,66].

4.2. Synergism of bedaquiline with pyrazinamide

Pyrazinamide (PZA) is a highly effective drug that targets vital bacterial process such as the proton motive force and ribosomal translation [68,69]. Due to the role of BDQ as an ATP synthase inhibitor, it seems their combination can suppress bioenergetic functions and both drugs potentially deplete cellular energy reserves [69]. More than one decade ago, the first study of BDQ efficacy in mice showed that the combination of BDQ and PZA with another first- or second-line anti-TB drugs diminished the bacterial load to change the lung culture to negative after 2 months of treatment [70]. In other parallel study undertaken in 2007, the BDQ and PZA combination had the most effective results compared with other combinations. Co-administration of BDQ and PZA converted 100% of mice to culture-negative after 2 months of treatment [71]. The efficacy of BDQ and PZA treatment has been determined for BALB/c, Swiss and C3HeB/FeJ mice infected with *M. tuberculosis* and decreased the bacterial load after 4 weeks of treatment [68]. Furthermore, the combination of BDQ and PZA revealed strong synergy and increased bactericidal activity in vitro. Inhibition of energy metabolism caused by BDQ combined with the front-line drug PZA resulted in a synergistic effect to reduce *Mycobacterium bovis* BCG used as a model [69]. In a randomised clinical trial of 105 patients, the antimycobacterial activity and pharmacokinetics of different combinations including BDQ, PZA and other supplementary first-line agents was evaluated as 14-day early bactericidal activity (EBA), expressed as the rate of change in $\log_{10}$ CFU counts over 14 days of treatment ($EBA_{CFU}0–14$). The highest mean $EBA_{CFU}0–14$ estimate was found with the BDQ, PZA and pretomanid (PA-824) combination regimen, which had activity identical to the current standard anti-TB regimen. The authors suggested longer clinical studies determining its efficiency as a potential new TB treatment regimen [72]. Another randomised EBA study performed by Diacon et al. on treatment-naive, drug-susceptible patients with uncomplicated pulmonary TB who received BDQ, BDQ + PZA, PA-824 + PZA, BDQ + PA-824, PA-824 + moxifloxacin + PZA or standard anti-TB treatment as a positive control. Although the mean 14-day EBA of PA-824 + moxifloxacin + PZA was significantly higher than the other combinations, the onset of activity of BDQ was delayed with an inflection point at 6.5 days. This result may be explained by the fact that PZA increases the activity of BDQ resulting in greater activity of BDQ and PZA than BDQ alone. Addition of PA-824 to BDQ seemed to have little if any effect on the activity of BDQ, albeit without causing clear antagonism [73].

As a conclusion, a possible explanation for this synergism might be that PZA interferes with the proton motive force and membrane integrity, so it indirectly inhibits ATP synthase and has a synergistic function with BDQ [71]. Thus, addition of BDQ to PZA can accelerate bacterial elimination and may help minimise the treatment duration for patients [74].

4.3. Synergism of bedaquiline with cephalosporins

A novel approach in pharmaceutical development is ‘new uses of older drugs’. Due to the high cost of developing a new drug and the appearance of resistance mechanisms in *Mycobacterium*, administration of existing drugs is arousing the interest of pharmaceutical companies. Cephalosporins, which disrupt synthesis of the peptidoglycan layer of the bacterial cell wall, have a synergistic effect with new anti-TB drugs. So they can be repurposed in new combination TB regimens.

An in vitro synergy assay of cefradine and faropenem with a panel of anti-TB drugs including BDQ was performed for *M. tuberculosis* H37Rv strains. The fractional inhibitory concentration of each drug in the combination was calculated. Isobologram curves showed a strong synergistic interaction of cephalosporins with BDQ, DLM and PA-824 but not with isoniazid, ethionamide, aminoglycosides or fluoroquinolones [75]. The authors did not elucidate the precise mode of action of these synergistic combinations, therefore further work is required to unravel the molecular mechanisms behind them and to facilitate adding cephalosporins in anti-TB combination therapies.

4.4. Synergism of bedaquiline with pretomanid

Pretomanid (PA-824), a nitroimidazo-oxazine, has shown significant bactericidal activity alone and in combination with novel agents both against replicating and non-replicating strains of *M. tuberculosis* [76,77]. Its activation pathway either diminishes intracellular ATP or inhibits cell wall mycolic acid synthesis (comparable with the activity of isoniazid) [78]. Several studies have investigated the interaction of BDQ and PA-824 as an anti-TB combination in a mouse model and also in patients with pulmonary TB.

Evaluation of several beneficial anti-TB agents against intracellular *M. tuberculosis* was performed on whole blood culture. Combination of BDQ, sutezolid (an oxazolidinone) and SQ109 (an ethambutol analogue) had a significant additive effect, whereas adding PA-824 to those regimens containing BDQ or sutezolid resulted in less than synergistic effect or antagonism [79]. The antagonistic effect of PA-824 with BDQ was examined in several studies and revealed the activity of BDQ plus PA-824 was the same as the first-line regimen during 2–3 months, however over the first month the combination had lower efficacy than BDQ alone [76,80,81].

On the other hand, in phase IIa clinical trials of new anti-TB drugs, PA-824 was combined with other agents for patients with drug-susceptible isolates. Among the different combinations, the PA-824, moxifloxacin and PZA group had the most favourable results compared with BDQ alone, BDQ with PA-824, or PZA [73].

Moreover, a double-blind, randomised assessment of multiple-agent combinations was performed on 15 patients with pulmonary TB. The 14-day EBA was assessed as decreasing CFU of *M. tuberculosis* per millilitre of sputum. The most effective combination was PA-824 + moxifloxacin + PZA, which was significantly higher than the other groups. It is important to note that a regimen lacking isoniazid and rifampicin would provide a beneficial step towards novel regimens with low interaction potential. Besides the activity of BDQ + PA-824 was identical to isoniazid + rifampicin + PZA + ethambutol, which was lower than PA-824 + moxifloxacin + PZA [73].

4.5. Synergism of bedaquiline with pretomanid plus linezolid

Linezolid (LZD), a first-generation oxazolidinone antibiotic, is effective for treatment of chronic pulmonary XDR-TB [82,83]. A prospective randomised trial demonstrated bacteriological conversion in XDR-TB patients administered a reduced LZD dosage (300–600 mg/day) [84].

A study published in 2016 found that the contribution of LZD to BDQ–PA-824 had sterilising activity in a mouse model of TB. In this study, the efficacy of BDQ and PA-824 with LZD singly and as a combination in a three-drug regimen was examined. All two-drug combinations had lower activity compared with the activity of the three-drug combinations of BDQ–PA-824 plus LZD at 2 months [80].

4.6. Bedaquiline interactions with antiretroviral drugs

Drugs that inhibit cytochrome P450 3A4 (CYP3A4) could result in increased concentrations of BDQ, which could increase risk toxicity, whereas drugs that induce CYP3A4 could result in reduced concentrations of BDQ. The WHO has suggested first- and second-line antiretroviral drugs that may affect BDQ exposure by inhibiting and/or inducing CYP3A4.

The protease inhibitor lopinavir/ritonavir and the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine are, respectively, a potent inhibitor and moderate inducer of CYP3A4. Various studies have shown only modest effects of lopinavir/ritonavir and nevirapine on BDQ exposure [4,85].

Ritonavir-boosted lopinavir (LPV/r) decreased the clearance of BDQ and its M2 metabolite to 35% [relative standard error (RSE), 9.2%] and 58% (RSE, 8.4%), respectively. Approximately two-fold (M2) and three-fold (BDQ) increases in exposure during chronic treatment with LPV/r are expected and dose alterations are recommended for evaluation. Safe, effective BDQ dosing for patients with MDR-TB receiving antiretrovirals is essential. The findings of this study show that BDQ can be co-administered with nevirapine without dose adjustments [86].

Another antiviral drug, efavirenz (EFV), induces CYP3A4, the metabolic enzyme responsible for BDQ biotransformation. Due to the induction of CYP3A4 by EFV, the drugs are predicted to interact. A study by Svensson et al. showed that during EFV co-administration, simple adjustments of the standard regimen can preclude reduced exposure to BDQ without increasing exposure to M2. Assessment of adjusted regimens is important to ensure proper dosing for HIV-infected TB patients receiving an EFV-based regimen [87]. Also, in a phase I study, 600 mg EFV once daily reduced exposures of single-dose BDQ by 18% and increased the maximum concentration (C_{max}) of M2 by 89% [88].

5. Pharmacokinetics and pharmacodynamics

The time to peak concentration and plasma half-life of BDQ are 4–6 h and 24–30 h, respectively. However, the terminal elimination half-life is much longer. This antibiotic can conjugate with blood transport proteins, is metabolised by the liver enzyme CYP3A4 to its main metabolite M2 and is eliminated in the faeces [89,90]. In a study by Dhillon et al., intracellular activity in a J774 macrophage-like cell line and in primary mouse peritoneal macrophages had little or no static phase, so that the bactericidal kill was apparent by 5–7 days probably due to decreased bacterial ATP levels. Overall, the intracellular activity of TMC207 was obviously greater than its extracellular mainly because the primary static phase was shorter [91].

Mild-to-moderate renal disorders have no influence on the pharmacokinetics of BDQ. It is unnecessary to adjust medication regimens for people with moderate hepatic or renal impairment, but we recommend caution for patients with severe renal or hepatic impairment. Several factors such as age, sex, body weight and concomitant HIV infection have not been reported to affect the pharmacokinetics of BDQ. Experiments showed that among different ethnicities, subjects of Black ethnicity had lower concentrations of BDQ than other races [2].

The sterilising activity of BDQ has been studied in guinea pigs and mouse models of TB infection and the results showed that the sterilising activity BDQ alone and in combination against drug-susceptible and several MDR-TB. It was also observed that BDQ interacts with histamine type 2 receptors (87%), sodium channels (71%) and dopamine transporters (54%), while there is low potential for interaction with either transport binding sites or other receptors (including, but not limited to, cholecystokinin, angiotensin, opioid, norepinephrine transporters or chloride channels) [92,93].

6. Adverse events

Antibiotics used for the treatment of drug-resistant TB are associated with high rates of side effects and are often poorly tolerated. Today with regard to the shortcomings and limitations that exist in the treatment, it is important to note that BDQ has an elimination half-life of 5.5 months owing to a combination of a high tissue distribution and long plasma half-life [3].

The most commonly reported side effects of BDQ include headache, dizziness, vomiting and arthralgia. In one study, 47 MDR-TB cases received either placebo (24 cases) or TMC207 (23 cases) in combination with a standard five-drug, second-line anti-TB regiment. In this study, nausea occurred significantly more frequently in the TMC207 group compared with the placebo group (26% vs. 4%; $P = 0.04$). But overall side effects were similar in the two study groups. The most common side effects observed included unilateral hypouricemic deafness, haemoptysis, limb pain, rash, arthralgia, nausea and chest pain [94].

One of the major concerns of the FDA Committee on BDQ safety is the unexplained increase in BDQ mortality in a randomised controlled trial [95]. Adverse reactions of BDQ in a study by Guglielmetti et al. were mostly mild [96]. The percentage of subjects who experienced a ≥60 ms increase in QTc_B during therapy (20%) was higher than in previous studies and, as found in the C209 Trial, was more marked in subjects receiving BDQ in association with CFZ. Although short-term safety results appear promising, careful and regular follow-up of patients for severe side effects is important even after discontinuation of the drug. This is of much significance for the combination of BDQ with other anti-TB drugs [96,97]. One of the most common side effects of BDQ observed in patients is increased QTc interval on the ECG [98]. Approximately 11.4% of cases taking BDQ died during clinical trials compared with 2.5% of those taking placebo. Because this drug carried significant risks, it is necessary to use it only in patients who have no other treatment options [99]. According to other results, among 45 MDR-TB patients, severe and serious adverse events were recorded in 27 (60.0%) and 7 (17.8%) of cases, respectively. Among 44 patients, the most frequent adverse effects were gastrointestinal side effects (32; 71.1%), otovestibular impairment (25; 55.6%) and peripheral neuropathy (18; 40.9%). A measured Fridericia-corrected QT interval (QTcF) >500 ms was recorded 11% of individuals, but neither arrhythmias nor symptomatic cardiac side effects were observed. BDQ was discontinued in 3 patients (6.7%) following QTcF prolongation. The study also found no significant differences in outcomes or side effects between patients treated with standard long-term BDQ. Regimens containing BDQ achieved excellent results in a large proportion of patients. Long-term treatment with BDQ was generally well tolerated in this group [100].

Furthermore, BDQ has a black box warning that it can affect the sudden electrical activity of the heart and also prolong the QT interval, which can lead to an abnormal and possibly lethal heart rhythm [99].

7. Clinical treatment

7.1. Use in multidrug-resistant tuberculosis (MDR-TB) cases

Conventional regimens for treating MDR TB are not the answer today, as studies have shown at least 20 months of treatment with a combination of second-line drugs is harmful, expensive and also little more efficacious than drugs applied to treat drug-susceptible TB. In a cohort study, just 50% of the group of patients observed responded well to treatment owing to the high frequency of death (16%), treatment failure (10%) and a lack of follow-up (16%) usually related to adverse drug reactions, among others [92].

Belarus in Eastern Europe was one country with concerning statistics regarding MDR-TB. The results of a previous study showed that MDR-TB was found in ~35% of new cases and ~75% of previously treated cases. Regarding the few patients with TB who undertake drug susceptibility testing in most high-outbreak countries, it is probable that the frequency of MDR-TB is higher than reported [29].

In June 2013, the WHO issued a temporary policy manifesto to provide instruction on the availability of BDQ in qualified patient groups [3]. The temporary policy is based on a document evaluation and advice by a specialist group convened with the WHO/Stop TB Department in Geneva, Switzerland, and resulted in the commendation that BDQ may be added to regimens in the adult group with pulmonary MDR-TB (conditional commendation, very low assurance in the assessment of effects).

Because of concerns about the prevalence of drug resistance in this group of patients, especially resistance to fluoroquinolones or second-line injectable drugs (kanamycin, amikacin, capreomycin), BDQ may have a major function in strengthening the regimen, increasing the number of drugs that may be effective to at least four, and preventing the development of additional resistance and progression to XDR-TB [36].

In a study conducted in 15 countries among people in aged 18–65 years who have recently been diagnosed with pulmonary MDR-TB, 160 persons were a randomised in a clinical trial to receive BDQ or placebo with a five-drug MDR-TB background regimen. The average period to culture conversion was for 83 days [95% confidence interval (CI) 56–97 days] in the BDQ group vs. 125 days (95% CI 98–168 days) in the placebo group.

Applying Cox symmetrical risk pattern (equal to lung cavitation and pooled centre) there was higher chance of rapid culture conversion in the BDQ arm compared with the placebo arm (hazard ratio = 2.44, 95% CI 1.57–3.80; $P < 0.0001$). The proportion of subjects with culture conversion at Week 24 (secondary efficacy endpoint) was 78.8% in the BDQ arm versus 57.6% in the placebo arm ($P = 0.008$) [13].

The drug has been approved relying on the results of a phase II trial. The study was in the form of a randomised clinical trial to test the protection and effect of BDQ when added to background regimen in recently recognised cases with pulmonary MDR-TB administrated. The results of the first experiment showed [98] the superiority of TMC207 (48%) to the standard drug regimen for this disease resulting in rapid conversion to a negative sputum culture compared with the placebo group (9%). The mean percentage of negative smear for fast acid bacilli the for TMC207 and placebo groups was 77% and 57% at Week 4 and 84% and 68% at Week 8, respectively.

In the second trial [101], the average time for sputum culture conversion for TMC207 was about 78 days compared with 129 days for placebo. Those receiving TMC207 were at a lower risk of acquisition of additional drug resistance during the entire follow-up period. The results showed that the percentage of side effects in cases who received BDQ was 82.6%, similar to those who received placebo (79.2%).

The results of a study showed that BDQ and DLM were safe and useful for remedying MDR-TB, with an early clue of consecutive administration of these two medicines as a viable therapeutic strategy for patients when enough therapeutic regimen cannot be manufactured. Among 55 participants who showed positive sputum cultures at the onset of BDQ and/or DLM treatment, 39 (70.9%) achieved sputum culture conversion within a median of 119 days. Treatment was halted in four cases (6.6%) because of prolonged QTcF [102].

Also, another study in 2017 by Achar J et al. described 27 children and adolescents aged <18 years who were taking BDQ for the treatment of MDR-TB. The results of their study showed a good therapeutic response and no termination because of adverse effects [103].

7.2. Use in drug susceptible tuberculosis cases

After the first therapeutic trials aimed at assessing single drugs that could increase cure rates and reduce mortality, it was clear

that a single drug was not enough to prevent the development of drug-resistant TB. The next therapeutic challenge was to combine this goal with a reduction in the long treatment duration [104]. Available anti-TB regimens are expensive and long-term, require high adherence, and are undermined by a high frequency of adverse effects, thus leading to low rates of treatment success. To improve adherence to treatment, in 2016 a shorter TB regimen was suggested by the WHO under specific microbiological and clinical conditions. Although new anti-TB drugs that may permit shortening of the duration of TB treatment and improve its outcome are favourable, in the last 50 years only BDG and DLM have been confirmed for MDR-TB treatment. Research should look for easily available, well tolerated and short regimens to get closer to the WHO aim. BDQ is an important drug to shorten the MDR-TB and XDR-TB regimen; in fact, a phase 3 study aimed at evaluating the efficacy and safety of a BDQ regimen associated with linezolid and pretomanid in adult individuals with pulmonary XDR-TB intolerant to conventional treatment or non-responsive MDR-TB is currently recruiting participants [105].

7.3. Use in latent tuberculosis infection (LTBI)

LTBI is defined as the situation of continuing immune response to stimulation by *M. tuberculosis* antigens with no record of clinically active TB. In many high-income and developed countries, LTBI has been a crucial part of TB control programmes for decades because it was first identified that progression of the disease could be prevented in guinea pigs and humans [106].

The bactericidal activity of BDQ in liquid culture medium begins with a bacteriostatic phase lasting 7 days, and afterwards a continued dose-related bactericidal phase. However, studies have shown that the intracellular activity of BDQ is greater than its extracellular activity because the preliminary static phase was shorter or absent.

BDQ may affect ongoing treatment for LTBI. This is especially true for LTBI therapy for close contacts of patients with drug-resistant TB. Unfortunately, there is no practical and standard approach to treating LTBI among patients with MDR/XDR-TB (DR-LTBI). In a study in a mouse model, BDQ displayed bactericidal activity against dormant (non-replicating) tubercle bacilli with substantial sterilising activity and may enable treatment of DR-LTBI in 3–4 months [107,108].

Another study by Lanoix et al. used three drugs alone and in combination in an experimental paucibacillary LTBI chemotherapy model using BALB/c and C3HeB/FeJ mice immunised with a recombinant strain of *M. bovis* BCG (rBCG30) and then challenged with a low-dose aerosol of *M. tuberculosis* H37Rv. The regimens tested included BDQ, PA-824 (Pa), sutezolid (PNU), and/or one of two fluoroquinolones. Control mice received rifampicin or isoniazid. The results showed that in BALB/c mice BDQ-containing regimens and the Pa-PNU combination were the most active tested regimens and were at a minimum as impressive as rifampicin. The results confirmed the potent activity of BDQ previously observed in BALB/c mice and highlight Pa alone or in combination with either PNU or a fluoroquinolone as worthy of assessment in clinical trials of MDR-LTBI [109].

7.4. Use in difficult-to-treat nontuberculous mycobacteria (NTM) infections

The prevalence of NTM pulmonary disease is increasing globally. *Mycobacterium kansasii*, *M. abscessus* and *Mycobacterium avium* complex (MAC) are the most common NTM. Azithromycin and clarithromycin are key antibiotics for treating NTM pulmonary disease. Previous studies have suggested that the MICs of BDQ for *M. tuberculosis* were very low. In a study conducted by Kim et al., DLM showed high MICs for all NTM except *M. kansasii*. BDQ had low MICs for MAC, *M. kansasii*, *M. abscessus* and *Mycobacterium massiliense*. This antibiotic also had low MICs against macrolide-resistant NTM. The results of their study showed that BDQ had a good in vitro effect against pathogenic NTM, but DLM did not. BDQ has the potential to be an effective antibiotic for treatment macrolide-resistant NTM pulmonary disease [110]. In 2020, Erber et al. reported the first reported case of successful in vivo use of BDQ for infection caused by *M. fortuitum* [111].

7.5. Use for immunodeficient patients

TB treatment has been completely clinical for a long time, and after 2008, based on phase 2 clinical trials, three new anti-TB drugs, namely BDQ, DLM and PA-824, were introduced [112]. At birth, human serum albumin (HSA) concentrations are approximately the same as in adults (75–80%), while alpha-1-acid glycoprotein (AAG) is initially half the concentration in adults. As a result, the rate of drug binding to HSA is closer to that of adults than for other drugs that bind more to AAG. A model that incorporates the fraction unbound in adults and the ratio of binding protein concentration between infants and adults has successfully predicted the unbound fraction in infants and children [113].

Svensson et al. reported a study on the pharmacokinetics of BDQ and its metabolite M2 in 335 patients with MDR-TB receiving 24 weeks of BDQ in addition to a longer individualised history regimen. Semi-physiological models described changes in weight and albumin over time. It correlated weight and albumin, increasing since the beginning of remedy, and affecting BDQ and M2 plasma disposition [114].

Applying a population pharmacokinetic model, the results of long-term co-administration of BDQ and efavirenz, a CYP3A inducer, was assessed. Among healthy adult volunteers, it was observed that a single dose of efavirenz alone minimally affected BDQ pharmacokinetics. Nevertheless, efavirenz could decrease concentrations of BDQ and its main metabolite by up to 52% following long-term co-administration [2].

Among HIV-positive patients with MDR TB, higher mortality rates are often observed. Efavirenz and nevirapine also induce CYP3A4. Ritonavir, a further promoter of protease suppressants, is a CYP3A4 inhibitor. When efavirenz is given with a single dose of BDQ, the concentration of BDQ is reduced by about 20%. About 50% reduction is predicted when mathematical modelling is evaluated to assess BDQ concentrations [88].

Concomitant use of ritonavir-boosted lopinavir (LPV/r) with BDQ may be troublesome. Albeit a single-dose drug–drug interplay study showed just a light rise in concentrations of BDQ and its basic metabolite, it is probably that remarkable reposition of BDQ and its metabolite will arise with extended usage of BDQ and LPV/r. As the clinical effects are not clear when using LPV/r and BDQ, one should use this combination with extreme caution and only in closely monitored conditions if no other options are available [115].

In a study of 91 drug-resistant TB patients followed-up until August 2014, 54 (59%) were infected with HIV. The average CD4 count was 239 cells/μL and all cases were receiving antiretroviral therapy at the beginning of BDQ treatment; 33 patients had XDR-TB, 41 were pre-XDR-TB with resistance to a fluoroquinolone and 17 were pre-XDR-TB with resistance to an injectable. Of the 91 cases in the study, 58 (64%) completed 24 weeks of BDQ, 28 (31%) were still on BDQ, 3 (3.2%) were lost to follow-up, 1 patient died and 1 patient was withdrawn following atrial fibrillation. Among 63 cases in the follow-up study for 6 months, 48 (76%) had either culture-converted or remained culture-negative after starting of BDQ. QTcF was monitored every month and exceeded 500 ms in three participants, which resolved in all three [116].

Diabetes and hypoglycaemic agents may affect anti-TB treatment. Information supporting this outcome are reported just for standard anti-TB therapies. For diabetics, the new MDR-TB drugs Sirturo® (BDQ) and Deltyba® (DLM) are recommended when another effective treatment regimen cannot be provided. There is particular concern about the consumption of BDQ and DLM in diabetic cases up the age of 65 years as well as in patients with severe renal or hepatic impairment or electrolyte imbalance. Simultaneous consumption of BDQ and DLM with insulin analogues as well as other hypoglycaemic factors that prolong the heart rate-corrected QT interval, such as sulfonylureas and glinides, may boost this adverse response. Hepatic-related side effects may be more likely to occur when these drugs are combined with thiazolidinediones and acarbose [117].

The WHO recommends BDQ in pregnant women and children below 18 years of age, but the US Centers for Disease Control and Prevention (CDC) said it could consider them it in these populations and in cases with extrapulmonary disease. This drug is considered in the FDA class B pregnancy category. It is not yet known whether BDG and its metabolites are excreted in human breast milk, although results show that milk is concentrated in rats. Both the CDC and the FDA raised concerns and stressed the need for critical oversight of several specific diseases, including liver disease, heart disease, and alcohol and drug abuse [118].

8. Other considerations for bedaquiline therapy

Based on the FDA strategies, BDQ was prioritised to patients and rapid determination and orphan-product designation of this drug was granted. This drug was approved a part of combination therapy to treat adults with pulmonary MDR-TB where other suitable options are not available [99]. In 2013, the WHO and CDC issued interim recommendations for the use of this drug for the treatment of MDR-TB patients [119]. BDQ should be prescribed for the treatment of patients with MDR-TB, if an effective strategy with PZA and four second-line medicines, as suggested by the WHO protocol, otherwise cannot be designed. It is also suitable to treat MDR-TB with referenced resistance to any fluoroquinolone. The suggested dose is 400 mg daily for 2 weeks, followed by 200 mg three times a week for 22 weeks. To maximise efficiency and absorption, the WHO recommended intake with food. It should also not be prescribed for over 6 months, while the CDC recommended that treatment be considered on a case-by-case basis for over 24 weeks unless an efficient regimen is otherwise prescribed [120].

The introduction of BDQ to patients at country level necessitates the consideration of several of concerns of public-health significance, including: wide availability; the recognition of fixed-dose or optimal combinations to be used according to the type of TB; and the expected effects and adverse events of the drug on patients' eligibility criteria. Additionally, it is necessary to certify programmatic practicability and cost-effectiveness of BDQ. India's success rate for MDR-TB was lower than 50%, so it accounts for one-quarter of the world's MDR-TB. Since 2015, BDQ was approved in India for use under a conditional access programme. A BDQ compassionate programme suggested that use of BDQ with additional monitoring may be safe and effective even in the field setting because of higher and faster culture conversion rates among MDR/XDR-TB patients and a lower toxicity profile when BDQ was used with a background regimen [121].

Five cohorts were conducted in the USA ($n = 205$), France ($n = 45$), South Africa ($n = 195$), Georgia ($n = 30$) and Armenia ($n = 62$) to evaluate treatment outcomes, safety and survival of BDQ. Data from the five cohorts reported that BDQ was successful in the treatment of MDR-TB, calculated as patients having 6-month sputum culture conversion (79.7%, 95% CI 75.2–83.5; 317/391). In addition, the cure rate, treatment success rate and the death rate (excluding Georgia and Armenia, $n = 351$) at the end of follow-up (18–24 months) were 63.8% (95% CI 57.8–69.4; 223/351), 69.1% (95% CI 59.1–77.6; 234/351) and 10.6% (95% CI 3.80–20.0; 37/351), respectively [122].

Suitable financial funds should be allocated to warrant successful and justifiable implementation of BDQ introduction at country level. The WHO planning and budgeting tool for TB control activities is a helpful resource to estimate the necessitated budget at country level [123].

A budget impact analysis conducted on managing MDR-TB in South Africa reported that despite the high cost of BDQ, a BDQ-based shortened regimen for the treatment of MDR-TB will result in improved treatment outcomes and cost savings for South Africa. Also, introducing BDQ to long-course treatment will result in a 5% increase in the cost per successful outcome (expected to be US $7739) in 2023 [124].

In a cost-effectiveness analysis, Ionescu et al. [125] compared the cost effectiveness of BDQ versus injectable-containing drug-resistant tuberculosis regimens (short-course regimen and long-course regimen) in India, Russia and South Africa. Across all countries, BDQ-containing regimens were most cost effective based on cost per treatment success compared with injectable-containing regimens, decreasing these in short-course regimen by 18–20% and in long-course regimen by 49–54%. Average cost effectiveness ratios of BDQ containing regimens are lower.

9. Conclusion

Many articles have been published on the promising results of BDQ in MDR-TB until now. However, it seems that more studies are still needed to draw conclusions. The most important issue about BDQ-containing regimens is precise consideration of resistant strains by specific drug susceptibility testing. Moreover, a comprehensive surveillance system is required for the evaluation of adverse effects and mechanisms of resistance and co-resistance with other anti-TB drugs. Therefore, efforts to appropriate BDQ prescribing and increasing its effectiveness should be considered.

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None declared.

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