Tuberculosis (TB) remains a major public health problem and ranks as the second leading cause of death among infectious diseases worldwide, after HIV (human immunodeficiency virus). As per World Health Organization (WHO) estimates, TB accounted for 8.6 million new cases and 1.3 million deaths globally in 2012 [1]. The majority of these cases were in the South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India and China together accounted for 38% of total worldwide case burden. During the same period nearly 450,000 people developed multidrug-resistant tuberculosis (MDR-TB) across the globe and there were an estimated 170,000 deaths from MDR-TB. MDR tuberculosis is defined as tuberculosis resistant to both isoniazid and rifampin and extensively drug resistant TB (XDR-TB) includes resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance. The proportion of new TB cases and previously treated cases diagnosed with MDR-TB has remained essentially unchanged since 2011 at 3.6% and 20.2% respectively. Several eastern European and central Asian countries continue to have the highest levels of MDR-TB where more than 20% of new cases and more than 50% of previously treated cases have MDR-TB. Extensively drug-resistant TB (XDR-TB) had been reported by as many as 92 countries and an estimated 9.6% of MDR-TB cases have XDR-TB worldwide [2].

Multidrug-resistant TB is difficult to cure, requiring 18–24 months of treatment after sputum culture conversion with a regimen that consists of four to six medications. Treatment for MDR-TB is complicated by lack of evidence based guidelines, limitations of second-line drug in terms of limited efficacy, high costs and frequent toxicities and lengthy treatment durations [3]. Additional issues include concurrent HIV infection, lack of facilities for resistance testing and isolation of cases, and irregular access to second-line drugs. MDR-TB treatment using currently available second-line drugs may cure only 65%–75% of patients [4]. Newer therapeutics are therefore needed to strengthen the existing arsenal of antitubercular agents if we are to achieve the WHO target of successfully treating ≥75% of MDR-TB cases by 2015 [5]. Desirable attributes of a novel antitubercular agent include a novel mechanism of action, high oral bioavailability, the ability to simplify or abbreviate treatment plans, a low incidence of adverse events, activity against resistant organisms, minimal interactions with other TB and HIV drugs and low costs [6,7].
1. The promise of bedaquiline

Bedaquiline (formerly known as TMC207, R207910 or ‘J’compound) is the first novel antitubercular drug to be approved in more than 40 years, the last being Rifampin [8]. It is also the first agent approved specifically for patients diagnosed with multidrug-resistant tuberculosis. The original discovery of bedaquiline involved a mass screening program of over 70,000 compounds with inhibitory activity against Mycobacterium smegmatis, a rapidly growing, saprophytic mycobacterium used as a model for tuberculosis [9]. Bedaquiline, a first-in-class antitubercular drug, is a diarylquinoline and its novelty lies in inhibiting ATP synthase, the proton pump of Mycobacterium tuberculosis [9]. Bedaquiline inhibits both actively replicating and non-replicating wild-type and multidrug-resistant M. tuberculosis. The distinct target and mechanism of action of bedaquiline minimizes the potential for cross-resistance with existing antitubercular agents. In addition, bedaquiline has a >20,000-fold lower affinity for human mitochondrial ATP synthase than it has for the mycobacterial ATP synthase. The drug was granted accelerated approval by the United States Food and Drug Administration (FDA) in December 2012 as part of combination therapy (minimum four drug therapy) administered by direct observation to adults aged ≥18 years with a diagnosis of pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided [10]. The recommended dose of bedaquiline for the treatment of pulmonary MDR-TB in adults is 400 mg administered orally once daily for 2 weeks, followed by 200 mg administered thrice weekly, for treatment duration of 24 weeks [11]. Subsequent to its marketing approval in US, nearly 15 months later in March 2014, European Commission (EC) has granted conditional marketing authorization to bedaquiline in the European Union [12].

1.1. Pharmacokinetics

Bedaquiline is >99% protein-bound, is metabolized primarily through the cytochrome P450 system and excreted mainly via the faeces. Administration of bedaquiline with a high fat food increases the relative bioavailability by about 2-fold as compared to administration under fasting conditions. The mean terminal half life of bedaquiline and its major N-monodesmethyl metabolite M2, is approximately 5.5 months. CYP 3A4 is the major CYP isozyme involved in the metabolism of bedaquiline. [13].

Long half-lives and prolonged effects of single-dose administrations in preclinical studies with bedaquiline provided the rationale for less-frequent administration. This long terminal elimination phase reflects the slow release of bedaquiline and M2 from peripheral tissues. Both bedaquiline and M2 have cationic amphiphilic characteristics, which may cause intracellular accumulation of phospholipids and lead to drug accumulation [14]. Current dosing guidelines recommend the administration of bedaquiline with meals to enhance its oral bioavailability.

1.2. Preclinical studies

Much of the information on preclinical efficacy of bedaquiline has been acquired through studies based on murine models of tuberculosis. In established infection models, bedaquiline monotherapy in a dose of 25 mg/kg was at least as active as the triple combination therapy of rifampin, isoniazid and pyrazinamide (RHZ) and more active than rifampin alone. When added to this triple combination therapy, bedaquiline yielded an incremental decrease in bacterial load in the lungs after 1 month and subsequently at 2 months of therapy (p < 0.0018 on both occasions). When each drug of the RHZ combination was substituted with bedaquiline, the activity of each combination containing the novel compound was significantly improved as compared to the standard triple therapy RHZ regimen (p < 0.0018). In addition, the bactericidal activity demonstrated by the RHZ after 2 months of treatment was paralleled by bedaquiline containing combinations with HZ and RZ after just 1 month of treatment [15]. Studies conducted in curative model of murine tuberculosis revealed synergistic interactions between bedaquiline and pyrazinamide. Combinations of these two drugs and along with add-on isoniazid, rifampin or moxifloxacin demonstrated culture negative lung homogenates in 70–100% of the treated mice, while mice in the RHZ treated group remained culture positive after two months of therapy [16].

The sterilizing activity of bedaquiline has also been studied in mice using the modified Cornell model. In this study, intravenously infected mice were treated with bedaquiline containing regimens for variable durations and followed for 3 months to determine the relapse rates. The study demonstrated that all bedaquiline treated mice were culture negative after 4 months of therapy. The relapse rate in the group treated with 4 months of bedaquiline plus RHZ was similar to that of mice treated for 6 months with the RHZ regimen and superior to that of moxifloxacin, rifampin and pyrazinamide combination therapy administered for 4 months [17].

Tasneen et al. in their efforts to determine the treatment shortening potential of bedaquiline, tested three-drug combinations composed of bedaquiline, pyrazinamide, novel nitroimidazole PA–824, moxifloxacin, and rifapentine. Two months of treatment with bedaquiline plus pyrazinamide plus either rifapentine or moxifloxacin was found to be the most effective, curing 100% and 67% of the treated mice, respectively [18].

1.3. Clinical efficacy

From 2005 to 2012, 11 Phase I studies have been conducted to evaluate pharmacokinetic and pharmacodynamic parameters, dosing regimens, and drug interactions of bedaquiline. Prior to initiation of randomized controlled trials, a phase 2a study was conducted in 75 treatment naïve patients with smear-positive pulmonary tuberculosis for assessment of bedaquiline’s early bactericidal activity. The study patients were randomized to receive either bedaquiline in doses of 25, 100 or 400 mg, 600 mg rifampin or 300 mg isoniazid once daily for 7 days. None of doses of bedaquiline were bactericidal during the first 2–4 days. However, significant bactericidal activity of 400 mg bedaquiline was observed from day 4 onwards and was similar in magnitude to those of isoniazid and rifampin over the same period [19]. The delayed antimycobacterial action of bedaquiline is possibly related to its mechanism of action involving disruption of cellular energy homeostasis. There were two phase 2b studies which supported accelerated approval of bedaquiline, one being a randomized controlled trial conducted in two consecutive but completely separate stages (C208 stage 1 and C208 stage 2) and other was a single arm, open label study (C209).

In the exploratory (C208 stage 1) double blind randomized, placebo controlled superiority trial conducted exclusively in South Africa, 47 newly diagnosed pulmonary MDR tuberculosis patients received either bedaquiline (n = 23) (400 mg daily for 2 weeks followed by 200 mg thrice a week for 6 weeks) or placebo (n = 24) in combination with a background regimen consisting of five second-line agents (pyrazinamide, kanamycin, ofloxacin, ethionamide and cycloserine/terizidone) [20]. After 8 weeks of treatment, bedaquiline/placebo was discontinued, and patients continued with their background therapy for a total duration of 18-24 months. At week 8, the addition of bedaquiline to standard therapy for multidrug-resistant tuberculosis reduced the time to conversion to a negative sputum culture, as compared with placebo (hazard
patients were allowed to enter the trial if they met some specific criteria. The primary purpose of this exploratory stage was to confirm achievement of anticipated serum bedaquiline levels at the proposed dosing scheme. Following the verification, the trial moved to the stage 2, where bedaquiline was administered in addition to the background therapy for 24 weeks in a new group of patients [14].

Proof of efficacy (C208 stage 2) study for bedaquiline was similar in design but involved multiple centers across the globe including South Africa, India, Russia, Latvia, Peru, Brazil, Thailand, and Philippines. In this study newly diagnosed MDR-TB cases were randomized to receive bedaquiline (n = 80) or placebo (n = 81) for 24 weeks in combination with a background regimen of second-line tuberculosis agents. Bedaquiline was administered as 400 mg orally once daily for the first 2 weeks and 200 mg three times per week for the following 22 weeks. The preferred background therapy regimen was the same as used in the stage 1 of the study. Beyond the investigational treatment phase of initial 24 weeks, the study participants continued on their background therapy for a total duration of 18–24 months designated as the overall treatment phase. The primary efficacy endpoint was the time to sputum culture conversion, defined as 2 consecutive negative mycobacterium growth indicator tube (MGIT) cultures collected at least 25 days apart and not followed by a confirmed positive culture. Bedaquiline was found to be superior as compared to placebo in time to sputum culture conversion (hazard ratio: 2.44, 95% confidence interval, 1.57 to 3.80, p < 0.0001) [13]. At week 24, a significantly greater percentage of patients in the bedaquiline group had culture conversion (79% vs. 58%, p = 0.008). Durable microbiological responses although non-significant continued to be observed at week 72 [13].

The final 120 week results of this study were recently presented. As per the study definitions whereby dropout subjects were considered treatment failures, 62% of patients receiving bedaquiline showed sustained culture conversion at the end of study period versus 44% of the placebo group (p = 0.035). When analyzed as per WHO definitions, the cure rates in the bedaquiline treated patients was 58% vs. 32% in the placebo group (p = 0.003) [22].

Study C209 was a multicenter, noncomparative, single arm, open label trial to evaluate efficacy, safety, and tolerability of bedaquiline on top of background regimen tailored either to the susceptibility pattern of M. tuberculosis isolates or to the patient’s treatment history. The trial was carried out at 33 sites in Asia, South Africa, Eastern Europe, and South America. The dose, treatment duration, follow-up duration and main efficacy endpoints were the same as C208 stage 2 study. However, HIV-infected subjects receiving antiretroviral drugs (ARVs) and also XDR tuberculosis patients were allowed to enter the trial if they met some specific criteria. Efficacy analyses were based on the modified ITT, which included 205 patients. The median time to sputum culture conversion was 57 days and consistent with C208 (stage 1 and stage 2) study results. Also 80% of cases achieved culture conversion at the end of Week 24, a secondary efficacy endpoint [13]. The final study results which were not available at the time of regulatory approval of bedaquiline, were recently presented. At the end of 120 weeks, the proportion of patients who were culture negative and deemed as responders was 72%. The culture conversion rates among the MDR-TB, Pre-XDR-TB and XDR-TB subgroup patients were 73%, 71% and 62% respectively [23].

A 14-day early bactericidal activity study in treatment naive patients with fully drug-susceptible pulmonary tuberculosis, assessing various combinations of bedaquiline, PA-824, moxifloxacin and pyrazinamide revealed that onset of activity of bedaquiline was accelerated after the addition of pyrazinamide resulting in greater activity of bedaquiline and pyrazinamide than bedaquiline alone [24]. The bactericidal curves of all treatment groups in this study closely matched the murine data of the combinations evaluated. The study lends support to the use of murine models for selecting promising antitubercular drug combinations to take forward into clinical development.

1.4. Clinical safety

Among healthy volunteers, analysis of pooled safety data from eight Phase 1 studies enrolling 189 healthy adults (5 single-dose studies, 132 participants; 3 multiple-dose studies, 57 participants) who received at least one dose of bedaquiline support the safety and tolerability of bedaquiline administered either alone or in combination therapy [21]. Safety of several formulations ranging from single doses as low as 10 mg—800 mg was explored [13]. No deaths or serious adverse events were reported in these volunteers. Majority of the reported adverse events belonged to nervous system (24.3%) and gastrointestinal tract (16.3%) system organ class. Headache, dizziness, dry mouth, diarrhea, fatigue, hyperuricemia, and erythema were the most frequent individual adverse events reported by more than 5% subjects in the pooled treatment group [13].

An analysis of safety data from C208 stage 1 study revealed the most commonly reported events in the bedaquiline treated patients as nausea (26.1%), bilateral hearing impairment (13.0%), extremity pain (17.4%), acne (8.7%) and noncardiac chest pain (4.3%). Except for more frequent nausea in the bedaquiline treatment group, the incidence of these events was not statistically different between the study groups [14]. As per C208 stage 2 safety data, the common adverse events reported more frequently in bedaquiline treated patients as compared to placebo group were nausea, arthralgia, headache and elevated liver transaminases [22]. Recently reported safety results from the open label C209 study identified hyperuricemia (16%), nausea (15%), arthralgia (15%), headache (13%), diarrhea (12%) and vomiting (12%) as common adverse events reported by more than 10% of bedaquiline treated patients during the overall treatment phase [23]. Bedaquiline was tested as an add-on therapy to standard MDR-TB regimens and most of these observed adverse effects are known to occur in patients receiving second-line antitubercular agents.

The principal safety concerns associated with the use of bedaquiline include QT interval prolongation, hepatic related adverse events, and deaths [25]. The prescribing information for the drug carries two black box warnings highlighting an increased risk of death and QT interval prolongation observed with the use of bedaquiline [11].

1.4.1. Cardiovascular safety

Pooled safety data from stage 1 and stage 2 of C208 trial, reveals an increased corrected QT interval (QTcF) in both the bedaquiline treated patients as well as placebo group with greater prolongations in the former group. Over the 24-week investigational treatment phase of C208 stage 2 study, more patients in the bedaquiline treatment group had QTcF values between 450 ms and 480 ms (26.6% vs. 8.6%) and more patients had QTcF increases >60 ms from reference values (9.1% vs. 2.5%) as compared to the placebo group. However, there were no episodes of Torsade de Points and no reported fatalities from sudden death in patients with QTcF prolongation. Increases from reference values in QTc occurred gradually over the first 8 weeks of treatment, and then remained stable until 24 weeks in pooled data from the two stages of C208 study [13]. In the open label, single arm C209 study, a total
of 10 (4%) patients developed an increase in QTcF from reference of >60 ms during the overall treatment phase, with two patients having a QTcF value of >500 ms [23]. Both these patients were receiving concomitant clofazimine. A subanalysis of patients receiving bedaquiline with clofazimine revealed a mean increase in QTcF from reference of 31.9 ms (n = 17) vs. 12.3 ms (n = 177) in patients receiving bedaquiline without concomitant clofazimine.

1.4.2. Drug related hepatic disorders

Pooled safety experience from the bedaquiline treatment phases of the two-stage RCT-C208 revealed a greater prevalence of hepatic disorders in patients receiving bedaquiline as compared to placebo (8.8% vs. 1.9%) [25]. Increases in transaminases accounted for the majority of these reported events. A Hy's law analysis to identify cases of severe liver toxicity revealed a case of a patient who experienced concurrent greater than threefold elevation of aspartate aminotransferase and greater than twofold elevation in total bilirubin, but was confounded by presence of alcoholic hepatitis and concurrent intake of hepatotoxic background drugs including para-aminosalicylic acid and ethionamide [13]. During the overall treatment phase of C208 stage 2 study, 11% subjects were found to have elevated transaminases as compared to 1% in the placebo group [22]. In the C209 study, drug related hepatic disorders were identified in 42 patients (18%) and 4 of these events were reported to be atleast possibly related to bedaquiline [23].

1.4.3. Deaths

In stage 1 of C208 trial, four deaths were reported: 2 each in the bedaquiline arm and the placebo arm. In the stage 2 trial, twelve deaths were reported: 10 came from the bedaquiline group and 2 from the placebo group (p = 0.017). TB itself was the cause of death in the two placebo arm patients and in 5 of the 10 bedaquiline arm deaths. The causes of death in rest of the patients were varied and only 1 death occurred during active treatment with bedaquiline. None of the deaths were considered related to bedaquiline by the investigator and they were not associated with high bedaquiline concentrations or prolongation of QTcF interval ≥500 ms. No evident associations were found to exist between deaths and culture conversion, relapse, drug susceptibility, HIV status, or severity of MDR-TB. Detailed analysis of pretreatment characteristics and risk factors for poor treatment outcomes did not reveal the reasons for imbalance in the deaths reported in the two study arms [25]. Out of 12 deaths reported in C209 study, 5 were considered due to underlying tubercular condition. Median time to death since last bedaquiline intake in these patients was reported to be 375 days and only one death was considered to be doubtfully related to renal impairment caused by bedaquiline [23].

1.5. Drug interactions

Since bedaquiline is metabolized by CYP 3A4, its plasma levels, therapeutic effects and toxicities are prone to modulation by concomitant administration of CYP 3A4 inhibitors and inducers. Drugs like protease inhibitors, triazole antifungals and macrolides can result in increased exposure to bedaquiline and predispose to its potentially toxicity. On the contrary, CYP 3A4 inducers like rifamycins, certain anticonvulsants and non nucleoside reverse transcriptase inhibitors can lead to significant reduction in the AUC of bedaquiline, rendering the drug potentially ineffective. Therefore caution should be exercised in patients treated with bedaquiline when they require concomitant therapy with interacting drugs for various comorbidities including HIV [11].

2. The pitfalls of bedaquiline

2.1. Surrogate endpoints and safety concerns

Few truly innovative antimicrobial products have been brought to the market in recent years. The drug regulatory agencies face substantial pressures to approve therapeutic agents for conditions like multidrug-resistant tuberculosis where only few treatment options are available. In such conditions, accelerated drug approvals are often based on surrogate endpoints. A surrogate endpoint could be used as a substitute for the composite clinical endpoint of treatment failure and relapse thereby substantially shortening the trial duration and improving the overall efficiency of drug development. Although sputum culture conversion following 8 weeks of treatment is the biomarker that is closest to validation at present, it has its own limitations in the form of relatively large sample size requirements, long duration of treatment and poor positive predictive value for relapse in individual patients [26]. Approval of bedaquiline based on sputum culture conversion rather than an actual clinical outcome has been scrutinized and criticized. As discussed above, 5 times as many people on bedaquiline died as compared to those in the control group with possible cause of death being drug related hepatotoxicity and cardiotoxicity. Parallels have been drawn with rosiglitazone fiasco, which was also approved on the basis of surrogate endpoints and was later on found to increase the risk for myocardial infarction in diabetic patients receiving the drug [27]. The FDA’s Anti-Infective Drugs Advisory Committee members were split eleven to seven when asked whether the safety data of bedaquiline supported its proposed indication [28]. The committee members raised concerns about the high mortality in the bedaquiline group, about evidence of QT prolongation as well as elevated transaminases. Active pharmacovigilance methods like cohort event monitoring, have been recommended by WHO as part of measures to ensure early detection and timely reporting of adverse events [25]. Clinical monitoring of symptoms, specific investigations at appropriate intervals, and engagement of the patients and caregivers to report untoward effects of bedaquiline therapy are essential to ensure effective management of adverse events in a timely manner.

2.2. Limitation of present studies

The limitation of currently available clinical data on bedaquiline has been recognized in the form of limited studies with small sample sizes, observational designs, use of modified intent to treat analysis, low quality evidence for the background MDR treatment regimens used in these studies and low cure rates observed in the placebo group when compared to those reported by recent reviews [25]. The lower cure rates seen in these studies might be attributed to use of cultures on liquid media, inclusion of only sputum smear-positive patients and possible geographical differences in time to culture conversion and culture conversion rates in liquid media [29]. No evidence to support the use of bedaquiline for XDR-TB is existing as of now, although it is likely to benefit these patients given the limited therapeutic options available for them.

2.3. Misuse of bedaquiline

There have been recent reports of unregulated use of bedaquiline in high MDR-TB burden regions like India [30]. Such widespread use and misuse in the absence of well defined standard treatment guidelines can rapidly limit the usefulness of bedaquiline and encourage emergence of resistance. The mechanism of resistance of M. tuberculosis to bedaquiline involves missense mutations (at position 63 with a proline substituting alanine or at
position 66 with a methionine substituting a leucine) of the atpE gene that disrupts the drug’s capacity to bind to the c subunit of the ATP synthase [9]. Regimens that contain bedaquiline need to be carefully designed to avoid an extended period of exposure to low levels of bedaquiline as a single drug. Because bedaquiline has a long terminal half life, acquired resistance might occur when bedaquiline is the only effective drug in circulation. Developing nations need to focus on regulating access to bedaquiline since unrestricted availability coupled with injudicious use can adversely affect patient care and facilitate the emergence of bedaquiline resistance and the possible loss of a novel therapeutic agent. Development of national guidelines on the use of bedaquiline can further facilitate rational pharmacotherapy of drug resistant tuberculosis.

2.4. Gaps in current knowledge

Research gaps that need to be plugged to strengthen the evidence base for bedaquiline include well designed, adequately powered Phase III studies relying on gold standard clinical outcomes like cure rates, safety and efficacy studies in special populations including children, elderly people, pregnant or nursing women, HIV patients, alcohol users, and people with extrapolumonary TB, safety studies investigating frequency and severity of short and long term toxicities as well as mortality. Given its likelihood to be involved in drug interactions, dedicated studies exploring effects of co-administration with ART and ART regimens and identification of optimal dose and duration of such therapies are needed. In addition, there is a need for reliable drug susceptibility tests for bedaquiline and adequate monitoring of acquired resistance in treated patients needs be undertaken. Lastly, patient acceptability and cost effectiveness of including bedaquiline in tuberculosis control programmes especially in resource limited settings needs to determined.

3. Conclusions

Bedaquiline is a first-in-class oral diarylquinoline approved for the treatment of adults with pulmonary MDR-TB on the basis of Phase Ib/II trial data under the provisions of accelerated approval regulations for serious or life-threatening conditions. Given the substantial limitations of presently used approaches for the treatment of MDR-TB, introduction of bedaquiline represents a welcome addition to the existing arsenal of anti-TB drugs. However, a cautiously optimistic approach is required to assess the benefit-risk profile profile of this novel molecule. Although based on surrogate endpoints of efficacy, bedaquiline has shown promise in preclinical, phase 1, phase 2 clinical and other additional studies supporting synergistic effect with existing agents. However, further larger studies with clinically meaningful endpoints are warranted to confirm the presently available data. This may apply to any new drug receiving accelerated approval, however, the findings of excess mortality, drug related hepatic events and QTc prolongations are a cause for concern. These findings become even more relevant taking into consideration that bedaquiline is administered only as a part of combination therapy for MDR-TB. Drug interactions with other hepatotoxic agents like pyrazinamide and drugs that prolong QT interval like fluoroquinolones, clofazimine can potentially be catastrophic in MDR-TB patients. Patients suffering from drug resistant TB-HIV coinfection may also be predisposed to unwanted interactions of bedaquiline with anti-retrovirals and other antimicrobials. While the approval of bedaquiline represents a major milestone in therapy of drug resistant tuberculosis, the paucity of available clinical data underscore the need for well designed Phase III trials and a timely analysis of studies on the real world use of the drug. This will not only be helpful in defining the exact role of bedaquiline but also ensure that benefits of this novel agent continue to outweigh its risks.

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