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Cost-effectiveness of incorporating bedaquiline into a treatment regimen for MDR/XDR-TB in Germany

The emergence of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) has re-established TB as a major worldwide health concern [1–3]. Compared with conventional TB drug regimens, treatments for MDR-TB and XDR-TB are more toxic, expensive and associated with poorer outcomes [3, 4]. In Germany, 102 (2.4%) of the 4318 TB cases reported for 2013 were MDR-TB, including 10 patients with XDR-TB [5], increasing from 54 (1.8%) cases in 2011 [5, 6]. An important factor behind the increase in Germany is migration, with more cases occurring in patients from the former Soviet Union than in native Germans [5].

Bedaquiline (BDQ) is a novel treatment that may be added for 24 weeks to a World Health Organization (WHO) recommended antibiotic background regimen (BR) for the treatment of MDR-TB [7]. WOLFSON *et al.* [8] developed a comprehensive model looking at cost-effectiveness of BDQ plus BR (BDQ+BR) in the UK, over a substantially longer time horizon than a previously published WHO analysis [8, 9].

In this study, we report findings from an adapted version examining cost-effectiveness in the German healthcare system, where typically routine hospitalisation of patients with MDR-TB is carried out. A previous study of patients with MDR-TB in Germany found the total cost of treating to be €64 429.23 [10].

After adjustment to the perspective of the German Statutory Health Insurance (SHI) system, a cohort-based Markov model was used to estimate the cost-effectiveness of BDQ as an add-on for 24 weeks to a weighted antibiotic BR containing pyrazinamide, one injectable, one fluoroquinolone and one WHO group 4 agent, taking into account different strain resistance patterns as described in the C208 trial and following local guidelines [4, 7, 11]. This regimen of BDQ+BR was then compared with BR alone for the treatment of MDR- and XDR-TB. Comparison of BDQ with Delamanid, an alternative treatment option that was introduced later [12], was outside the focus of our analysis. Costs and effectiveness were discounted at an annual rate of 3% [13]. The time horizon for the model was 10 years. The model state structure was designed to reflect initial clinical care in patients with TB.

The goal of drug treatment in the simulation was to induce the sputum culture converted state (SCC) in the sputum culture positive patient cohort and maintain the SCC until treatment completion (and thus assumed to be cured of MDR-TB) [14].

Patients failing to achieve SCC during the first year were considered treatment failures and were transited to the “active secondary MDR-TB” state by no later than month 12 of the long-term MDR-treatment, to begin a new treatment. Patients who failed to achieve SCC with the new treatment were assumed to occupy the same state until death or loss to follow-up for simplifying the model structure. Still, it is valid to consider further treatment options with a third-line or even fourth-line treatment, but these were outside the scope of our model when examining MDR-TB. The probability of death was assumed to be positively dependent on the sputum status of the cohort (active TB *versus* SCC *versus* cured), their status in terms of MDR- and XDR-TB, and whether they were lost to follow-up.

A cohort of 65 MDR-TB patients was included in the model simulation, reflecting current epidemiological data for Germany at the time of model design. Of these, 87.7% were assumed to have been treated in hospital for a mean duration of 89.1 days [10].

Inputs into the model for clinical outcomes (transition probabilities) and dosages were derived from a randomised, placebo-controlled phase IIb trial of BDQ [15], and an open-label, single-arm phase IIb study of BDQ efficacy [16]. Other model parameters, including the costs of the regimen under consideration, were adapted either from a previous German study [10] or international literature where data specific to Germany were not available. According to the approval criteria of BDQ, any replacement of other drugs from the BR with BDQ was not taken into consideration.

Inpatient costs were based on data from the German G-DRG system, with reimbursement dependent upon disease type and severity, as well as the cumulative time spent in hospital [17]. Health utility weights were adapted from a previous study in a low incidence setting, as local data for Germany are not available [9]. Deterministic sensitivity analyses were conducted to assess the impact of varying model assumptions and parameters by $\pm 20\%$ on model results, in terms of utility, clinical parameters, transition probabilities and drug costs, following international recommendations [18].

Using a combination therapy (BDQ+BR) for a cohort of 65 patients with MDR-TB over a 10-year time period, the results demonstrated substantially better quality-adjusted life-year (QALY) outcomes compared with treatment with BR alone (incremental outcome of 73.29 QALYs gained with an incremental cost-effectiveness ratio of €22 118 for a 3% discount rate). Furthermore, this result was seen despite increased total costs for the cohort associated with BDQ+BR compared with BR alone (€5 583 515 and €3 962 499, respectively). In addition to QALY gains, treatment with BDQ+BR led to an extra incremental 74.58 life-years gained compared with those treated with BR alone (incremental cost of €21 736 per life-year gained (LYG)).

A cost-effectiveness analysis was performed for a cohort of 10 patients with XDR-TB according to current epidemiological data at the time of model design [5] and based on efficacy data from the open-label phase II study C209 [19]. In this trial, BDQ was given as an add-on for 24 weeks to a weighted, individualised BR containing at least one injectable, one fluoroquinolone and one WHO group 4 agent, taking into account individual strain resistance patterns. Findings from this trial indicated that adding BDQ as described also yields comparable rates of SCC in patients with XDR-TB, which was confirmed in real world settings [20, 21]. Although BDQ+BR was associated with higher total costs compared with BR alone (€1 662 746 *versus* €1 609 831, respectively), treatment led to better outcomes both in total QALYs (29.72 *versus* 20.57) and LYG (40.72 *versus* 31.05). The incremental cost per LYG were €5780.54 and €5472.13, respectively, suggesting that BDQ+BR is more cost-effective than BR alone, and more cost-effective compared with treatment of a MDR-TB cohort.

Multiple deterministic sensitivity analyses were performed to ensure the model robustness and to assess the impact of individual parameters. The data suggest that the hazard ratio of SCC is the most influential parameter in the model, with changes to the input of $\pm 20\%$ resulting in changes to the cost per QALY of 39% and -20% , respectively. Changes to all other input parameters had a very minor impact on the results ($<3\%$ change to the cost per QALY).

The probability that BDQ+BR is cost-effective *versus* BR alone at an affordability threshold of €30 000 per QALY gained was 67% (fig. 1). When adapting the British thresholds used for orphan drugs of £50 000 per QALY gained (€63 400, 2014 conversion values), the probability of BDQ being cost-effective *versus* BR was 95%.

A previous study described a model that demonstrated the cost-effectiveness of adding BDQ to a BR from the UK healthcare perspective [9]. The present German adaptation of this model demonstrates that adding BDQ to a BR for the treatment of MDR-TB proves cost-effective in most scenarios. This finding further reinforces our previously drawn conclusions that the model and its results are generalisable to other high income settings [9, 22].

FIGURE 1 Cost-effectiveness acceptability curve for the bedaquiline+background regimen (BR) versus BR alone from a German payer perspective (multidrug-resistant tuberculosis cohort).

As with most other European countries, the prevalence of TB has reached a low but relatively stable level in Germany [5, 6]. However, the resources needed to treat MDR- and XDR-TB imply that these diseases remain a substantial challenge. Our analysis demonstrates that treatment costs for MDR- and XDR-TB are primarily driven by hospitalisation and drug costs. Despite higher drug-related costs (acquisition and monitoring), it is likely that the addition of BDQ will lead to cost savings, primarily due to lower hospitalisation rates and more patients being managed in an outpatient setting in Germany. Such effects may be gained by both a reduction in the time to SCC and a higher proportion of patients achieving SCC when treated with BDQ+BR compared with BR alone.

The model described here is subject to a number of assumptions and limitations. First, the use of trial efficacy data may not accurately reflect results found in German clinical practice. However, recent publications with data from France and South Africa demonstrate that high rates of SCC (up to 97%) are also obtained in real-world practice for patients with MDR- and XDR-TB [20, 21], thus confirming clinical trial data in at least one cohort which is comparable to the German setting [20]. In contrast to the mortality imbalance observed in the placebo-controlled phase II clinical trial of bedaquiline [15], our model incorporates mortality data derived from literature relating to both general and German-specific values [23–25]. This discrepancy arises because there were no identified reasons that explained the trial-observed mortality imbalance [7, 26].

In conclusion, addition of BDQ to the standard of care for treatment of MDR- and XDR-TB is likely to be highly cost-effective from a German SHI perspective.

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Adding bedaquiline to the background regimen is likely to be cost-effective for treatment of MDR/XDR-TB in Germany <http://ow.ly/SwMdv>

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Comparison of the association with sleep apnoea of obesity *versus* insulin resistance

To the Editor:

Obesity is considered to be both a risk factor for the development of obstructive sleep apnoea (OSA), and a contributor to the abnormal sleep patterns that characterise this syndrome [1]. Obesity is also associated with insulin resistance [2]. These two phenomena may be unrelated, and represent two untoward effects of