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Clinical Experience of Filipino Clinicians on the Use of Bedaquiline for Treating Multidrug-resistant Tuberculosis

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RESEARCH ARTICLE

Abstract

Background: The Philippines is among the countries globally with a high multidrug-resistant tuberculosis (MDR-TB) burden. An operations research on Bedaquiline (BDQ), a new drug for MDR-TB, was launched by the Department of Health (DOH) in 2016.
Objective: This paper aimed to gather the opinions and first-hand experiences of clinicians in the Philippines regarding BDQ.
Methodology: A facilitated roundtable discussion among nine clinicians included in the operations research on BDQ in the Philippines was conducted in June 2018. Topics covered (a) considerations in the use of BDQ, (b) outcomes of patients given BDQ, and (c) perceptions on effectiveness and safety of BDQ. Recordings and field notes from the discussion were subjected to a framework analysis.
Results and Conclusion: Participants gave BDQ an overall positive feedback due to its effectiveness, less toxicity, and ease of administration compared to other anti-TB drugs. Issues on BDQ included the novelty of the drug that caused doubts at first use and limited application of the drug as dictated by the inclusion criteria within the context of the operations research, among others. The significant number of patients lost to follow up and ways to address this challenge were also discussed.

Keywords: *Bedaquiline, multidrug-resistant tuberculosis, clinical experience, physicians, Philippines*

Introduction

Multidrug-resistant tuberculosis (MDR-TB), a form of tuberculosis resistant to both isoniazid and rifampicin, is a global public health concern. In 2016, there were an estimated 490,000 new cases of MDR-TB globally, with the Philippines contributing a substantive number as one of the 20 high-TB and MDR-TB burden countries [1,2]. An estimated 2.6% of new and 29% of previously treated TB cases in the Philippines in 2017 have either rifampicin-resistant or multidrug-resistant strains of the *tubercle bacilli* [2].

The challenges posed by MDR-TB such as the high cost of treatment, absence of drugs that can effectively cure the condition, and adverse effects of existing second-line treatment regimens prompted a search for and development of a new medicine that can be added to the clinician's armamentarium [3].

One breakthrough came in the form of Bedaquiline (BDQ), developed by Janssen Pharmaceuticals more than 40 years after the introduction of rifampicin, which targets one of the metabolic enzymes of Mycobacterium essential for energy generation [4]. BDQ is used primarily to treat MDR-TB and is administered along with conventional treatment regimens, as defined by the interim guidance released by the World Health Organization [5].

The drug was approved by the Philippine Food and Drug Administration for local use in 2014 and was introduced in the country by way of assistance from Janssen Pharmaceuticals and the United States Agency for International Development

(USAID). In 2016, the Department of Health (DOH) launched an operations research in nine study sites to determine the fidelity, feasibility, acceptability, effectiveness, and safety of the programmatic approach in introducing BDQ in the country [6].

After two years of field implementation, there is interest among stakeholders in determining the outcomes of using BDQ for MDR-TB treatment in the local setting. Pending a formal assessment within the ambit of the operations research, this study was conducted among clinicians involved in the operations research on their first-hand experience in the use of BDQ among MDR-TB patients. It aimed to document their perceptions and experiences on the process and outcomes of BDQ introduction and use in the local setting and identify clinical and programmatic facilitators and barriers on field use of bedaquiline.

Methodology

All clinicians (N = 9) involved in the operations research on BDQ in the Philippines were invited to participate in a facilitated group discussion held on June 6, 2018 in Makati City. This format was used since the study was interested not only in eliciting individual responses on the use of a new drug in the local setting but also in determining the extent to which such clinician perceptions and experiences are common (or divergent) across the nine field sites.

The documentation team (CTA, ACB) and a freelance consultant (VSL) prepared the guide questions for the forum, which covered the following broad topics: (a) process of introduction and use of BDQ and (b) experiences in use of BDQ in terms of patient recruitment, retention, and treatment outcomes. All three (CTA, ACB, VSL) also served as facilitators during the discussion.

Discussion points were summarized and immediately relayed to the participants as a means of validation. Clarifications and refinements on points raised were noted and incorporated in the data.

Documentors (CHT, AHT) audio-recorded and took notes of the discussion. The recordings, as well as the field notes, were used as basis for preparing the transcription of the discussion, which was then validated by the facilitators (CTA, ACB).

Framework analysis was carried out thereafter. Framework analysis is a specific type of thematic analysis which matches cases (listed in rows) with pre-specified analytic codes (listed in columns, and in our case; the intersection of these two (cells) contains the summarized data [7]. It is a useful method for sorting data from group discussions [8]. Specifically for this paper, participant (row) responses (cells) were coded to their corresponding question (columns). The general idea that emerged from these responses was then regarded as the answer of the group. Unique responses were also noted.

This project involved documentation of discussion in a public forum. Nonetheless, we still sought and obtained consent for participation and documentation of their responses.

Results

A total of nine clinicians from different regions in the Philippines involved in the BDQ operations research participated in this facilitated group discussion. Were presented responses into three clusters: (a) considerations in the use of BDQ, (b) outcomes of patients given BDQ, and (c) perceptions on effectiveness and safety of BDQ.

Considerations when using BDQ as a second-line drug for MDR-TB patients

Since WHO guidelines, as well as the protocol of the operations research, were given to the clinicians, they do not prescribe the drug unless patients meet the inclusion criteria stated in these policy documents. The use of the drug is principally dictated by the guidelines, and not the doctor's choice (Region V). Therefore, their basic consideration is the clinical profile of the patients. BDQ is usually given to, among others, those resistant to first-line drugs, unresponsive to other second-line drugs, or patients with failing kidneys. On the other hand, part of the exclusion criteria are the pediatric (18 years old and below) and elderly patients (65 years old and above). This makes the use of BDQ limited, although the new guidelines [9] released have broadened its application.

These guidelines also help the physicians feel confident in using BDQ. They only had few concerns regarding its use because "...it is just one of the regimens available. It still has a long way to go given that there is still an ongoing research." (Region I). Of the few mentioned, one was the novelty of the drug. The physicians expressed that there have been doubts in their minds at first because it is a new drug with potential side effects. This fact is not easy to forego even with trainings conducted for them (Region VI).

Besides this, a doctor from Region X involved with NTP for seven years talked about her experience of drug-drug interaction in an HIV-positive patient. She said that it was difficult to resolve this situation, but what she did was to change the antiretroviral (ARV) regimen of the patient. Due to the rising trend of HIV incidence in the Philippines, drug-drug interaction should be anticipated as an important concern later on.

Furthermore, shifting from the current BDQ treatment of six months to a modified short course where Linezolid is indicated as replacement drug was discussed. All of the physicians expressed their willingness to do this because like they said, "the shorter, the better for us and the patients." If this will be the case, the concern will be on the dosing and duration (Region V).

Clinical outcomes of patients under BDQ treatment

BDQ treatment was still ongoing for most patients during the time of inquiry. But according to the clinicians, most of the patients who were done with the treatment achieved positive outcomes. Many among them have been successfully treated. There were even patients who were culture converted after a month. There were only few deaths, and some clinicians claimed that they were not due to the drug.

But what stood out was the considerable number of patients who were lost to follow up (LTFU). These patients were already known for frequent defaulting, so the clinicians said that this cannot be attributed to BDQ. The behavior of the patients was identified as the primary reason for this. These defaulters only come back "…when they feel the symptoms or when they are already dying" (Region IX), but it is their duty as physicians to accept them again. However, they can be a source of drug resistance (Region III).

Furthermore, they said that majority of the LTFU happen during decentralization or the transfer of the patients from the central healthcare facility to a clinic nearer their hometown. This was probably due to "…the health centers being overburdened with DOH projects, so the healthcare workers might think that BDQ is just added work" (Region I) or the timing of drug administration (NCR-Caloocan). There were also patients who actually prefer going to the central clinic.

How the physicians manage LTFU was also discussed. A Region I doctor said:

"If there are one-day interrupters, the staff will take care of it; if there are frequent interrupters, I talk to them directly. I do not accept frequent interrupters right away. I ask them if they are really ready this time."

Meanwhile, a Region X doctor shared that the presence of "enablers" such as transportation allowance and food allowance helped maintain the compliance of her patients. Moreover, the halfway house within their facility has encouraged them to stay because of free accommodation. It also paved the way for patients to develop relationships among them, and to encourage and support each other during therapy. This is the reason for the lone case of LTFU in their site. However, halfway houses can be easily abused by patients. For instance, one patient brought his family with him in the facility, so the doctor called him out for it. The patient became afraid of him, so he became LTFU (Region VII). The representative of NTP-DOH also said that they discourage the establishment of halfway houses because health centers for tuberculosis are now being built in different towns.

Employment of the patients, on the other hand, was not considered a major problem. Drug administration can be merely adjusted. Treatment in the workplace or reassignment at work until culture conversion can also be done. The Technical Education and Skills Development Authority and other non-government organizations can also serve as enablers by training the patients or providing them businesses (Region I & Region III). Partial disability benefits under the Social Security System and PhilHealth were suggested as other sources of financial support.

Forming support groups among patients under BDQ was also discussed. According to a doctor from NCR-Quezon City, support groups were previously established in their clinic. But due to the shortened treatment, meetings were lessened and these groups were discontinued. Instead, some patients who were cured are invited to share their experiences and encourage other patients. There are also some who act as treatment partners by helping give out second-line drugs at the health facility.

Perceptions on effectiveness and safety of BDQ

The physicians were asked to rank their clinical experience (i.e. effectiveness and safety) in using BDQ, with five being the highest. Five of them gave a score of five, and the other four gave a score of four. Thus generally, the drug received a good feedback from the clinicians. According to a doctor from Region V, her patients, now cured but were hopeless cases then, even dubbed BDQ as a "miracle drug"

because of its very minimal side effects compared to other second-line anti-TB drugs. These side effects include gastrointestinal irritation and headache. Furthermore, these cannot be solely attributed to BDQ since it is given in combination with other second-line anti-TB drugs (Region V). There is improved compliance due to less toxicity of the drug (Region III).

Another advantage of using BDQ is its ease of administration. Contrary to other TB drugs which are injected to patients, BDQ is orally administered. This setup is more convenient for patients and the medical staff. Moreover, it has a shorter culture conversion time. Patients recover faster so they are able to go back to work earlier (Region I).

The downside of using BDQ, however, lies again on its newness. Several aspects of the drug have yet to be understood. The relapse rate and safety of the drug when used beyond six months are still unknown. As of now, it is only applicable for pulmonary tuberculosis and its effectiveness on extrapulmonary tuberculosis has not yet been established (Region III). More importantly, the cost and sustainability of the drug may present as a problem in the future. The Global Fund is currently supporting the use of the drug in the Philippines. But when this assistance is discontinued, there is no certainty that the supply of the drug will be maintained (Region IX). The longer duration of treatment was also raised as a concern.

Discussion

The facilitated group discussion showed that the clinicians involved in the implementation research perceived the introduction of BDQ as a breakthrough in the fight against MDR-TB in the Philippines. This was mainly because of the positive clinical outcomes of patients given BDQ. However, programmatic barriers have led some patients to default their treatment regimen.

Other studies also demonstrated similar results on BDQ effectiveness. In a multicenter study by Borisov *et al.*, 71.3% of the culture-confirmed MDR-TB cases succeeded, 13.4% died, 7.3% defaulted, and 7.7% failed [10]. Lu *et al.* reported that adding BDQ to the background regimen of the patient resulted in an increased percentage of successful outcomes (i.e. cure or completed treatment), with the incremental change ranging from 51.62% in China to 60.78% in the Philippines. In the latter, the increase was from 17.85% to 28.69%. They also found that the introduction of BDQ augmented the number of disability-adjusted life years averted. [11] In addition, Diacon *et al.* showed that BDQ did not only increase culture conversion but it also reduced its median time. This observation was also mentioned by the participants [12].

BDQ was also regarded as safe by the clinicians because of the relatively lower number of deaths and only minor side effects that were not considered grounds for discontinuation of the drug. In a study by Diacon *et al.*, the most frequent adverse events of BDQ were nausea, arthralgia, and vomiting which were similar with those commonly observed in TB patients receiving second-line treatment for MDR-TB [12]. This outcome suggests that the adverse events are probably due to the background regimen [10]. Thus, in terms of safety, BDQ performs better than other TB drugs. This important finding can help clinicians feel complacent in using the drug despite its novelty.

Meanwhile, a study by Cariem *et al.* on the experience of BDQ implementation at a decentralized clinic in South Africa [13] has similarities with the experience of the clinicians. The staff also had initial doubts in using the drug, but later found it to be not as challenging as they assumed it to be. Their workload did not seem to increase, and they thought that MDR-TB was treated "more straightforward" compared when BDQ was still unavailable. The primary problem they encountered was the logistics concerning the supply of the drug. But overall, they considered BDQ a positive experience that met enthusiasm among providers and patients alike. [13]

Another highlight is the significant number of reported LTFU that poses a challenge to the clinicians. It is notable that in other studies, LTFU does not reach a considerable number. Therefore, one of the strengths of this is the in-depth discussion on why it happens and how it is prevented which were not tackled in other literature. The ironic effect of decentralization of treatment is an unexpected reveal. The pros and cons of halfway houses were also explored. The NTP can regard these findings as basis for improvising other ways to manage LTFU.

This paper gave a partial overview of the performance of BDQ in the Philippines since its use two years ago. So far, the drug has been doing good in the perspective of the physicians. A number of concerns were also raised by them including the sustainability of BDQ in the country. Codecasa *et al.* found that in Italy, BDQ plus the background regimen is more cost-effective than the latter alone [14]. Further

studies can then explore the cost-effectiveness of the drug to help the NTP decide whether BDQ is worth investing on or not in the future. Moreover, the interaction of BDQ with other drugs can also be a separate research. An important topic to focus on is the association between BDQ and ARVs since the incidence of HIV in the Philippines is rising alarmingly.

Facilitated roundtable discussions were conducted to inquire about the clinical experiences of the clinicians. This method is most appropriate to address the objectives of the activity because all participants had the chance to share their thoughts and encounters on BDQ. The topic was discussed in an organized way while also allowing the participants to answer the questions flexibly. Their answers steered the conversation to arrive on the key points and ideas, but the facilitator also made sure that it would not veer away from the guide questions. The drawback of this method, however, is the presence of a dominant personality and seating arrangement that can influence the opinions of other participants but were coped with through effective facilitation.

The findings presented in this paper are solely based on the perceptions of the physicians in the nine field sites. Group setting may have resulted in some form of information bias, although facilitators tried to probe for answers and elicit responses from all participants as much as possible.

In conclusion, clinicians gave BDQ an overall positive feedback. Among the reasons for this are the effectiveness, less toxicity, and ease of administration of the drug. Physicians, however, were of the perception that the use of the drug was bounded by the inclusion criteria for the operations research, thus limiting the use of BDQ in the clinical setting. The novelty of BDQ also opens the need for further studies to investigate different aspects of the drug such as the relapse rate, effectiveness against extrapulmonary tuberculosis, and the sustainability of use in the Philippines.

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Author Disclosures

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Statement of Authorship

CTA, EGB, and SML conceptualized the project. CTA, ACB, and VSL developed the discussion format and guide questions. CTA, ACB, VSL, CHT, and AHT participated in data collection and analysis. CHT and CTA drafted the initial manuscript for publication. All authors contributed to revising the manuscript critically for important intellectual content and approved this version of the manuscript to be published.

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