Safety and tolerability of clarithromycin in the treatment of multidrug-resistant tuberculosis

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are an emerging global threat. An estimated 3.3% of newly diagnosed TB patients and 20% of previously treated patients worldwide have MDR-TB [1]. Moreover, 9.7% of MDR-TB cases are suffering from XDR-TB. Treatment of TB is becoming more difficult since the resistance pattern of *Mycobacterium tuberculosis* is expanding and treatment success rate is decreasing, with newly emerging drug-resistant strains [2]. Therefore, evaluation of antimicrobial drugs active against *M. tuberculosis* is necessary. Clarithromycin (CLR) is a macrolide antibiotic previously listed as a World Health Organization (WHO) group 5 drug, but not included in the new WHO classification because it has only modest bacteriostatic effects against *M. tuberculosis* [3]. However, the *in vitro* synergy of CLR in combination with linezolid, ethambutol and spectinomycin, and its immunomodulatory effects, hold promise [4–6]. Despite the introduction of newer drugs such as bedaquiline and delamanid, clarithromycin may have added value for the treatment of TB patients in cases of extensive resistance but proven susceptibility to clarithromycin. Unfortunately, real-life data on the use of clarithromycin to guide physicians in the treatment of MDR-TB is scarce.

CLR is generally a well-tolerated and safe antimicrobial agent. The most frequently reported adverse reactions were nausea, diarrhoea and abdominal pain. Headache was reported frequently [7], and to a lesser extent hepatotoxicity was observed [8]. For MDR-TB treatment, CLR is used for longer treatment periods than initially intended for its labelled indication. In addition, CLR is used in combination with at least three to five other antimicrobial drugs in an MDR-TB treatment regimen. This may potentially result in drug–drug interactions [9] or aggravation of adverse drug reactions. Long-term safety and tolerability have been assessed in HIV patients with nontuberculous mycobacterial infections, but not in MDR-TB patients [10]. Therefore, we evaluated the safety and tolerability of CLR in patients treated for MDR-TB.

MDR-/XDR-TB patients treated with CLR as part of an antituberculosis regimen were selected from seven hospitals in five countries (Belarus (two hospitals), Italy (two hospitals), Sweden, the Netherlands and the United Kingdom). Subsequently, CLR-induced adverse effects were collected from the medical charts of patients that received CLR as part of their treatment regimen. On average, laboratory monitoring was preformed once monthly until the end of treatment and ECG was performed at baseline. Because of the retrospective nature of this chart review study, the need for informed consent from the patients was waived.

In order to evaluate safety of CLR during TB treatment, recorded side-effects were retrieved from the medical charts, focusing on CLR-induced side-effects including nausea, vomiting, diarrhoea, headache and elevated hepatic enzyme levels. Furthermore, ECGs were evaluated when available (56%), corrected QT interval (QTc) was calculated using Bazett's formula ($QT/\sqrt{(RR\text{-interval (s)})}$). A QTc of >450 ms was chosen as threshold for increased risk of cardiac events [11]. Hepatic enzymes were defined as elevated if the value of one of the hepatic enzymes exceeded five times the upper limit of normal (ULN) during CLR treatment, reflecting grade 3 common toxicity criteria (L-alanine aminotransferase (ALAT) ULN 40 $IU \cdot L^{-1}$ and L-aspartate aminotransferase (ASAT) ULN 45 $IU \cdot L^{-1}$) [12]. To attribute a certain adverse drug reaction to CLR treatment, the Naranjo algorithm was used [13]. This algorithm uses a score from 0 to ⩾9. With a score of ⩾9, a definite causality between CLR treatment and the adverse drug reaction is accepted, probable causality is assumed with a score of 5–8 and with a score of 1–4 causality is considered

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possible. With a score of 0 causality is doubtful and the adverse drug reaction could be related to factors other than CLR.

The 39 patients who received CLR had a median (interquartile range (IQR)) age of 41 (29–49) years, with median (IQR) body mass index of 20.7 (20.0–22.6) $kg \cdot m^{-2}$. 13 (33%) patients were female. Patients were diagnosed with MDR-TB; 13 had XDR-TB. All suffered from pulmonary TB. Results are shown in table 1. Tobacco and alcohol abuse were reported in 15 (38%) and 13 (33%) patients, respectively. Two patients suffered from diabetes mellitus type II and one from diabetes mellitus type I. Hepatitis C was reported for one patient. Most patients were treated with a regimen of at least four other anti-TB drugs, among which amoxicillin–clavulanic acid, para-aminosalycilic acid, cycloserine, prothionamide and moxifloxacin were the most frequently used. Doses of CLR ranged from 500 mg to 1000 mg per day and were based on the patient's clinical condition and on the minimal inhibitory concentration (MIC) of clinical isolates of *M. tuberculosis* (the latter only for patients in the Netherlands). The dose of 500 mg was administered as an immediate-release formulation, and for most patients 1000 mg was administered as an extended-release formulation. MICs for CLR ranged from <2 to 8 $mg \cdot L^{-1}$, based on six patients for whom MIC was available. Four patients received 1000 mg as an immediate-release formulation. Median (IQR) CLR treatment duration was 336 (183–526) days. Total median (IQR) anti-TB treatment duration was 548 (323–608) days. The total anti-TB treatment duration was unclear for one patient.

CLR was well tolerated. Nine (23%) patients experienced nausea, vomiting and diarrhoea. These adverse events were mild and CLR causality was considered possible (Naranjo scores 1–4), since other anti-TB drugs with possible gastrointestinal side-effects were administered concomitantly. For one patient, treatment with CLR was stopped due to excessive nausea and vomiting. However, the patient had experienced these side-effects before CLR was administered and the symptoms did not resolve after cessation of CLR (Naranjo score 1). For another patient, hepatic enzyme levels were elevated after a month of treatment with 1000 mg of CLR (Naranjo score 2). ALAT values exceeded five times the ULN (244 $U \cdot L^{-1}$; baseline 19 $U \cdot L^{-1}$), leading to a dose reduction of CLR from 1000 mg to 750 mg, after which ALAT levels dropped (92 $U \cdot L^{-1}$). This patient was treated with prothionamide, clofazimine, amoxicillin–clavulanic acid, tigecycline, imipenem and linezolid concomitantly, but his enzyme levels increased after administration of CLR. For one further patient treated with 1000 mg CLR, a QTc was detected above the threshold of 450 ms (465 ms; 370 ms baseline before CLR treatment) (Naranjo score 1) (table 1). The patient was treated with capreomycin, levofloxacin, para-aminosalicylic acid, prothionamide, cycloserine and amoxicillin–clavulanic acid concomitantly.

No other studies to date have addressed the safety and tolerability of CLR in TB patients. The long median treatment duration of 336 (IQR 183–526) days allows for good evaluation of the safety and tolerability of CLR in MDR-TB patients. Overall, this retrospective study confirms the results found in patients treated

TABLE 1 Characteristics and treatment data of multidrug-resistant tuberculosis (MDR-TB) patients

Patients	
Age years	41 (29–49)
Male	26 (67)
BMI $kg \cdot m^{-2}$	20.7 (20.0–22.6)
ASAT $IU \cdot L^{-1}$	25 (18–33)
ALAT $IU \cdot L^{-1}$	20 (11–27)
QTc ms	395 (368–413)
Tuberculosis	
MDR-TB	26 (67)
XDR-TB	13 (33)
Pulmonary	39 (100)
Sputum culture converted	28 (72)
Recurrence	6 (15)
Clarithromycin	
500 mg once daily	3 (8)
750 mg once daily	1 (3)
1000 mg once daily	35 (90)
Total use days	336 (183–526)
Duration of TB treatment months	18 (11–20)

Data are presented as median (interquartile range) or n (%). n=39. BMI: body mass index; ASAT: L-aspartate aminotransferase; ALAT: L-alanine aminotransferase; XDR: extensively drug-resistant.

with CLR for other infectious diseases; indeed, CLR is well tolerated and free from major toxicity [7, 14]. In the patient with a QTc above threshold, elongation could also be related to concomitant administration of levofloxacin, a drug with known torsade de pointes risk. In the two patients for whom CLR had to be discontinued, a Naranjo score of 1 was reached, and thus classified only as a possible adverse drug reaction. Earlier, prothionamide treatment had to be terminated for the first of these two patients, due to nausea and vomiting. In the second patient, with XDR-TB, elevated hepatic liver enzymes during CLR treatment could also be associated with concomitant prothionamide use, while interpretation of the treatment data of this patient was extremely complex. Several former group 4 drugs (now groups C and D anti-TB drugs), such as cycloserine, prothionamide and p-aminosalicylic acid show more severe adverse drug events, including gastrointestinal side-effects, gastritis, depression, hepatotoxicity, neurotoxicity and peripheral neuropathy [15]. Therefore, based on its safety and tolerability CLR might be a valuable addition to an MDR-TB regimen, although its effect on clinical outcome must be further assessed. Future studies should address the synergistic potency of CLR and its host-directed effect.

Limitations of this study are its relatively small sample size and retrospective nature, rendering some information less robust. In general, hospitals recorded side-effects in medical charts, but the attribution of adverse events to CLR was difficult, since it was administered as part of a multidrug regimen.

In conclusion, CLR had a good tolerability and safety profile as assessed in MDR-TB patients receiving prolonged treatment. With its immunomodulatory and synergistic characteristics, this makes CLR a relevant candidate for further exploration as XDR-TB treatment. Based on MIC testing, clarithromycin can be used to complement a treatment regimen in difficult-to-treat cases.

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