Pretomanid-Resistant Tuberculosis

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Keywords: MDR-TB, TDM, high-dose therapy, precision medicine, ADR

Highlights

- Moxifloxacin daily doses of 2400mg were tolerated over several months.
- M. tuberculosis drug resistance could be overcome by a high-dose treatment regimen.
- No occurrence of cardiac AEs despite high doses of QTc interval prolonging drugs.
- No eradication of M. tuberculosis despite longstanding culture conversion.
- Development of pretomanid resistance on an insufficient treatment regimen.

Dear Editor,

We read with great interest the Letter by Lee and colleagues describing proteome analysis of a Mycobacterium tuberculosis strain that caused tuberculosis (TB) relapse in a young Korean patient and ultimately acquired resistance to several of the most relevant second-line anti-TB drugs (1). We share the experience of additional clinical applications of precision medicine for the management of a patient with drug-resistant tuberculosis who is the first patient with pretomanid-resistant tuberculosis to our knowledge.

M. tuberculosis antimicrobial resistance is challenging the global control of tuberculosis (TB). For 2021, the World Health Organization (WHO) estimates that 450 000 people developed a form of drug-resistant tuberculosis that was at least resistant to the most important anti-TB drug, rifampicin (rifampicin-resistant-TB; RR-TB) (2). Simultaneous occurrence of isoniazid-resistance is common in rifampicin-resistant tuberculosis and defines multi-drug resistance (MDR-TB). Additional resistance to fluoroquinolones (levofloxacin or moxifloxacin) is defined as pre-extensively drug-resistant (preXDR)-tuberculosis and further resistance to bedaquiline and/or linezolid as extensively drug-resistant (XDR)-tuberculosis. Treatment of all these forms of drug-resistant tuberculosis requires second-line drugs that exhibit lower efficacy and higher toxicity with a higher risk of treatment failure or death (2).

The FDA/EMA-approval of the new drug pretomanid and the results of two recent large-scale clinical trials have revolutionised the treatment of RR- and MDR-TB: The WHO now recommends under certain conditions to treat patients with MDR/RR-tuberculosis with a 6-month-regimen of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM); pre-XDR-tuberculosis with the same regimen but without moxifloxacin. XDR-tuberculosis still requires ≥18-months regimens according to the WHO priority grouping of medicines (3). In these regimens, high-dose therapy and individualized dosing based on plasma drug concentration measurements (therapeutic drug monitoring, TDM) are tools to increase the therapeutic effect and avoid under-exposure to the drugs.

Here, we report a patient with advanced XDR-tuberculosis, who was treated with individualized high-dose therapy with support of an international expert group. Individualized treatment under therapeutic drug monitoring resulted in M. tuberculosis culture conversion and longstanding remission, yet the mycobacteria could not be eradicated sustainably, and the patient subsequently experienced a relapse with acquired totally drug-resistant tuberculosis including pretomanid resistance.

The patient originated from Ukraine and was 34 years old on admission in November 2018. He had been treated for pulmonary tuberculosis since 2008 and had undergone eight treatment episodes with several therapy failures and relapses.

Sputum liquid culture grew Mycobacterium tuberculosis within 7 days (culture time-to-positivity, TTP) (Figure 1: Mycobacterial Load), phenotypic and genotypic drug susceptibility testing (pDST/gDST) indicated an advanced level XDR-tuberculosis.

An individualized intensified treatment with high-dose therapy was initiated and weekly monitoring of TTP, regular pDST and minimal inhibitory concentration (MIC) testing in mycobacteria growth

indicator tubes (MGIT), gDST by whole-genome sequencing (WGS), TDM (4, 5), and electro-cardiographic (ECG) monitoring of the QTc-interval were performed. Drug concentrations were compared to reference values (6) and observational studies (7, 8).

Drug-resistance to all first- and second-line drugs was found apart from delamanid and pretomanid, due to multiple resistance-conferring mutations: first-line drug-resistance due to rpoB S450L, katG S315T, embB M306I, and pncA G132S. A gyrA D94G-mutation conferred resistance to moxifloxacin (MIC: 2µg/ml), and two mutations in Rv0678, 141_ins_c and I108V, were associated with bedaquiline and clofazimine resistance (both: MIC: 2µg/ml). Linezolid was tested resistant due to rplC C154R (MIC: >1µg/ml), Terizidone resistant in gDST with an insertion in ald 193, the MIC for its active metabolite cycloserine was 30µg/ml. Further, amikacin resistance: rrs 1401_a>g (>128µg/ml), and prothionamide resistance due to a large deletion in ethA (>5µg/ml). Delamanid was tested susceptible (MIC: 0.03µg/ml) (Figure 1: WGS/MIC).

In an attempt to overcome the MICs of moxifloxacin, bedaquiline, clofazimine, and terizidone, escalating doses of these drugs plus meropenem/amoxicillin-clavulanate, delamanid, para-amino-salicylic acid (PAS), and verapamil (as bedaquiline/clofazimine-sensitizer (9)) were administered under TDM. Culture conversion was achieved after 11 months of treatment, under daily doses of 1600mg moxifloxacin, 300mg bedaquiline (three times per week, TW), 200mg clofazimine, 1000mg terizidone, 200mg delamanid, and prolonged infusion of 3*2g meropenem plus 875/125mg amoxicillin/clavulanate (Figure 1: Treatment history). TDM showed high exposure to bedaquiline, delamanid, and terizidone. Moxifloxacin exposure was still subtherapeutic despite dose escalation (Figure 1: PK/PD). Under these conditions, culture negativity was sustained until January 2020, and from January until November 2020 only 3/43 weekly sputum cultures grew M. tuberculosis, each time in the context of catheter associated candidemia.

Treatment cessation in December 2020, after 26 months of treatment, unfortunately led to an immediate relapse. Presuming better efficacy, delamanid was replaced with pretomanid and meropenem/amoxicillin/clavulanate was administered by continuous infusion of 9.6/6/1.2g over 24 hours. Experimental meropenem/clavulanate MIC testing in MGIT showed an elevated MIC of 16µg/ml which we did not overcome with our dosing strategies (Figure 1: PK/PD).

Culture negativity was again achieved for four months of, but re-emerging mycobacteria showed high-level delamanid and pretomanid resistance with three high-frequency mutations in fbiC: 1303916_ins_G, 1303919_ins_C (both 96.8% of alleles in WGS), and 1303999_ins_TC (41.3%); as well as MICs of >0.24 and >4µg/ml for delamanid and pretomanid, respectively (Figure 1: WGS/MIC). Despite further escalation to daily doses of 2400mg moxifloxacin, 400mg bedaquiline (TW), 200mg clofazimine, 1500mg terizidone, 300mg delamanid, and 18/9/1.8g meropenem/amoxicillin/clavulanate over 22 hours, there was no therapy response any more. The patient experienced no adverse events apart from QTc prolongation up to 560ms (Figure 1: QTc).

In November 2021, the patient was transferred to another hospital where he died from gram-negative pneumonia in March 2022.

This case illustrates the possibility to overcome drug-resistance with precision medicine, based on gDST, pDST, QTc-monitoring, and TDM - allowing even patients with advanced XDR-tuberculosis to achieve M. tuberculosis culture negativity temporarily. TDM and high-dose therapy effectively

suppressed mycobacterial growth and improved the patient's quality of life. High doses of up to 6-fold the recommended dose were well tolerated over long periods of time, and no adverse cardiac events occurred. However, high-dose therapy could not eradicate M. tuberculosis in 26 months of treatment, so that the patient experienced an immediate relapse when therapy was stopped. It could also not prevent the selection of a delamanid- and pretomanid-resistant mycobacterial clone that likely caused the second relapse few months later.

To our knowledge, this is the first case of acquired drug-resistance to pretomanid in a patient with advanced-level XDR-tuberculosis, hence with resistance to all medicines of the new BPaL(M)-regimen and all other anti-tuberculosis drugs. The case confirms that adding single drugs to failing regimens selects for additional drug-resistance and suggests that patients with advanced levels of drug-resistant tuberculosis likely need entirely new treatment regimens to achieve cure.

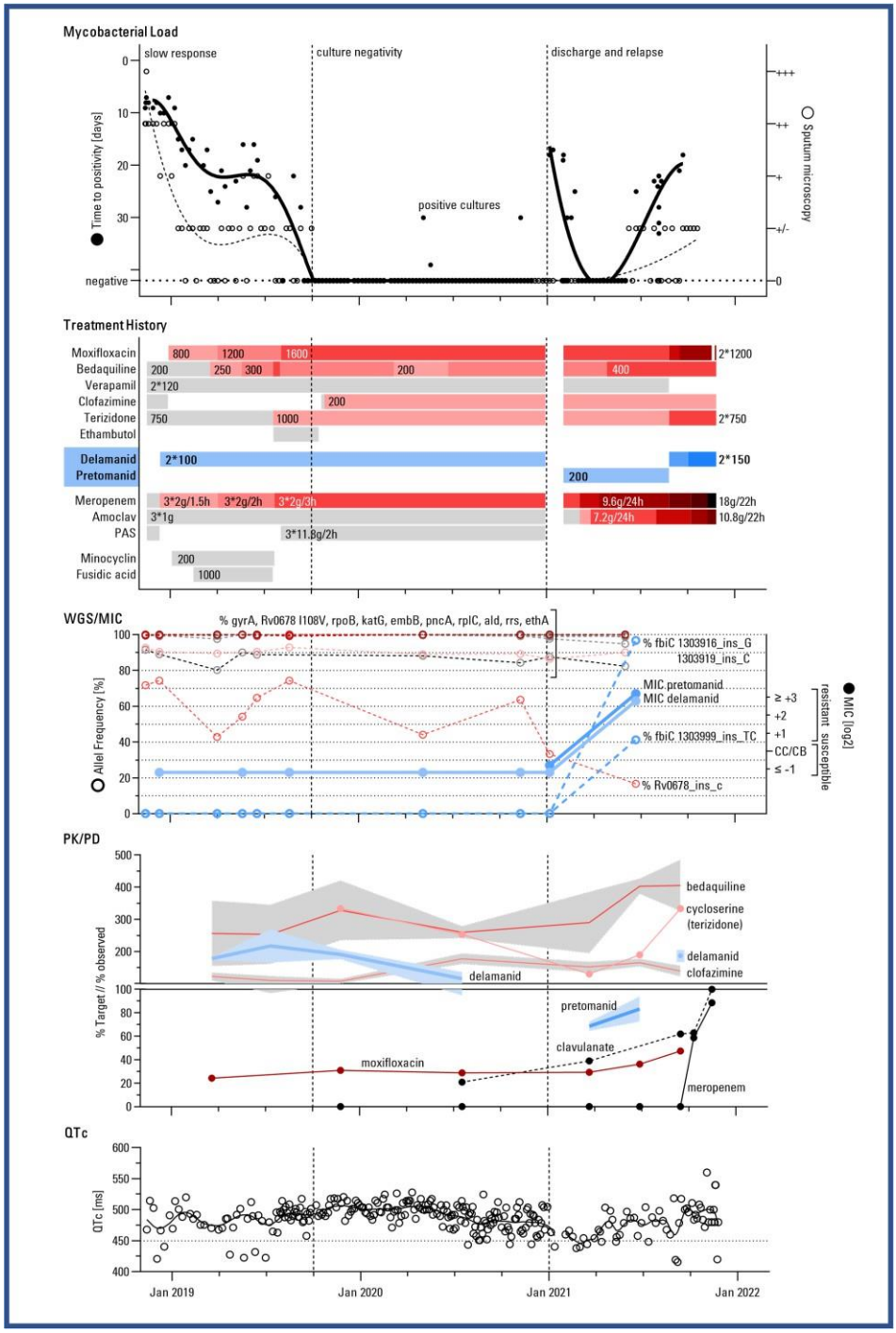
Mycobacterial Load
slow response
culture negativity
discharge and relapse
Time to positivity [days]
positive cultures
negative
Sputum microscopy
Treatment History
Moxifloxacin
Bedaquiline
Verapamil
Clofazimine
Terizidone
Ethambutol
Delamanid
Pretomanid
Meropenem
Amoclav
PAS
Minocyclin
Fusidic acid
2*1200
2*750
2*150
18g/22h
10.8g/22h
WGS/MIC
% gyrA, Rv0678 I108V, rpoB, katG, embB, pncA, rplC, ald, rrs, ethA
% fbiC 1303916_ins_G
1303919_ins_C
MIC pretomanid
MIC delamanid
% fbiC 1303999_ins_TC
% Rv0678_ins_c
Allel Frequency [%]
resistant
susceptible
MIC [log2]
PK/PD
bedaquiline
cycloserine
(terizidone)
delamanid
clofazimine
% Target // % observed
pretomanid
clavulanate
moxifloxacin
meropenem
QTc
QTc [ms]
Jan 2019
Jan 2020
Jan 2021
Jan 2022

Figure 1: Mycobacterial load, treatment history, whole genome sequencing/minimal inhibitory concentrations (WGS/MIC), pharmacokinetics/pharmacodynamics (PK/PD) and QTc intervals over the 36 months of treatment. Mycobacterial load: Time to liquid culture positivity (line) and sputum smear microscopy (dots) as polynomial regressions. Treatment history: Different shades of red/blue represent higher-than-normal doses or longer-than-normal infusion intervals. Numbers represent the daily dose in mg (the thrice weekly dose for bedaquiline) unless otherwise specified. WGS/MIC: Whole-genome sequencing resistance conferring alleles as % of total reads. Minimal inhibitory concentrations of delamanid and pretomanid displayed as log2-steps in relation to the critical concentration (CC) of 0.06µg/ml and 1µg/ml for delamanid and pretomanid, respectively. PK/PD: Pharmacokinetic/pharmacodynamic parameters. Plasma drug concentrations from TDM for bedaquiline, clofazimine, and delamanid as % of observed population concentrations: Minimal concentration and maximal concentrations of bedaquiline, clofazimine, delamanid, and pretomanid (shaded areas) are displayed in relation to minimal and maximal concentrations from observational cohorts (7, 8). Plasma drug concentrations for cycloserine (the active metabolite of terizidone), moxifloxacin, and meropenem + clavulanate as % of target: for cycloserine (terizidone) a time for concentration above MIC (T>MIC) of 30%, for moxifloxacin a free area under the concentration-time curve divided by the MIC (fAUC/MIC) of 53 (6), for meropenem an fT>4xMIC of 100% based on tissue penetration (10) and a T>2µg/ml for clavulanate based on the clavulanate concentration in pDST. QTc: QTc-intervals in ms, commonly used threshold of 450 ms as dotted line, LOWESS-interpolation as continuous line.

Funding: This work was supported by the German Center for Infection Research (DZIF) [grant number 02-709 to C.L.).

Conflict of interest: C.K. received personal fees from INFECTOPHARM outside the scope of this work;

C.K. received speakers honoraria from GILEAD and SHIONOGI outside the scope of this work; B.K. received personal fees from INSMED outside the scope of this work; S.N. received grants from German Center for Infection Research, Excellence Cluster Precision Medicine in Chronic Inflammation EXC 2167, and Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG), during the conduct of the study; S.N. received consultation fees from ILLUMINA outside the scope of this work;

C.L. received consulting fees from INSMED outside the scope of this work; C.L. received speakers honoraria from INSMED, GILEAD, and JANSSEN outside the scope of this work; C.L. is a participant on Data Safety Boards of Medicines sans Frontiers outside the scope of this work; all other authors have nothing to disclose.

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