Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis

Bloemberg, Guido V; Keller, Peter M; Stuckia, David; Trauner, Andrej; Borrell, Sonia; Latshang, Tsogyal; Coscolla, Mireia; Rothe, Thomas; Hönke, Rico; Ritter, Claudia; Feldmann, Julia; Schulthess, Bettina; Gagneux, Sebastien; Böttger, Erik C

Abstract: Treatment of multidrug-resistant Mycobacterium tuberculosis is a challenge. This letter describes the emergence of resistance to new therapies, bedaquiline and delamanid.

DOI: https://doi.org/10.1056/NEJMc1505196

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-116926
Published Version

Originally published at:
Bloemberg, Guido V; Keller, Peter M; Stuckia, David; Trauner, Andrej; Borrell, Sonia; Latshang, Tsogyal; Coscolla, Mireia; Rothe, Thomas; Hönke, Rico; Ritter, Claudia; Feldmann, Julia; Schulthess, Bettina; Gagneux, Sebastien; Böttger, Erik C (2015). Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis. New England Journal of Medicine, 373(20):1986-1988.
DOI: https://doi.org/10.1056/NEJMc1505196
a diagnosis of multiple primary tumors. In our patient, we had identified two different truncating germline NTHL1 mutations in trans: the above-mentioned c.268C>T,p.Q90* mutation and c.709+1G>A, which results in abnormal splicing (Fig. 1B, and Fig. S1 in the Supplementary Appendix). In so doing, we extended the previous report to include benign and malignant extracolonic tumors. The mutation spectrum was significantly shifted in favor of C:G→T:A transitions (Fig. S2 in the Supplementary Appendix), as reported previously. Among other driver mutations, we identified the frequently reported FGFR3 mutation c.742C>T,p.R248C in one seborrhoeic keratosis (Fig. S3 in the Supplementary Appendix).

A single NTHL1 mutation, p.Q90*, was identified by investigators in Nijmegen, the Netherlands, which is only 150 km from Dortmund, Germany, where the paternal relatives of our patient were born. This finding suggests that the p.Q90* allele was inherited paternally. The c.709+1G→A mutation has been reported only once in 118,482 alleles that were collated by the Exome Aggregation Consortium (exac.broadinstitute.org). A complete list of authors is available with the full text of this letter at NEJM.org.

TO THE EDITOR: Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are an increasing public health threat. Bedaquiline and delamanid are two drugs that were recently approved by the Food and Drug Administration for treatment of MDR-TB and XDR-TB. Here we describe the stepwise amplification of drug resistance in a patient who had emigrated from Tibet to Switzerland in December 2010 and who presented to a Swiss hospital with preextensively drug-resistant tuberculosis at that time.

Figure 1 (facing page). Clinical Features, Treatment History, Amplification of Drug Resistance, and Phenotypic Drug-Susceptibility Testing in the Patient.

Mutations that confer drug resistance are shown. Resistance to bedaquiline, intravenous capreomycin, and delamanid developed. Percentages on the y axis are based on the number of genome-sequencing reads supporting the corresponding drug resistance–confering mutation (details are provided in Table S4 in the Supplementary Appendix). Large colored circles indicate measurements, and dashed lines linking these circles indicate the changes in mutation frequency. The loss of the start codon is indicated with an asterisk, and fs indicates frame shift. The mutations listed on the left side of the graph were detected in the first and all subsequent isolates obtained from the patient. All these mutations were seen in 100% of sequencing reads in each isolate. X indicates the stop codon, and del indicates deletion. On the x axis, isolate numbers are listed under the month when the isolate was obtained. TMP-SMX denotes trimethoprim–sulfamethoxazole.
Genome sequencing revealed that the initial Mycobacterium tuberculosis isolate harbored nine mutations in genes associated with resistance to seven drugs (Fig. 1, and the Supplementary Appendix, available with the full text of this letter at NEJM.org). The isolate also showed a compensatory mutation in rpoC, indicating a “mature” preextensively drug-resistant strain that had evolved...
under drug pressure for some time. Given that the patient reported no previous treatment for tuberculosis, he was probably infected with a strain that was already resistant to these drugs.

In September 2011, bedaquiline was added to the regimen, which had consisted of four drugs (ethambutol, aminosalicylic acid, intravenous capreomycin, and cycloserine). The patient was considered to be clinically cured in March 2013, but he had a relapse in August 2013. Genome sequencing of five follow-up isolates revealed a mutation in mmpR that was associated with bedaquiline resistance. This mutation persisted even though bedaquiline was discontinued in February 2012; this suggests that it did not cause any clinically significant reduction in the virulence of the infecting bacteria.

Additional resistance to second-line injectable agents (such as capreomycin) also developed. This was reflected in the emergence of mutations in fbgA and rrs. The latter mutation remained at low frequency and was detected only in drug-containing bacterial cultures (Table S3 in the Supplementary Appendix). All the molecular findings were supported by phenotypic drug-susceptibility testing.

Following this amplification in resistance, delamanid was added to the regimen in March 2014. However, two mutations in fbgA and fgd1 increased in frequency by June 2014, which coincided with the emergence of phenotypic resistance to delamanid. These genes have previously been associated with delamanid resistance. The fgd1 mutation decreased in frequency thereafter, indicating the presence of multiple delamanid-resistant clones in the patient. In August and September 2014, the patient underwent a lobectomy. After surgery, the sputum specimens obtained from the patient were culture-negative, and the patient received treatment on an ambulatory basis.

This case highlights the development of resistance in the context of inadequate MDR-TB and XDR-TB treatment regimens, despite personalized patient care in a well-resourced health care setting. It serves as a warning for the future rollout of new antituberculosis drugs and emphasizes the need for the use of appropriate companion drugs when bedaquiline and delamanid are administered. Our results add to previous findings showing that the development of drug resistance is a dynamic process involving multiple heterogeneous populations of bacteria within individual patients.

Guido V. Bloemberg, Ph.D.
University of Zurich
Zurich, Switzerland

Sebastien Gagneux, Ph.D.
Swiss Tropical and Public Health Institute
Basel, Switzerland
sebastien.gagneux@unibas.ch

Erik C. Böttger, M.D.
University of Zurich
Zurich, Switzerland

and Others

A complete list of authors is available with the full text of this letter at NEJM.org.

Supported by the Swiss Federal Office of Public Health, the University of Zurich, SystemsX.ch, the Novartis Foundation, and grants from the Swiss National Science Foundation (PPO0P3_150750), the National Institutes of Health (AI090928), and the European Research Council (309540-EVODRTB).

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


DOI: 10.1056/NEJMc1505196
Correspondence Copyright © 2015 Massachusetts Medical Society.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

• Letters in reference to a Journal article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article.
• Letters not related to a Journal article must not exceed 400 words.
• A letter can have no more than five references and one figure or table.
• A letter can be signed by no more than three authors.
• Financial associations or other possible conflicts of interest must be disclosed. Disclosures will be published with the letters. (For authors of Journal articles who are responding to letters, we will only publish new relevant relationships that have developed since publication of the article.)