Effectiveness and Safety of Imipenem-Clavulanate Added to an Optimized Background Regimen (OBR) Versus OBR Control Regimens in the Treatment of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

To the Editor—Treating patients with multidrug-resistant (MDR) or extensively drug-resistant (XDR) tuberculosis is long, expensive, and complicated, particularly when 4 active drugs recommended to design an effective regimen are missing [1–5]. New drugs (ie, bedaquiline and delamanid [6,7]) and a few repurposed ones (linezolid [8, 9] and carbapenems [10–12]) are attracting interest. To date, the largest clinical study evaluating imipenem-clavulanate (IC) in the treatment of MDR tuberculosis included 10 cases [12].

The aim of our observational study was to compare the therapeutic contribution (effectiveness, safety, and tolerability profile) of IC added to an optimized background regimen (OBR) designed according to World Health Organization...
controls. They also showed more resistances (8[7]–1[0]6.0%) than OBR controls (all prevalence of XDR tuberculosis (67.9% vs 13.5%) and a higher kanamycin (75.8% vs 18.2%), and capreomycin (63.9% vs 13.0%), amikacin (50.0% vs 13.0%), and resistance to fluoroquinolones (79.0% vs 16.8%), amikacin (50.0% vs 13.0%), kanamycin (75.8% vs 18.2%), and capreomycin (63.9% vs 13.5%) and a higher prevalence of XDR tuberculosis (67.9% vs 6.0%) than OBR controls (all P < .001).

An OBR regimen was administered after drug susceptibility testing carried out by externally quality-assured laboratories [10, 11]. Physicians prescribed antituberculosis drugs without any compelling criteria for experimental protocols, so blinding and randomized methods were not followed. Imipenem was administered at a dose of 500 mg 4 times a day for a median (interquartile range [IQR]) of 187 (60–428) days.

Patients treated with IC had more previous exposures to antituberculosis drugs lasting >1 month (median [IQR], 2 [1–3] vs 1 [0–2]) and higher number of resistances (8 [7–8] vs 5 [4–6]) than OBR controls. They also showed more resistance to fluoroquinolones (79.0% vs 16.8%), amikacin (50.0% vs 13.0%), kanamycin (75.8% vs 18.2%), and capreomycin (63.9% vs 13.5%) and a higher prevalence of XDR tuberculosis (67.9% vs 6.0%) than OBR controls (all P < .001).

The median (IQR) time to sputum smear conversion was similar in IC-treated patients and controls (30 [30–60] vs 30 [0–56] days; P > .001), whereas the time to culture conversion was longer in IC-treated patients, although not significantly so (60 [30–90] vs 42 [30–90] days; P = .08; Figure 1). Sputum smear and culture conversion rates were lower in IC-treated patients than in OBR controls (sputum smear, 79.7% vs 98.0%; culture conversion, 71.9% vs 100.0%; both P < .001), as were success rates (59.7% vs 85.8%; P < .001), whereas death (17.9% vs 1.8%; P < .001) and failure (6.0% vs 0.0%; P < .001) rates were higher. Adverse events (minor) due to IC were reported in only 5.4%.

Our findings show that IC-containing regimens achieved nondifferent or worse results than IC-sparing ones. Perhaps the severity of IC-treated cases favored the administration of a carbapenem in the absence of alternatives, so selection bias related to the retrospective, observational nature of the study cannot be excluded. Interestingly, the success rates among IC-treated patients is similar to that achieved in other major international MDR tuberculosis cohorts, confirming that IC may have a role in MDR tuberculosis treatment [1, 2, 12]. To our knowledge, this is the first large study evaluating the effectiveness, safety, and tolerability of IC-containing regimens while comparing their clinical performance with outcomes in a control group.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.


1Division of Infection, and 2Department of Respiratory Medicine, Barts Health NHS Trust, 3Department of Respiratory Medicine, Queen Mary University, and 4Division of Infection and Immunity, University College London and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, United Kingdom; 5Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari, Research, Medical Education and Professional Development Unit, AOU Sassari, WHO Collaborating Centre for TB and Lung Diseases, and 6Pneumology Unit, Fondazione IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico), Clinical and Research Institute, Tradate, 7Respiratory Infectious Diseases Unit, National Institute for Infectious Diseases “L. Spallanzani,” Rome, University Department of Infectious and Tropical Diseases, World Health Organization Collaborating Centre for TB/HIV Coinfection and for TB Elimination, University of Brescia and Brescia Spedali Civili General Hospital, 8Unit of Infectious Diseases, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, 9Division of Infections, and 10Department of Respiratory Medicine, University of Insubria, Varese, Italy; 11Public Health Consulting Group, Lugano, Switzerland; 12University Center of Araraquara and 13Hospital Nestor Goulart Reis, São Paulo State Secretary of Health, Brazil; 14International Union against Tuberculosis and Lung Disease (The Union), 15International Tuberculosis Control Programme, Ministry of Health, and 16National Hospital Hipólito Unanue, Public Health Institute, Ministry of Health, Lima, Peru; 17MDR-TB Unit, Tuberculosis Division, 18International Union against Tuberculosis and Lung Disease (The Union), Paris, France; Departments of 19Clinical Pharmacy and Pharmacology, and 20Pulmonary Diseases & Tuberculosis, University of Groningen, University Medical Center Groningen, TB Center Beatrixoord, and 21KNCO Tuberculosis Foundation, Den Haag, The Netherlands; 22Pneumology Department, Hospital General de Gran Canaria “Dr. Negrín,” Las Palmas de Gran Canaria, Spain; 23National Referral Centre for Mycobacteria, Athens Chest Hospital, Ministry of Health, Greece; 24Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, and 25Educational Institution, Gendris State Medical University, Belarus; 26Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, and 27Educational Institution, Gendris State Medical University, Belarus; 28Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, and 29Educational Institution, Gendris State Medical University, Belarus; 30National Institute for TB, Lung Diseases and Thoracic

**Figure 1.** Time to sputum culture conversion in patients with multidrug-resistant tuberculosis exposed or not exposed to imipenem-clavulanate (P = .77).
References


*S. T., G. S., L. D. A., and R. C. contributed equally to this work.

Correspondence: G. B. Migliori, World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Via Roncaccio 16, 21049 Tradate, Italy (giovannibattista.migliori@fsm.it).