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In Vitro and Intracellular Activity of Imipenem Combined with Tedizolid, Rifabutin, and Avibactam against *Mycobacterium abscessus*

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ABSTRACT *Mycobacterium abscessus* infections are difficult to treat because of their resistance to many antibiotics. *In vitro*, tedizolid combined with imipenem displayed a moderate synergistic effect (fractional inhibitory concentration index, 0.41) but no bactericidal activity. Intracellularly, tedizolid 2 μg/ml (half of the MIC), corresponding to the peak serum concentration, increased the efficacy of imipenem at 8 and 32 μg/ml. Addition of avibactam and rifabutin, alone or in combination, improved the activity of the imipenem-tedizolid combination.

KEYWORDS *Mycobacterium abscessus*, avibactam, cystic fibrosis, imipenem, rifabutin, tedizolid

Among nontuberculous mycobacteria, *Mycobacterium abscessus*, a rapidly growing mycobacterium, has emerged in recent years as an important opportunistic pathogen responsible for chronic lung disease in patients with cystic fibrosis (CF), bronchiectasis, or chronic obstructive pulmonary disease (1–9).

The treatment is particularly complex and difficult because *M. abscessus* is intrinsically resistant to a broad range of antibiotics, including those used for the treatment of tuberculosis (10, 11). In CF patients, the typical treatment consists of an initial phase with the combination of a carbapenem (imipenem), a macrolide (azithromycin), an aminoglycoside (amikacin), and a glycylcycline (tigecycline) for 3 to 12 weeks (12). For the continuation phase, four oral drugs (azithromycin, minocycline, clofazimine, and moxifloxacin) and inhaled amikacin are proposed (12). In spite of these lengthy courses of antibiotics, the prognosis of pulmonary infections is poor in the context of CF, with a cure rate of 30% to 50% (13, 14). In case of inducible or constitutive macrolide resistance, present in 40% to 60% of the isolates (15), the rate of bacteriological eradication is on the order of 25% (13). In this context, there is an urgent need to identify additional therapeutic options. This may be achieved in the short term by repurposing existing drugs approved for the treatment of other bacterial infections.

M. abscessus isolates produce a broad-spectrum β-lactamase, Bla_{Mab}, which hydrolyzes most β-lactams, except cefoxitin, and inactivates imipenem at a very slow rate (16, 17). Imipenem is currently used in the absence of any β-lactamase inhibitor, although Bla_{Mab} was recently shown to limit the intracellular activity of imipenem in human macrophages (16, 18, 19). First generation β-lactamase inhibitors, clavulanate, tazobactam, and sulbactam, are inactive against Bla_{Mab} (20). However, Bla_{Mab} is inhibited by a novel β-lactamase inhibitor, avibactam (16), which has been developed in combination with ceftazidime for the treatment of infections due to multidrug-resistant *Enterobacteriaceae* (21). Avibactam extends the spectrum of β-lactams active against *M. abscessus* (16, 19) and improves the efficacy of imipenem, both in macrophages and in zebrafish embryos (18).

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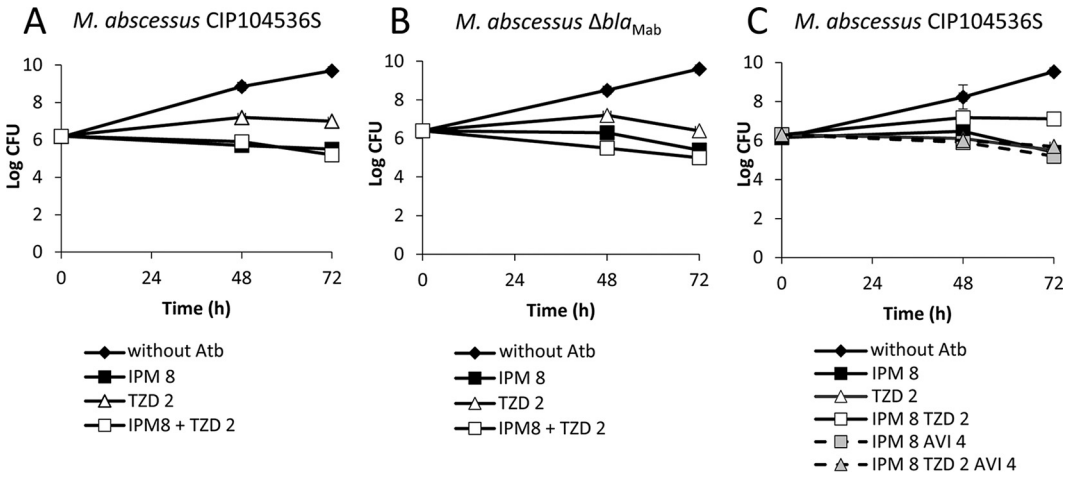

FIG 1 Bactericidal activity of tedizolid (TZD) alone and in combination with imipenem (IPM) and the β-lactamase inhibitor avibactam (AVI) against *M. abscessus* CIP1045636 and its Δ*bla*$_{Mab}$ derivative. Time-kill curves of TZD 2 μg/ml alone or in combination with IPM 8 μg/ml against CIP104536 (A) and its Δ*bla*$_{Mab}$ derivative (B). (C) Time-kill curves of TZD and IPM with and without AVI 4 μg/ml against CIP104536. without Atb, without antibiotic. Results are means ± standard deviations from three experiments.

Tedizolid is a recently developed once-daily oxazolidinone antibiotic that has been approved for the treatment of acute bacterial skin and soft tissue infections (22). In *M. abscessus*, a recent *in vitro* study showed that tedizolid has better *in vitro* activity than linezolid, in that the MIC$_{50}$ and MIC$_{90}$ of tedizolid (2 and 8 μg/ml, respectively) were 2- to 16-fold lower than those of linezolid (23).

In this study, we investigated the interest of repurposing tedizolid for *M. abscessus* infections in combination with imipenem alone or with imipenem, avibactam, and rifabutin. We report the *in vitro* and intracellular antibacterial activities of various combinations of these four drugs. The impact of β-lactamase production was assessed by comparing *M. abscessus* CIP104536 and a derivative obtained by deletion of the gene encoding Bla$_{Mab}$.

The MIC of tedizolid, determined in 96-well round-bottom microplates using the microdilution method (24), was 4 μg/ml against both *M. abscessus* subspecies *abscessus* CIP104536 and its β-lactamase-deficient (Δ*bla*$_{Mab}$) derivative (16). The MICs of imipenem were 4 and 2 μg/ml against CIP104536 and its Δ*bla*$_{Mab}$ derivative, respectively. Against CIP104536, the combination of tedizolid with imipenem showed a moderate synergistic effect by the two-dimensional dilution checkerboard method (24), with a fractional inhibitory concentration (FIC) index of 0.41 at one-fourth of the MIC of imipenem and one-eighth that of tedizolid. Against the Δ*bla*$_{Mab}$ derivative, the FIC index was 0.38 at one-fourth the MIC of imipenem and one-eighth the MIC of tedizolid. *In vitro* killing of *M. abscessus* by tedizolid alone, in combination with imipenem, or in combination with imipenem and avibactam was determined using the time-kill assay (19, 24). Tedizolid was tested at half-fold the MIC (2 μg/ml) corresponding to the peak serum concentration for an administration of 200 mg/day (25) and imipenem at 2-fold the MIC (8 μg/ml). Against CIP104536, tedizolid alone had no effect in the reduction of CFU (Fig. 1A and Table S1 in the supplemental material). A 0.7-log$_{10}$ reduction in CFU was observed for imipenem alone at 8 μg/ml. The addition of tedizolid did not increase bacterial killing by imipenem (1.0-log$_{10}$ reduction in CFU). Similar results were obtained for the Δ*bla*$_{Mab}$ derivative of CIP104536 (Fig. 1B and Table S2 in the supplemental material).

Since the addition of tedizolid to imipenem did not improve the activity of imipenem against *M. abscessus* CIP104536, we investigated the benefit of adding avibactam (4 μg/ml) (Fig. 1C and Table S3 in the supplemental material). Avibactam did not potentiate the killing by imipenem alone. The triple combination of imipenem-tedizolid-avibactam was not more active than the imipenem-tedizolid combination.

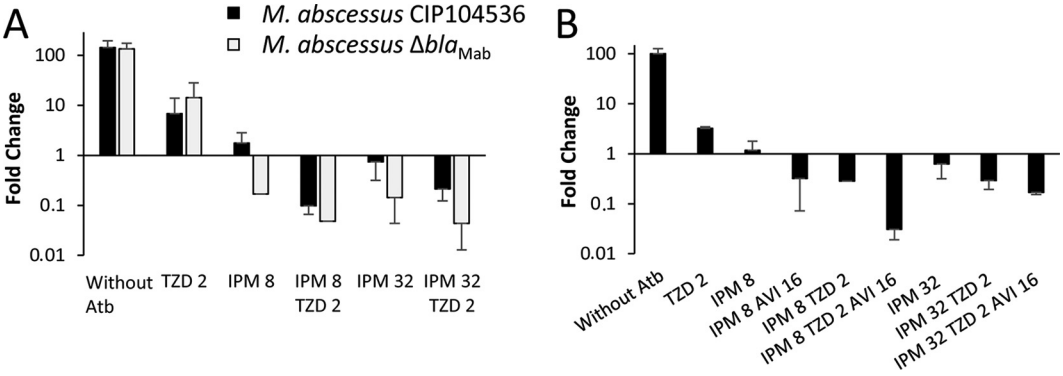

FIG 2 Intracellular activities of antibiotics against *M. abscessus* CIP104536 and its Δ*bla*$_{Mab}$ derivative in the macrophage model. (A) Tedizolid (TZD) 2 μg/ml and imipenem (IPM) 8 or 32 μg/ml were tested alone and in combination against *M. abscessus* CIP104536 and its Δ*bla*$_{Mab}$ derivative. (B) IPM 8 and 32 μg/ml and TZD 2 μg/ml were tested with and without AVI 16 μg/ml against *M. abscessus* CIP104536. Without Atb, without antibiotic. CFU were enumerated after 4 days of incubation at 30°C by plating serial dilutions of macrophage lysates. Results are means ± standard deviations from three experiments.

Inhibition of Bla$_{Mab}$ by avibactam and comparison of *M. abscessus* CIP104536 and its Bla$_{Mab}$-deficient derivative both indicated that hydrolysis of imipenem by Bla$_{Mab}$ had a minor impact on the *in vitro* activity of imipenem.

The intracellular activity of antibiotics was studied on a THP1 macrophage infection model, as previously described (18, 24). Statistical analysis was performed with the Mann-Whitney *U* test. In the absence of antibiotic, *M. abscessus* CIP104536 grew in the macrophages, leading to a 143-fold increase in the number of CFU in 48 h (Fig. 2A and Table S4 in the supplemental material). Tedizolid 2 μg/ml partially prevented intramacrophage growth (6.85- versus 143-fold increase in the number of CFU; $P < 0.05$). Imipenem 8 μg/ml was more active than tedizolid (1.75- versus 6.85-fold increase in CFU; $P < 0.05$). Increasing the concentration of imipenem from 8 to 32 μg/ml increased the activity of this drug, but the difference was not statically significant (1.75- versus 0.74-fold change in CFU; $P = 0.13$). The combination of tedizolid and imipenem 8 μg/ml was more active than imipenem alone (0.10- versus 1.75-fold change in CFU; $P < 0.05$). Of note, the combination of imipenem 8 μg/ml and tedizolid 2 μg/ml achieved 90% killing of *M. abscessus* in the macrophage. Increasing the concentration of imipenem from 8 to 32 μg/ml did not improve killing (90% versus 79%; $P = 0.13$). A 10- to 15-fold intracellular accumulation of tedizolid has been reported in human macrophages (26). The intramacrophage accumulation may account for the observed activity of tedizolid in the macrophage model at a concentration lower than the MIC (4 μg/ml).

The combinations of imipenem and tedizolid were also tested against the isogenic strain of *M. abscessus* CIP104536 Δ*bla*$_{Mab}$ to evaluate the impact of the production of the β-lactamase Bla$_{Mab}$ on the intracellular activity of the drugs (Fig. 2A and Table S5 in the supplemental material). Tedizolid alone displayed similar activity against Δ*bla*$_{Mab}$ and CIP104536 (14.27- versus 6.85-fold change; $P = 0.72$) (see Table S6 in the supplemental material). Deletion of *bla*$_{Mab}$ significantly improved the activity of imipenem alone at the two tested concentrations (0.17- versus 1.75-fold change at 8 μg/ml and 0.14- versus 0.74-fold change at 32 μg/ml; $P < 0.05$ for both). Addition of tedizolid improved the activity of imipenem at 8 and 32 μg/ml against the Δ*bla*$_{Mab}$ derivative, leading to 95% and 96% killing, respectively. At a low dose of imipenem, production of Bla$_{Mab}$ moderately reduced the activity of imipenem-tedizolid, but the difference was not statistically significant (95% versus 90% killing, respectively; $P = 0.37$). This difference was slightly more pronounced for the combination involving the high dose of imipenem (96% and 79% killing, respectively), reaching statistical significance ($P < 0.05$). In contrast to the *in vitro* results, Bla$_{Mab}$ significantly impaired the activity of imipenem in the macrophage model. As previously described, this difference may be accounted for by a 20-fold induction of Bla$_{Mab}$ synthesis in the macrophage (18).

Because production of Bla$_{Mab}$ reduced the efficacy of the imipenem-tedizolid

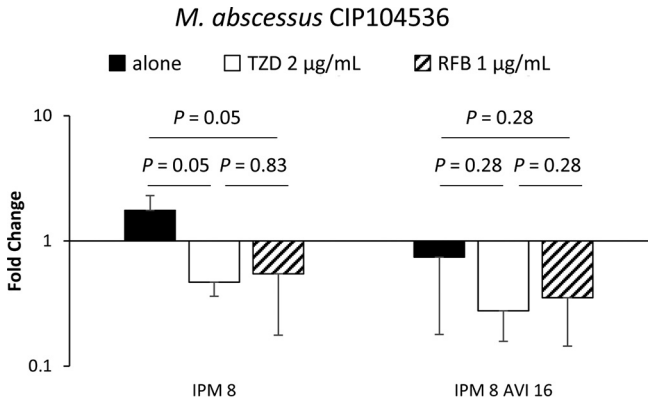

FIG 3 Impact of the addition of rifabutin (RFB) and tedizolid (TZD) on the activity of imipenem (IPM) alone and in combination with avibactam (AVI) against *M. abscessus* CIP104536 in the macrophage model. RFB 1 μg/ml and TZD 2 μg/ml were tested in combination with IPM 8 μg/ml alone and combined with AVI 16 μg/ml. CFU were enumerated after 4 days of incubation at 30°C by plating serial dilutions of macrophage lysates. Results are means ± standard deviations of three experiments.

combination, we tested whether inhibition of Bla_{Mab} by avibactam at 16 μg/ml would improve the intramacrophage activity of the combination against *M. abscessus* CIP104536 (Fig. 2B and Table S7 in the supplemental material). As previously described (18, 24), the activity of imipenem at 8 μg/ml was improved by avibactam, leading to a 0.32-fold change in the number of CFU. This fold change is similar to that observed for the imipenem-tedizolid combination (0.28-fold change). The triple combination comprising tedizolid, imipenem, and avibactam was the most active regimen, leading to 97% killing. Increasing the concentration of imipenem from 8 to 32 μg/ml did not improve the activity of the triple combination. In conclusion, the addition of avibactam significantly increases the activity of the imipenem-tedizolid combination when imipenem is used at a low concentration (8 μg/ml).

Since it was recently shown that rifabutin has promising activity against *M. abscessus* (24, 27), the second objective of our study was to compare the activity of tedizolid and rifabutin in the macrophage model and to evaluate whether combinations comprising these two drugs have a potential therapeutic interest (Fig. 3 and Table S8 in the supplemental material). Tedizolid and rifabutin were similarly active in improving the activity of imipenem alone (Fig. 3). Rifabutin at 1 μg/ml, corresponding to a concentration achievable in the serum, significantly improved the activity of the imipenem-avibactam-tedizolid triple combination (0.09- versus 0.28-fold change; $P = 0.05$) (Fig. S1 in the supplemental material and Table S8). Increasing the concentration of rifabutin (8 μg/ml) did not improve the activity of the quadruple combination (Fig. S1 and Table S8).

To explore the mechanism underlying the improved activity of imipenem at a low dose (8 μg/ml), when combined with tedizolid, we determined the β-lactamase specific activity in crude bacterial extracts by spectrophotometry at 480 nm using nitrocefin (100 μM) as the substrate. Growth of *M. abscessus* CIP104536 in the presence of subinhibitory concentrations of tedizolid (1and 2 μg/ml, corresponding to one-fourth and one-half of the MIC) decreased the β-lactamase specific activity from 50 ± 3 to 28 ± 6 nmol/min/mg ($P = 0.05$) and from 50 ± 3 to 14 ± 8 nmol/min/mg ($P = 0.03$), respectively. These results suggest that a decrease in the production of the β-lactamase Bla_{Mab} by subinhibitory concentrations of tedizolid may contribute to the antibacterial activity of the tedizolid-imipenem combination.

In conclusion, the assessment of the efficacy of drug combinations in the macrophage indicates that imipenem-avibactam-tedizolid-rifabutin should be clinically evaluated, particularly in infections caused by macrolide-resistant *M. abscessus*. However, avibactam is only available in combination with ceftazidime, and this cephalosporin would be administered without any benefit because it is not active against *M. abscessus*

(16). The advantage of tedizolid and rifabutin as potential therapeutic options for the treatment of lung infections in CF patients is also supported by the relatively good tolerance of these drugs and their oral route of administration. Tedizolid and rifabutin in particular should be considered alternatives to amikacin in the recommended treatment combining imipenem, azithromycin, amikacin, and tigecycline.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01915-18.

SUPPLEMENTAL FILE 1, PDF file, 0.6 MB.

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