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Challenges in achieving the guideline-recommended amikacin level for *Mycobacterium avium* complex pulmonary disease

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ABSTRACT

Background: The addition of aminoglycosides to a macrolide-based regimen is recommended for refractory *Mycobacterium avium* complex pulmonary disease (MAC-PD). For intravenous amikacin (AMK) administration three times a week, the ATS/ERS/ESCMID/IDSA guidelines recommend targeting a peak serum concentration of 65–80 μg/mL. However, the feasibility of achieving the guideline-recommended AMK concentration remains unclear.

Methods: From 2018 to 2022, we retrospectively analyzed patients with refractory MAC-PD treated with AMK thrice weekly for ≥3 months combined with an oral regimen of ≥2 drugs, including macrolides. The peak serum concentration and therapeutic effects of AMK were evaluated.

Results: The median age of the 9 patients was 70 years (range: 50–79 years; 2 men and 7 women). The causative organism was *M. avium* in all cases. All cases demonstrated susceptibility to AMK, which was administered at a median dose of 700 mg/day (15.8 mg/kg/day) for a median duration of 6 months. One patient experienced hearing loss, which led to AMK discontinuation at 4 months. The median AMK peak concentration was 47.1 μg/mL, with a tendency to be higher in the clinical efficacy group compared to the nonefficacy group. None of patient, except one, achieved the target AMK peak concentration.

Conclusions: In this preliminary study, the guideline-recommended AMK concentration for MAC-PD was not achieved in the majority of patients. Due to the small sample size and retrospective design, robust conclusions regarding the association between AMK concentrations and clinical outcomes could not be drawn. Prospective randomized controlled trials are required to better define the optimal AMK concentration for efficacy and safety.

Trial registration: Not applicable.

1. Introduction

In the last decade, the prevalence of nontuberculous mycobacteria (NTM) pulmonary disease, particularly *Mycobacterium avium* complex pulmonary disease (MAC-PD), has drastically increased and posed a significant clinical challenge [1]. When oral therapy fails to achieve culture conversion or in severe cases with cavitary lesions, intravenous amikacin (AMK) therapy is recommended. The official American Thoracic Society (ATS)/European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/Infectious Diseases Society of America (IDSA) clinical practice guidelines for NTM suggest targeting a maximum concentration of 65–80 μg/mL for AMK administered three times per week [2]. However, the optimal AMK dose remains unclear because of lack of evidence, especially in the setting of long-term (approximately 3–6 months) treatment for NTM diseases, which makes the validity of these recommendations uncertain [3–7]. This preliminary retrospective study aimed to determine the feasibility of achieving the guideline-recommended AMK concentration

Abbreviations: NTM, nontuberculous mycobacteria; MAC-PD, Mycobacterium avium complex pulmonary disease; AMK, amikacin; ATS, American Thoracic Society; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America.

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with or without dose adjustment using the standard dose of 15 mg/kg, administered thrice weekly, in patients with refractory MAC-PD. Additionally, it aimed to evaluate the relationship between serum AMK concentrations and treatment outcomes, while recognizing the limitations of the small sample size and retrospective study design.

2. Material and methods

The study was approved by the ethics committee of The Jikei University School of Medicine [approval number 34-208(11359), approval date: October 11, 2022]. Considering the retrospective nature of the study, informed consent was obtained using an opt-out method.

We initially screened 22 patients aged >18 years who received intravenous amikacin (AMK) treatment at The Jikei University Kashiwa Hospital from 2018 to 2022 (Fig. 1). Patients were evaluated based on the ATS/ERS/ESCMID/IDSA or British Thoracic Society guidelines and included if they were diagnosed with MAC-PD and required additional AMK treatment for refractory MAC-PD. Eligible patients were those with refractory MAC-PD, defined as persistent culture positivity with deterioration of radiological findings despite receiving >6 months of two or three oral drug combinations, including macrolides and ethambutol, in accordance with international guidelines [2,8]. Patients were excluded if they met any of the following criteria. (1) They were treated for general bacterial infections caused by non-mycobacteria or by non-MAC NTM (n = 6). (2) They received intravenous AMK treatment for less than 3 months (n = 2). (3) They underwent surgery concurrently with AMK administration (n = 2). (4) Their regimens did not include macrolides (n = 1). (5) Intravenous AMK and oral therapy were initiated concurrently, making it impossible to evaluate the effect of AMK alone (n = 1). (6) They had insufficient culture or radiological data (n = 1). (7) Evaluation was not possible due to less than 12 months of follow-up, including transfer to another hospital or death (n = 0). After applying these criteria, 9 patients with refractory MAC-PD were included in the analysis. These patients were treated with intravenous AMK thrice weekly for over 3 months alongside oral therapy with at least two drugs, including macrolides. Clinical data were obtained from electronic medical records.

The study variables included peak and trough AMK blood concentrations, measured under steady-state conditions after at least two administrations of the same dose. In six cases, blood concentrations were measured multiple times (2–4 times) based on the attending physician's discretion, primarily during the initiation phase of AMK treatment. However, due to insurance restrictions, measurements were performed only once in three cases. As a result, most measurements were conducted at the beginning of treatment, and continuous monitoring throughout the treatment period was not performed. Following standard clinical pharmacokinetic protocols, trough concentrations were measured immediately before the next administration, and peak concentrations were determined 1 h after the infusion. In principle, AMK concentrations were measured only once at the same dose. Other variables included imaging findings, sputum mycobacterial test results, side effects such as renal dysfunction and hearing impairment, and the minimum inhibitory concentration of AMK against the causative agents, determined according to the Clinical and Laboratory Standards Institute M24 guidelines [9]. The causative organisms isolated from sputum were identified using matrix-assisted laser desorption ionization–time of flight mass spectrometry.

3. Results

Of the 22 cases retrieved during the study period, 9 patients were eligible for inclusion. As shown in Table 1, the cohort included 2 men and 7 women with 70 years (range: 50–79 years) as the median age of the patients. The causative organism was *M. avium* in all cases. The types of MAC-PD were nodular bronchiectatic in three cases, cavitary nodular bronchiectatic in one case, and fibrocavitary in five cases. Among the cases, six were susceptible and three were resistant to clarithromycin. All isolated organisms were susceptible to AMK. The median creatinine clearance (CrCl) was 66.9 mL/min. AMK was administered at a median dose of 700 mg/day (range: 500–900 mg) or 15.8 mg/kg/day (range: 13.1–23.5 mg/kg/day) for a median duration of 6 months (range: 4–8 months).

Fig. 2a illustrates the maximum AMK concentration observed at the final AMK dose for each case, while Fig. 2b presents the peak AMK concentrations at each dose adjustment. At the final AMK dose, none of the patients, except one, reached the guideline-recommended peak serum AMK concentration. In most cases, the AMK concentration increased proportionally with the dose per body weight, as shown in

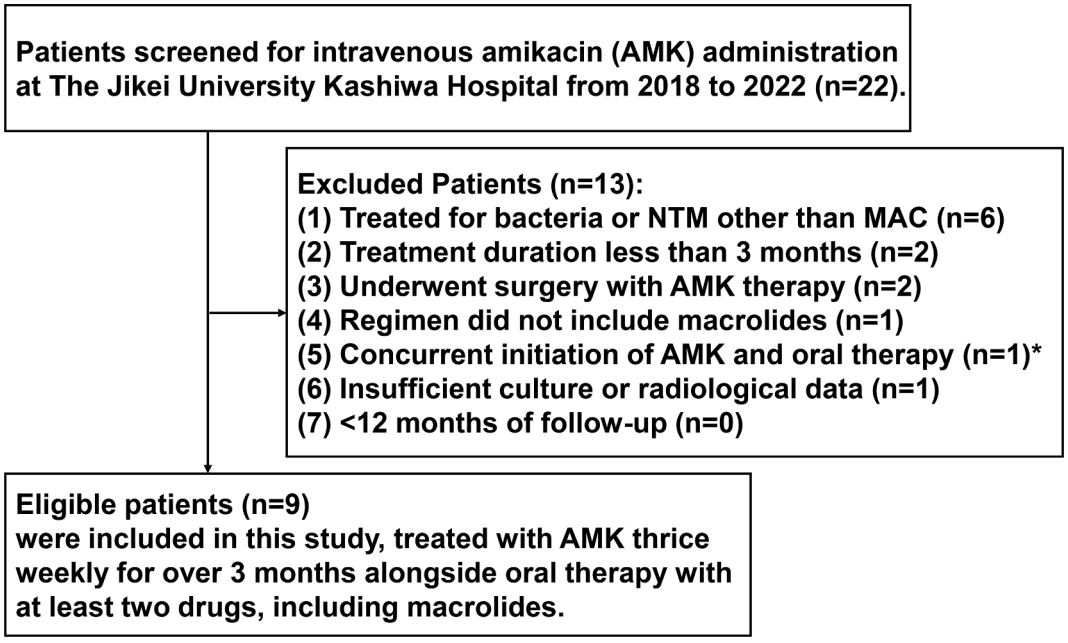

Fig. 1. Flow diagram of patient selection for analysis. Screening of patients with *Mycobacterium avium* complex pulmonary disease treated with amikacin, detailing exclusions based on predefined criteria.

Table 1
Patient profiles and microbiological data in this study (N = 9).

Median age (years)	70
range	50–79
Sex	
men	2 (37.5 %)
women	7 (62.5 %)
Species	
Mycobacterium avium	9 (100 %)
Mycobacterium intracellurare	0 (0 %)
Radiologial pattern	
nodular-bronchiectatic pattern	3 (33.3 %)
cavitary nodular-bronchiectatic pattern	1 (11.1 %)
fibrocavitary pattern	5 (55.6 %)
Drug susceptibility	
AMK	
Susceptible	9 (100 %)
Resistant	0 (0 %)
CAM	
Susceptible	6 (66.7 %)
Resistant	3 (33.3 %)
IV AMK dose	
Median (range) mg/body/day	700 (500–900)
Median (range) mg/kg/day	15.8 (13.1–23.5)
Duration of IV AMK (months)	6 (4–8)
CrCl (mL/min)	66.9

Continuous variables, including age, drug dose, duration, and CrCl, are presented as medians with interquartile range in parentheses. Discrete variables, such as sex, species, radiological patterns, drug susceptibility, and adverse events, are presented as numbers with percentages of the total in parentheses.
AMK: amikacin, CAM: clarithromycin, IV: intravenous, CrCl: creatinine clearance.

Fig. 2b. In case 2, the second course of AMK treatment led to cumulative toxicity, manifesting as dizziness. To mitigate this, the attending physician reduced the dose to prioritize patient safety, as indicated by the dotted line in Fig. 2b. By contrast, in case 3, the AMK concentration failed to increase despite dose escalation, indicating pharmacokinetic variability. The trough concentration was 1.0 μg/mL in one patient and <0.7 μg/mL in rest of the patients. As shown in Fig. 3, the peak AMK concentration, analyzed using the Mann–Whitney *U* test, did not significantly differ between the group with radiological improvement and the group with radiological worsening ($p = 0.26$) and between the group with sputum smear or culture conversion and the group without sputum conversion ($p = 0.17$).

As shown in Supplement 1, no remarkable deterioration in CrCl was observed (Wilcoxon matched-pairs signed-rank test, $p = 0.64$). One patient experienced hearing loss as an adverse event after 4 months of treatment, despite an AMK trough level of <0.7 μg/mL and peak level of 44.8 μg/mL, which were considered relatively low.

4. Discussion

In refractory MAC-PD, addition of aminoglycoside is recommended, because massive hemoptysis or chronic respiratory failure can be fatal, and failure to achieve sputum culture conversion worsens prognosis [2,10]. Although inhaled AMK liposome suspension therapy is useful for refractory MAC-PD [11], intravenous AMK therapy remains an important option [2]. Among the previous reports that investigated the AMK concentration for the treatment of mycobacterial diseases, none evaluated the association between AMK concentration and efficacy for MAC-PD, because these studies mainly focused on AMK dose, not Cmax, and toxicity (Table 2) [3–5,7]. Therefore, we conducted this preliminary study to explore the association between AMK concentration and efficacy for refractory MAC-PD treatment.

Although the AMK concentration increased in a dose-dependent manner, the guideline-based target peak AMK concentration was not achievable in this cohort except in one case. The median peak AMK concentration was 47 μg/mL, and there was no statistically significant difference between the clinical efficacy and nonefficacy groups. These findings raise the question of whether the proposed target peak AMK concentration is universally achievable or optimal for radiological and microbiological improvement. However, it is important to note that only one patient in this study achieved the guideline-recommended target concentration, which limits the ability to draw definitive conclusions about the correlation between achieving the target concentration and treatment outcomes. Furthermore, as therapeutic drug monitoring was primarily conducted during the initiation phase of AMK treatment, the findings regarding the maintenance of therapeutic concentrations throughout the entire treatment period remain speculative, limiting insights into long-term maintenance of therapeutic concentrations. This underscores the need for further prospective studies with larger sample sizes to rigorously evaluate the relationship between AMK concentration and its clinical efficacy, as well as to assess the feasibility of achieving the guideline-recommended target concentration in diverse patient populations. The observations in this study can be attributed to several factors. First, the small sample size might not have provided sufficient power to detect statistically significant differences in peak AMK concentrations between the groups. Second, individual variability in pharmacokinetics and pharmacodynamics can lead to different responses, even in the setting of similar peak AMK concentrations, regardless of AMK susceptibility. Targeting the currently recommended peak AMK concentration may improve clinical outcomes, but it may increase the risk of adverse effects, such as nephrotoxicity and ototoxicity.

Peloquin et al demonstrated that the incidences of ototoxicity and nephrotoxicity did not significantly differ between different dosing regimens (15 mg/kg daily vs. 25 mg/kg three times weekly) over a median treatment duration of 15 weeks [3], although the cumulative

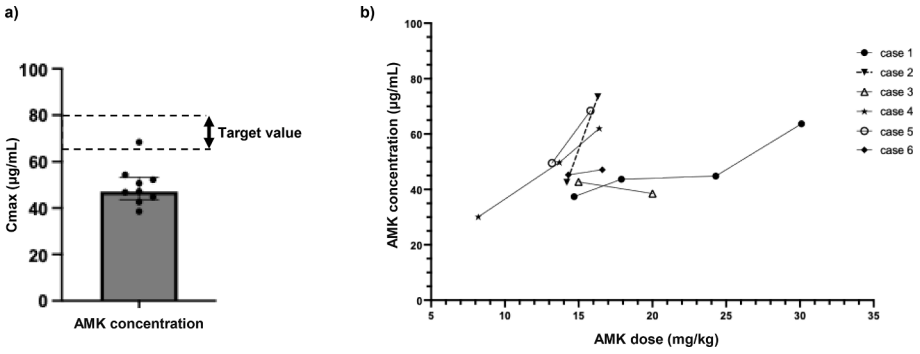

Fig. 2. Maximum AMK concentration data. a) Maximum blood AMK concentration observed at the final AMK dose for each case. None of the patients, except one, reached the guideline-recommended peak serum AMK concentration. b) Peak AMK concentrations at each dose adjustment. The increase in AMK concentration was generally proportional to the dose per body weight. In case 2, the AMK dose was reduced (dotted line) during the second course of treatment due to cumulative toxicity causing dizziness. By contrast, case 3 showed pharmacokinetic variability, with AMK concentration failing to increase despite dose escalation. AMK: amikacin.

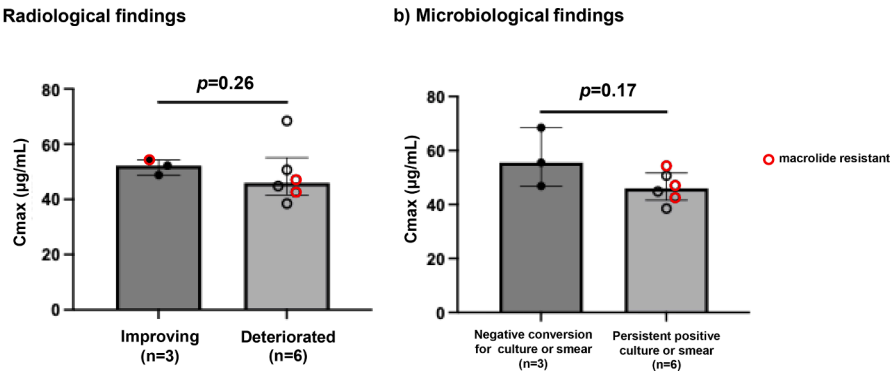

Fig. 3. Correlation of AMK peak concentration with radiological and microbiological improvement. The AMK peak concentration is not significantly different between the group with radiological improvement and the group with deterioration (a) and between the group with microbiological improvement and the group without microbiological improvement (b), although the median concentration is slightly higher in the clinically improved group compared to the group without clinical improvement (Mann–Whitney *U* test). The macrolide-resistant cases are indicated by red circles. AMK: amikacin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of studies on intravenous amikacin concentration for mycobacterial pulmonary infection.

	n	Species(strain numbers)	Dose	Duration	Cmax(μg/mL)	Cmin(μg/mL)	Efficacy/Toxicity
Peloquin et al. 2004 [3]	11	*M. tuberculosis* (2) *M. avium* (5) other NTM (4)	15 mg/kg/day, median 800 mg (600–1,400 mg)/day daily	16 (1–22) weeks	46(26–54)	ND	ND/D
	11	*M. tuberculosis* (2) *M. avium* (7)other NTM (2)	25 mg/kg/day, median 1,300 mg (1,100–1,900 mg)/day thrice weekly	23 (2–43) weeks	79(54–98)	ND	ND/D
Ellender et al. 2016 [4]	45	*M. avium* (6)*M. intracellulare* (25) *M. abscessus* (13)other NTM (1)	22 mg/kg/day (IQR 14–25)thrice weekly	8.6 (±4.5) weeks	ND	1.06 (±1.5)	D/D
Lyu et al. 2011 [5]	41	*M. abscessus* (41)	15 mg/kg/day(maximum 1,000 mg/day)	230 (60–601) days	ND	ND	D/D
Aznar et al. 2019 [7]	107	*M. avium* complex (69)*M. abscessus* (21) other NTM(17)	9.5 (8.3-10.4) mg/kg/day thrice weekly	28 (16–44) weeks	ND	ND	D/D

NTM: nontuberculous mycobacteria, Cmax: maximum concentration, Cmin: minimum concentration, IQR: interquartile range, ND: not described, D: described.

AMK dose was significantly associated with ototoxicity. In another study, Aznar ML et al demonstrated that a median AMK dose of >1.81 g/kg (interquartile range: 0.85–3.13 g/kg) was associated with a risk of ototoxicity [7]. In this study, one patient previously received two AMK treatments, which resulted in a cumulative dose of 1.1 g/kg and dizziness; although the AMK peak concentration reached the target value (73.5 μg/mL), the decision was to reduce the AMK dose. Considering the insights from the aforementioned reports and the results of this study, achieving a target Cmax with high-dose AMK can be feasible for short-term therapy but may not be realistic for longer and repeated AMK treatment. One patient in this study experienced auditory impairment after the first AMK treatment at a dose and peak and trough concentrations that were not high; the etiology of this impairment remains undetermined. This suggested the importance of audiogram monitoring and medical interviews pertaining to 8th cranial nerve disorders, such as hearing loss and balance issues, even in patients receiving AMK doses below the cumulative risk threshold for ototoxicity. Although, one patient temporarily achieved culture conversion and completed six months of treatment with the target AMK peak concentration, the patient experienced recurrence of sputum positivity and deterioration in radiological findings within six months after the conclusion of treatment, which necessitates AMK readministration. Consequently, the optimal AMK peak concentration and the appropriate duration of AMK intravenous therapy warrant further investigation and discussion.

Future randomized controlled trials with larger sample sizes are needed to determine the optimal target concentration to achieve better clinical outcomes without increasing adverse events. Moreover, comparing different AMK concentrations and investigating other pharmacokinetic parameters, such as area under the curve, may provide a more comprehensive understanding of the efficacy and safety of AMK for the treatment of MAC-PD.

5. Conclusions

This preliminary study showed that the guideline-recommended AMK concentration for MAC-PD was rarely achieved. This limitation hindered the ability to evaluate significant relationships between AMK concentrations and treatment outcomes. Prospective randomized controlled trials focusing on NTM pulmonary diseases are warranted to determine the optimal serum concentration of intravenous AMK for both efficacy and safety.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI or AI-assisted technologies were used in the preparation of this manuscript.

CRediT authorship contribution statement

Takuya Akutsu: Writing – original draft, Data curation. **Kazuya Tone:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Airi Hasegawa:** Writing – review & editing. **Takaaki Kitayama:** Writing – review & editing. **Shunsuke Inaki:** Writing – review & editing. **Mina Gochi:** Writing – review & editing. **Masamichi Takagi:** Writing – review & editing. **Jun Araya:** Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Kazuya Tone reports writing assistance was provided by Enago. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper].

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Ethical approval

The ethics committee of The Jikei University School of Medicine approved this study [approval number 34-208(11359), approval date: October 11, 2022]. Informed consent was obtained using an opt-out method because of the retrospective nature of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2025.100514.

References

[1] Namkoong H, Kurashima A, Morimoto K, Hoshino Y, Hasegawa N, Ato M, et al. Epidemiology of pulmonary nontuberculous mycobacterial disease. Japan Emerg Infect Dis 2016;22:1116–7.
[2] Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace Jr RJ, Andrejak C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 2020;56.
[3] Peloquin CA, Berning SE, Nitta AT, Simone PM, Goble M, Huitt GA, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. Clin Infect Dis 2004;38:1538–44.
[4] Ellender CM, Law DB, Thomson RM, Eather GW. Safety of IV amikacin in the treatment of pulmonary non-tuberculous mycobacterial disease. Respirology 2016;21:357–62.
[5] Lyu J, Jang HJ, Song JW, Choi CM, Oh YM, Lee SD, et al. Outcomes in patients with Mycobacterium abscessus pulmonary disease treated with long-term injectable drugs. Respir Med 2011;105:781–7.
[6] Albin OR, Kaye KS, McCreary EK, Pogue JM. Less is more? Antibiotic treatment duration in Pseudomonas aeruginosa ventilator-associated pneumonia. Clin Infect Dis 2023;76:745–9.
[7] Aznar ML, Marras TK, Elshal AS, Mehrabi M, Brode SK. Safety and effectiveness of low-dose amikacin in nontuberculous mycobacterial pulmonary disease treated in Toronto. Canada BMC Pharmacol Toxicol 2019;20:37.
[8] C.S. Haworth, J. Banks, T. Capstick, A.J. Fisher, T. Gorsuch, I.F. Laurenson, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017;72:ii1-ii64.
[9] Clsi. M24-A: susceptibility testing of mycobacteria, Nocardia, and other aerobic actinomycetes; approved standard. Wayne, PA: Clinical and Laboratory Standards Institute; 2003.
[10] Lee JK, Kim S, Chong YP, Lee HJ, Shim TS, Jo KW. The association between sputum culture conversion and mortality in cavitary Mycobacterium avium complex pulmonary disease. Chest 2024;S0012–3692(24):00397.
[11] Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study. Am J Respir Crit Care Med 2018;198:1559–69.