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Pharmacokinetics and Tolerability of Once Daily Double Dose Tobramycin Inhalation in Cystic Fibrosis Using Controlled and Conventional Nebulization

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Abstract

Background: Better treatment outcomes in cystic fibrosis (CF) may be expected by changing standard twice daily (BID) tobramycin inhalation with the conventional nebulizer to once daily (OD) inhalation at double the standard BID dose with a controlled-inhalation nebulizer. We aimed to determine the pharmacokinetics and tolerability of inhaled double-dose tobramycin with the controlled-inhalation AKITA[®] and conventional PARI-LC[®] Plus nebulizer in patients with CF.

Methods: Randomized, open label, crossover study. Pharmacokinetics were assessed in 10 adult CF patients following inhalation of tobramycin (Bramitob[®]) at double the recommended BID dose with the AKITA (300 mg fill dose) and PARI-LC Plus (600 mg fill dose).

Results: No significant differences were found in pharmacokinetic parameters between the two nebulizers. Median maximum serum levels were 3.44 (2.25–5.49) and 2.84 (0.82–6.63) mg/L for AKITA and PARI-LC Plus, respectively. Trough serum levels were very low for both nebulizers: 0.03 (0.00–0.09) and 0.02 (0.00–0.06) mg/L for AKITA and PARI-LC Plus, respectively. Time to maximum level was comparable: 0.44 (0.08–0.96) and 0.40 (0.08–0.96) hours for AKITA and PARI-LC Plus, respectively. Serum levels were well below the toxic limit. Inhalations were well tolerated and no serious adverse events occurred. Nebulization time was 33% shorter with the AKITA.

Conclusions: OD tobramycin inhalation of the double standard BID dose with a controlled-inhalation and conventional nebulizer resulted in similar pharmacokinetics in the doses given, with serum levels below the toxic limit. Further research demonstrating clinical efficacy and safety of this treatment approach is required. Dutch trial register number NTR4525.

Key words: cystic fibrosis, inhaled therapy, nebulizer, small airways

Introduction

SMALL AIRWAYS DISEASE (SAD), mainly caused by chronic infections with *Pseudomonas aeruginosa* (*Pa*), plays an important role in the pathophysiology of cystic fibrosis (CF).^(1,2) *Pa* infections are often treated with inhaled tobramycin. Unfortunately, small airways are difficult to target

with standard nebulizer therapy. With the controlled-inhalation AKITA nebulizer, lung deposition of 70% of the loaded dose is reached, compared to approximately 10%–15% with standard nebulizer therapy.^(3–5) Moreover, nebulization with the AKITA results in an increased deposition in the small airways,⁽⁶⁾ which might lead to improved treatment of SAD.⁽¹⁾

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Current standard therapy of chronic *Pa* lung infection requires twice daily (BID) 300 mg tobramycin inhalation with the conventional PARI-LC Plus nebulizer. Nevertheless, various dosage regimens were investigated, with dosages ranging from 80 mg twice daily to 600 mg thrice daily,^(7,8) and other nebulizers than the standard nebulizer are used in daily practice. The bactericidal efficacy of tobramycin is known to be concentration-dependent and there is a post-antibiotic effect.⁽⁹⁾ As a consequence, inhalation of the complete daily dose in a single inhalation may have advantages over delivering the dose in two sessions and might also reduce adaptive resistance. For intravenous use, tobramycin once daily (OD) has already been shown to be as effective as thrice daily administration,⁽¹⁰⁾ and to result in less toxicity.⁽¹¹⁾ Specific targeting of SAD with the AKITA nebulizer in routine CF care may improve bacterial killing even better by delivering a higher fraction of the drug in the targeted lung region. Moreover, OD instead of BID inhalation will most likely improve adherence. Therefore, changing standard BID tobramycin nebulization to OD nebulization with the AKITA nebulizer might lead to better treatment outcomes in patients with CF.

However, tobramycin is potentially toxic with a narrow therapeutic index, and high trough levels can lead to nephro- and ototoxicity. Although this risk is considerably lower for nebulized compared to parenteral administered tobramycin, since only 9%–17.5% of the nominal dose is systemically absorbed after inhalation,⁽⁷⁾ doubling the dose can theoretically result in higher serum levels and there are some case reports available of inhaled tobramycin related toxicity.^(12–15)

It is not entirely clear if increased deposition in the small airways with the AKITA does have a significant impact on pharmacokinetics, as tobramycin is likely to be absorbed with similar kinetics from the (large) airways and alveoli. Therefore, before initiating a long-term efficacy and safety study investigating OD tobramycin inhalation at double the standard BID dose in patients with CF, it is necessary to determine pharmacokinetics and tolerability of this dosing scheme first. To our knowledge, OD dosing of inhaled tobramycin delivered by the PARI-LC Plus or AKITA nebulizer has never been studied. Two studies investigated the pharmacokinetics of a single inhalation of 600 mg tobramycin in patients with CF.^(16,17) However, these studies used different nebulizers and tobramycin solutions compared to the present study, so data cannot simply be extrapolated.

The aim of this study was to determine the pharmacokinetics and tolerability of OD inhalation of the double recommended tobramycin dose with the controlled-inhalation AKITA and the conventional PARI-LC Plus nebulizer in patients with CF.

Materials and Methods

Patients and study design

In a randomized, open-label, crossover study, pharmacokinetics of inhaled tobramycin were assessed in 10 consecutively selected adult CF patients, following a single inhalation of the double recommended dose with the conventional PARI-LC Plus and the controlled-inhalation AKITA nebulizer. The study consisted of two separate visits

for tobramycin inhalation in random order, separated by at least a week washout period.

The study was performed in the Centre for Cystic Fibrosis, Haga Teaching Hospital, The Hague, The Netherlands, between March and June 2014. Inclusion criteria were: age 18 years or older, confirmed diagnosis of CF (genetic analysis) and chronic *Pa* infection. Exclusion criteria were: acute pulmonary exacerbation requiring intravenous treatment; intravenous tobramycin; aminoglycoside hypersensitivity; impaired renal function (estimated glomerular filtration rate (eGFR) <60 mL/min); use of loop diuretics; and pregnancy or lactation. Chronic tobramycin inhalation therapy was stopped at least 3 days prior to the first study visit.

This work was approved by the local ethics committee (METC Zuidwest Holland, The Netherlands, METC nr 13-097), the Central Committee on Research Involving Human Subjects (CCMO, The Hague, The Netherlands) and was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients.

Nebulization

Bramitob (4 mL = 300 mg tobramycin, Chiesi Pharmaceuticals B.V., Rijswijk, The Netherlands) was used as investigational drug. Bramitob is licensed for use with the PARI-LC Plus nebulizer, with a recommended fill dose of 300 mg (BID). Dose recommendation for the AKITA is 150 mg tobramycin for inhalation (BID). This is based on *in vivo* study data that showed an equal predicted lung dose when comparing filling doses of 150 mg tobramycin with the AKITA to 300 mg with the PARI-LC Plus. This corresponded to nebulized doses of 60 mg with the AKITA and 240 mg with the PARI-LC Plus.⁽¹⁸⁾

In the present study, patients inhaled the double recommended tobramycin dose in one inhalation, corresponding to 300 mg with the AKITA and 600 mg with the PARI-LC Plus nebulizer. Taking deposition rates of 70% of the nebulized dose for the AKITA and 15% for the PARI-LC Plus nebulizer, we expected this to relate to a deposited dose of 84 mg for the AKITA and 72 mg for the PARI-LC Plus.

The PARI-LC Plus (PARI GmbH, Starnberg, Germany) is a reusable breath-enhanced jet nebulizer that was combined with the PortanebTM compressor (Philips Respironics, Chichester, UK). Patients operated the compressor and inhaled until “sputtering.” The AKITA system (combined with a PARI-LC SPRINT nebulizer, Vectura GmbH, Gemünden, Germany) is a controlled-inhalation device that allows aerosol production during inspiration only. The AKITA directs the flow and depth of each inhalation by coaching the patient in correct inhalation technique. In this study, the device was programmed to preferentially target the small airways. Prior to the actual controlled inhalation, patients were trained on how to inhale with the AKITA nebulizer. The inhalation volume was individualized for each patient and was stored on an individual smart card, which was inserted into the device. Inhalation flow rate was fixed at 200 mL/second. The patient received constant feedback on his/her inhalation performance to maintain a slow and deep inhalation, which allowed improved small airways targeting.

Nebulization time, defined as the time from turning on the compressor until “sputtering” (PARI-LC Plus) or starting and switching off the device (AKITA) was measured.

Spirometry

Spirometry (Jaeger Masterscreen PFT, CareFusion, Hoechberg, Germany) was performed before and 15 minutes after inhalation according to the ATS/ERS guidelines.⁽¹⁹⁾ Measured parameters were: forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), and forced expiratory flow 25%–75% (FEF_{25–75}). Prediction equations of the Global Lung Function Initiative were used (Quanjer GLI-2012 equations).⁽²⁰⁾ Post dose measurements were compared to baseline values to detect potential bronchospasm following high dose tobramycin inhalation. Clinically significant bronchospasm was defined by a 20% or more reduction in FEV₁.^(21,22)

Blood sampling

A venous blood sample was taken before inhalation to measure kidney function. Dried blood spots (DBS) using a finger prick were collected before ($t=0$) and 30, 60, and 90 minutes after completion of inhalation for tobramycin analysis. Patients collected additional dried blood spots at home, 3 and 24 hours after inhalation.⁽²³⁾ To prevent contamination of tobramycin on the blood spot paper or the patient's fingers, several precautions were taken: 1) patients were not allowed to fill their nebulizers with medication themselves, 2) nebulization was performed in a different room than where the blood spots were collected, 3) before each finger prick, patients had to wash their hands thoroughly with warm water and soap.

Tobramycin analysis

Tobramycin was measured in the blood samples with a DBS assay using high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS/MS).⁽²⁴⁾ The lower limit of quantification (LLOQ) was 0.1 mg/L with a coefficient of variation of <2.2%. The DBS assay was previously developed in our laboratory and validated with venous blood samples from CF patients.

Pharmacokinetic analysis

Individual pharmacokinetic parameters were calculated and assimilated with patient tobramycin serum values using a computerized CF-based two-compartment population pharmacokinetic model (MW-Pharm version 3.60, Mediware, Groningen, The Netherlands).⁽²⁵⁾ Data on the patients' gender, age, height, weight, kidney function, and tobramycin dosages were used to calculate the following parameters: maximum serum level ($C_{\max}$), trough serum level 24 hours after nebulization (C_{trough}), time to $C_{\max}$ ($T_{\max}$), and area under the concentration-time curve from 0 to 24 hours ($AUC_{0-24\text{hr}}$).

Systemic absorption can be used as safety signal. Based on once daily intravenous administration, a tobramycin trough level below 1 mg/L is considered to be safe.⁽¹⁰⁾ No clear toxic limits have been defined for tobramycin inhalation yet.

Tolerability and nebulizer satisfaction

Adverse events were monitored. Furthermore, patients were asked to answer questions regarding tolerability of the two inhalations and nebulizer satisfaction.

Statistical analysis

Statistical analysis was performed with SPSS version 17.0 (PASW Statistics, IBM Corporation, Armonk, USA). Paired *t*-tests were used to compare differences between the two nebulizers and study visits. The Wilcoxon Signed Ranks Test was used when data were not normally distributed. *P* values below 0.05 were considered statistically significant.

Results

Patients

Ten patients with CF were included in the study (Table 1). Overall, there were no significant differences in eGFR, FEV₁, FVC and FEF_{25–75}% predicted between the two study visits (respectively, $p=0.557$, $p=0.702$, $p=0.102$ and $p=0.414$).

Pharmacokinetics

The individual calculated pharmacokinetic parameters are summarized in Table 2. No significant differences were found in $C_{\max}$, C_{trough} , $T_{\max}$, and $AUC_{0-24\text{h}}$ between the controlled and conventional inhalation. Lower variability in serum concentration was found with the AKITA, illustrated by a lower coefficient of variation (Table 2). C_{trough} was well below the toxic limit for both nebulizers and for all patients. Figure 1 shows the serum concentration-time curves for individual patients after tobramycin nebulization with both nebulizers.

Nebulization time

Mean nebulization time was significantly shorter ($p=0.005$) with the AKITA (19.20 ± 7.50 min) compared to the PARI-LC Plus (29.50 ± 4.85 min). Except for Patient 2, all patients had a shorter treatment time with the AKITA. During observation, it was noticed that Patient 2 did not actively inhale with the AKITA all the time. This explains the higher treatment time since aerosol is only delivered when the patient is actively inhaling and until the preset dose is attained.

Tolerability

Overall, no clinically relevant declines in FEV₁ values were seen 15 min after completion of nebulization. Individual changes in FEV₁ values from baseline are shown in the Supplementary Table S1 (supplementary material is available online at www.liebertpub.com/jamp).

Nebulizations of tobramycin were well tolerated by all patients with both nebulizers and no major adverse events were reported (Table 3). Patients reported more side effects during nebulization with the PARI-LC Plus than with the AKITA. Dislike of taste was reported most often (60%) for this nebulizer. One patient reported mild dyspnea, however, he did not have a significant change in lung function

TABLE 1. PATIENT CHARACTERISTICS

Patient	Sex	Age (year)	Height (cm)	Weight (kg)	eGFR ^a (ml/min)	FEV ₁ ^a (% predicted)	FEF ₂₅₋₇₅ ^a (% predicted)
1	M	28	175	72	118	86	64
2	M	59	188	93	83	70	56
3	M	36	181	68	126	28	7
4	F	52	163	50	91	53	22
5	M	29	180	65	91	36	10
6	M	23	188	73	137	90	78
7	M	50	179	60	106	52	18
8	F	26	166	55	93	79	43
9	M	22	180	66	94	71	68
10	F	36	157	59	128	61	19
Median		32.5	179.5	65.5	100.0	65.7	32.4
Range		22-59	157-188	50-93	83-137	28-90	7-78

eGFR, estimated glomerular filtration rate based on Modification of Diet in Renal Disease (MDRD) equation; FEV₁, forced expiratory volume in the first second; FEF₂₅₋₇₅, forced expiratory flow 25-75%.

^aAverage baseline values of study visit 1 and 2.

measurements after nebulization (FEV₁% predicted 78% before vs. 76% after nebulization).

Patient 3 suffered from a viral infection at the second study visit (PARI-LC Plus) with increased cough, sputum, and mild deterioration of lung function (FEV₁% predicted 30% at visit 1 vs. 26% at visit 2). He did not require intravenous treatment and thus did not have to be excluded from the study. However, to prevent bronchospasm on top of his cold, salbutamol was administered before start of tobramycin nebulization of the study medication. The nebulization was well tolerated and his post dose FEV₁ measurement remained the same as at baseline.

Nebulizer satisfaction

Responses on the questions regarding nebulizer satisfaction are shown in Table 3. Patients tended to be more positive for the AKITA than for the PARI-LC Plus. However,

most patients preferred their own inhalation device for tobramycin over one of the study nebulizers (90%). Inhalation devices used at home were the I-neb (40%), eFlow (40%), and TOBI Podhaler (20%). One patient (10%) preferred the PARI-LC Plus over his own device for tobramycin inhalation. This patient already used the PARI-LC Plus for home treatment as a back-up nebulizer. Almost all patients preferred OD inhalation of a double tobramycin dose over BID inhalation of the standard dose (90%).

Discussion

This is the first study investigating the pharmacokinetics and tolerability of once daily inhalation of the double recommended dose of tobramycin with the AKITA and the PARI-LC Plus nebulizer in patients with CF. The main finding is that similar pharmacokinetics were assessed for OD tobramycin inhalation with the AKITA and the PARI-

TABLE 2. PHARMACOKINETIC RESULTS AFTER CONTROLLED INHALATION (AKITA; 300 MG FILL DOSE) AND CONVENTIONAL INHALATION (PARI-LC PLUS; 600 MG FILL DOSE)

Patient	AKITA				PARI-LC Plus			
	C _{max} (mg/L)	C _{trough} (mg/L)	T _{max} (h)	AUC _{0-24h} (h.mg/L)	C _{max} (mg/L)	C _{trough} (mg/L)	T _{max} (h)	AUC _{0-24h} (h.mg/L)
1	2.71	0.00	0.16	9.57	2.19	0.00	0.24	8.17
2	2.85	0.04	0.96	9.08	1.61	0.02	0.96	5.36
3	3.26	0.00	0.40	9.40	0.82	0.00	0.40	3.42
4	3.14	0.09	0.48	14.05	2.65	0.06	0.40	12.04
5	4.48	0.05	0.24	12.90	5.85	0.05	0.08	15.31
6	3.61	0.03	0.64	10.67	3.02	0.03	0.80	9.26
7	3.69	0.01	0.32	14.83	5.46	0.01	0.16	17.65
8	5.49	0.03	0.56	12.76	4.42	0.03	0.64	11.15
9	4.53	0.00	0.40	11.74	6.63	0.00	0.40	16.14
10	2.25	0.05	0.80	7.21	0.97	0.02	0.80	3.62
Median	3.44	0.03	0.44	11.21	2.84	0.02	0.40	10.21
Range	2.25-5.49	0.00-0.09	0.08-0.96	7.21-14.83	0.82-6.63	0.00-0.06	0.08-0.96	3.42-17.65
CV (%)	27.34	96.86	50.32	21.73	62.42	95.35	61.07	50.45
<i>p</i>	0.721	0.102	0.748	0.445				

C_{max}, maximum serum level; C_{trough}, trough serum level, 24 h after nebulization; T_{max}, time to maximum serum level; AUC_{0-24h}, area under the concentration-time curve from 0 to 24 h.

CV, coefficient of variation. *P* values were calculated with the Wilcoxon Signed Ranks Test.

FIG. 1. Serum concentration-time curves for all patients after tobramycin inhalation with the two nebulizers. P, patient number; number position in the graph corresponds with maximum serum concentration reached.

LC Plus nebulizer in the doses given, with serum levels that were not toxic. Furthermore, both inhalations were well tolerated, although patients reported more side effects during nebulization with the PARI-LC Plus. All reported side effects are well-known for inhaled tobramycin and described in the manufacturer product information.

When comparing the pharmacokinetics of OD tobramycin inhalation in this study to pharmacokinetic data from the literature regarding standard BID inhalation with the PARI-LC Plus, we found higher peak levels in our study, while trough levels were low. Mean serum peak levels in literature range from 0.7–1.3 mg/L, compared to 3.4 mg/L and 3.6 mg/L with the PARI-LC Plus and AKITA, respectively, in our study population.^(21,22,26,27) Nephrotoxicity is linked to trough levels above 2 mg/L, while levels above 4 mg/L and high cumulative exposure to aminoglycosides are associated with ototoxicity.^(28,29) The very low trough levels found in our study population indicate that OD inhalation of a double tobramycin dose has an acceptable safety profile. Hence, considering the concentration-dependent bactericidal efficacy of tobramycin, the OD treatment regimen proposed in our study might result in better efficacy of tobramycin therapy in patients with CF, without the occurrence of acute toxicity.

The mean nebulization time was significantly shorter with the AKITA than with the PARI-LC Plus. This was to be expected, considering the reduced volume of drug needed for nebulization with the AKITA. The results from the questionnaire showed that 30% of patients thought nebulization with the PARI-LC Plus took too long, while none of the patients indicated that AKITA nebulization was too long. Interestingly, almost all patients preferred OD nebulization with a longer duration over BID nebulization with a shorter duration.

The most commonly reported side effect, ‘a dislike of taste’, was only reported for nebulization with the PARI-LC Plus. This can probably be explained by increased deposition of tobramycin in the oropharyngeal region when nebulizing with the PARI-LC Plus due to continuous aerosol production during inspiration and expiration.⁽³⁰⁾ Even though dislike of taste is not severe, it does increase the treatment burden for patients.

When asking the patients’ impression, most patients were more satisfied with the AKITA than with the PARI-LC Plus,

but preferred their own inhalation device for tobramycin over one of the study nebulizers. Shorter treatment times with their own nebulizer might be the explanation for this. Especially tobramycin inhalation powder requires significantly less time than nebulized tobramycin.⁽³¹⁾ However, the AKITA is known to have an increased deposition in the small airways.⁽⁶⁾ The deposition pattern for tobramycin is less well described for other nebulizers nor the powder inhaler.⁽³²⁾

Limitations

The fact that patients preferred their own inhalation device over one of the study nebulizers can be seen as a limitation of the study design. As seen in our cohort, the PARI-LC Plus nebulizer is not commonly used in routine CF care anymore, as it is considered less effective compared to newer nebulizers. However, as tobramycin solution for inhalation is licensed with the PARI-LC Plus nebulizer, we have chosen to compare the controlled-inhalation to the standard nebulizer. Our study design did not include the gold standard for *Pa* infections, which is BID nebulization of 300 mg tobramycin. However, it was not our aim to compare the new dosing regimen to the gold standard, but to determine the pharmacokinetics of a higher dose.

From the results of this study, no concrete statements about efficacy and safety can be made, since it was a single dose study with a small sample size. Although a sample size of 6 to 16 patients is common in this type of pharmacokinetic studies,^(16–18,22,33,34) it should be kept in mind when applying the OD treatment regimen in clinical practice and also warrants the need for further research.

The exact inhaled dose of tobramycin was not measured in this study. The smartcard inserted in the AKITA nebulizer was set to deliver a specified dose of 120 mg to the lungs to achieve bioequivalence to the PARI-LC Plus. Unfortunately, the lung dose for the PARI-LC Plus was unknown. To make the most reliable comparison, we have used the filling doses of both nebulizers for calculation of the results.

Finally, one patient (#3) received salbutamol before start of tobramycin nebulization with the PARI-LC Plus to prevent bronchospasm on top of his cold. This may have influenced his post dose spirometry measurements. Also, due to the bronchodilator effects of salbutamol, deposition

TABLE 3. QUESTIONS AND RESPONSES ABOUT TOLERABILITY OF TWO INHALATIONS AND SATISFACTION OF NEBULIZERS

1. How was the nebulization session tolerated?		☐ Well tolerated		☐ Cough		☐ Bronchospasm		Other:	
Patient results		AKITA 100%	PARI 100%	AKITA 0%	PARI 10%	AKITA 0%	PARI 0%	Dislike of taste Mild dizziness Mild dyspnea Increased saliva production Irritated throat Hoarseness	
2. Did you think this nebulization was annoying?		☐ Not annoying at all		☐ A little annoying		☐ Moderately annoying		☐ Very annoying	
Patient results		AKITA 20%	PARI 30%	AKITA 80%	PARI 40%	AKITA 0%	PARI 20%	AKITA 0%	PARI 10%
3. What did you think of the duration of the nebulization?		☐ Not long at all		☐ A little long		☐ Moderately long		☐ Too long	
Patient results		AKITA 10%	PARI 0%	AKITA 40%	PARI 20%	AKITA 50%	PARI 30%	AKITA 0%	PARI 50%
4. What did you think of this nebulizer?		☐ Fine		☐ A little bothersome		☐ Rather bothersome		☐ Did not like it at all	
Patient results		AKITA 40%	PARI 20%	AKITA 40%	PARI 10%	AKITA 0%	PARI 40%	AKITA 20%	PARI 30%
5. Do you have a preference for one of the nebulizers?		☐ PARI-LC Plus		☐ AKITA		☐ Own nebulizer			
Patient results		10%		0%		0%		90%	
6. What would you think of once daily nebulization of the double dose of tobramycin?		☐ Better than twice daily		☐ I do not care		☐ Rather twice daily shorter nebulization			
Patient results		90%		10%		0%		0%	

Questions 1 to 4 were asked at both study visits. The responses of questions 1 to 4 are divided per study nebulizer: PARI, PARI-LC Plus. Question 5 and 6 were additional questions after the second inhalation.

^aSome patients reported more than one side effect after inhalation with the PARI-LC Plus nebulizer.

beyond the central airways might have been increased, which could affect the pharmacokinetic results and result in higher serum levels. However, serum concentrations were very low following the patient's PARI-LC Plus inhalation, thus salbutamol administration did not play a significant role.

Conclusion

OD tobramycin inhalation of the double standard BID dose with the controlled-inhalation AKITA and conventional PARI-LC Plus nebulizer resulted in similar pharmacokinetics in the doses given. Nebulization time was significantly shortened, less side effects were reported, and a higher degree of satisfaction was attained with the AKITA nebulizer. OD inhalation of tobramycin might reduce the treatment burden and contribute to better treatment adherence. Since OD inhalation treatment was well tolerated and serum levels were below the toxic limit, further research demonstrating clinical efficacy and long-term safety of this dosing regimen is in place.

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Author Disclosure Statement

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