

Early-phase efficacy and adverse effects of liposomal amikacin inhalation for refractory *Mycobacterium avium* complex lung disease: A case series

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Abstract

Background

Amikacin liposome inhalation suspension (ALIS), which efficiently allows amikacin to reach the pulmonary periphery for drug effect while minimising systemic adverse effects, was recently approved for the treatment of *Mycobacterium avium* complex (MAC) infections. The international phase 3 open-label clinical trials showed promising results, contributing to sputum culture conversion, but few reports have examined the efficacy and adverse effects using real-world data. We have identified the clinical outcome and adverse effects in the early-phase of treatment to use ALIS more effectively and safely in clinical practice.

Methods

The study population consisted of patients with MAC lung disease (MAC-LD) who were introduced to ALIS therapy after July 2021 at Keio University Hospital due to poor response to multidrug therapy. The sputum smear/culture results, symptoms and adverse effects of the early-phase of ALIS inhalation therapy were retrospectively reviewed. The serum amikacin concentrations in the earliest phase were also measured to assess PK/PD.

Results

A total of 11 cases (9 women; median age 64.6 years) were included in this study. The median disease duration of MAC-LD was 13.7 years, and all patients had a positive culture at the beginning of ALIS inhalation. Eight patients (72.7%) completed ALIS inhalation without interruption during the first month of treatment. Five patients (45.5%) were smear-negative at the start and none were positive at the 1 month follow-up. Three of the six patients (50.0%) who were sputum-smear-positive at the initiation were confirmed to have become sputum-smear-negative within one month, including one culture conversion. ALIS inhalation therapy caused some adverse effects in nine patients (81.8%); however, no serious systemic adverse effects were observed. The most common adverse effect was hoarseness (72.7%), which mostly occurred around 1 week after initiation. The medians of peak serum amikacin concentrations were 1.4 and 2.3 µg/mL for the first and third inhalations, respectively. On the other hand, trough serum concentrations just before the third inhalation were < 1.2 µg/mL in all patients.

Conclusions

ALIS therapy might be a treatment option for patients having refractory MAC infection with long disease duration who have had a poor response to guideline-based therapy.

Background

The prevalence of lung disease caused by nontuberculous mycobacteria (NTM) has been increasing worldwide in recent years.^{1,2,3} There are over 200 different species of NTM, and the *Mycobacterial avium* complex (MAC) accounts for the highest percentage of these species in most regions of the world.⁴ The annual prevalence of NTM infections is estimated to be 24.9 cases/100,000 population (2016) in Japan, which is higher than that of tuberculosis.⁵ MAC lung disease (MAC-LD) accounts for approximately 90% of these cases.^{6,7} Currently, a 3-drug combination therapy including macrolide is recommended for patients with macrolide-susceptible MAC-LD.⁸ However, intolerance and adverse effects caused by treatment with multiple antimicrobial agents for MAC-LD are major challenges in long-term management.^{9,10} The annual mortality rate of this disease is estimated to be 1–2% owing to the increase in refractory and long-course cases, and the recent extension in life expectancy.⁷

In 2007, the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) recommended parenteral aminoglycoside therapy as an initial treatment for cavitary MAC disease and for cases previously treated with a standard multidrug regimen.¹¹ Hence, aminoglycoside antibiotics, including amikacin (AMK) and streptomycin (SM), have been intravenously or intramuscularly administered for refractory cases.^{12,13} Such systemic administration sometimes causes renal, auditory, and vestibular toxicity;¹⁴ moreover, the low penetration of these antibiotics into the lung, owing to their chemical nature, is problematic.¹⁵ Several researchers including our group reported on inhalation therapy using a commercially available compressor nebuliser to improve the efficacy, safety, and feasibility of using injectable AMK sulfate solution, with promising results.^{16,17,18}

Under this context, amikacin liposome inhalation suspension (ALIS) was developed to achieve high concentrations of AMK in peripheral lung tissue and alveolar macrophages while minimising systemic exposure. ALIS contributed to the primary endpoint of improving the sputum

culture conversion rate at up to 6 months in the international phase 3 open-label trial (CONVERT).¹⁹ In response, the ATS/European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/IDSA Clinical Practice Guideline published in 2020 recommended the addition of ALIS to the treatment regimen for patients with MAC-LD who have failed to recover after at least 6 months of guideline-based therapy (GBT).⁸ Some studies outside of clinical trials have examined the efficacy and adverse effects of ALIS, but have been limited to surveillance of symptoms.²⁰ Moreover, *in vitro* studies have shown that liposomal AMK is readily taken up by macrophages, but details on the pharmacokinetics (PK)/pharmacodynamics (PD) in real-world clinical settings are unknown. Since it was approved in Japan in March 2021, we have administered ALIS to 11 patients with MAC disease who had an inadequate response to previous therapy. The aim of this study was to accumulate knowledge on the effects, PK, and adverse effects of ALIS in the early stages after its introduction, in order to achieve more effective and safer treatment.

Methods

Study population and data collection

The study population consisted of patients with MAC-LD who had an inadequate response to prior treatment with multi-drug combination therapy at Keio University Hospital. MAC-LD was diagnosed based on the ATS/ERS/ESCMID/IDSA guidelines published in 2020.⁸ The medical records of 11 patients who commenced ALIS treatment after July 2021 were retrospectively reviewed and analysed. We obtained informed consent from all these patients. The Research Ethics Committee of Keio University Hospital reviewed and approved this study (20110267).

ALIS inhalation

A 590 mg dose of ALIS (Arikayce; Insmid Inc., Bridgewater, NJ, USA) was administered once daily by inhalation using the dedicated eFlow® rapid nebuliser system (Lamira; PARI Pharma GmbH Co., Ltd., Munich, Germany), according to the procedure specified by the manufacturer. To learn the inhalation technique, patients were hospitalised for approximately 5 days to receive training from the medical staff. After discharge from the hospital, inhalation was continued at a fixed time every day in principle, but the frequency of inhalation was reduced based on adverse events.

Microbiological examinations

Sputum specimens were cultured either in mycobacteria growth indicator tubes (Becton, Dickinson and Company, Sparks, MD, USA) or on egg-based solid media (Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan), as previously described.²¹ All the isolates were identified as *Mycobacterium tuberculosis* or each NTM species using the AccuProbe culture identification test (Gen-Probe Inc., San Diego, CA, USA) and real-time polymerase chain reaction (Cobas Amplicor; Roche Diagnostics, Indianapolis, IN, USA). The minimum inhibitory concentration (MIC) of clarithromycin (CLA) and AMK were determined using BrothMIC NTM with 7H9 Middlebrook liquid media (Kyokuto Pharmaceutical Industrial Co., Ltd.) formulated using the Clinical and Laboratory Standards Institute's (CLSI) standard 24A. An MIC ≥ 32 $\mu\text{g}/\text{mL}$ was defined as CLA resistance.²² Based on the exclusion criteria of the CONVERT study,¹⁹ an MIC > 64 $\mu\text{g}/\text{mL}$ was considered as AMK resistance. In all cases, smear test results of all sputum submitted within one month of initiation and the first culture results after one month were recorded. Sputum cultures were performed for up to 8 weeks in order to determine results.

Clinical symptoms

The presence or absence of clinical symptoms, including cough, sputum production, dyspnea, hemoptysis, and fever, were evaluated before and after ALIS inhalation therapy, based on medical records.

Adverse events

Patients were monitored for subjective symptoms after ALIS inhalation. Ototoxicity and vestibular toxicity were assessed by an otorhinolaryngologist before the therapy for all cases. Assessment by an otorhinolaryngologist was performed 1 month after ALIS introduction and at the time when patients complained of symptoms. When it was deemed difficult to continue treatment due to adverse events, ALIS was temporarily discontinued and then considered for resumption at an appropriate time. The serum AMK concentrations were evaluated immediately before and 1 h after the first and third ALIS inhalations.

Statistical analysis

Summary statistics for quantitative markers were expressed as medians and interquartile ranges.

Results

Patient characteristics

Eleven patients who met the ATS/ERS/ESCMID/IDSA guideline's diagnostic criteria for MAC-LD were administered ALIS by inhalation. The patient characteristics are shown in Table 1. The majority of patients (81.8%) were women, and the median age at the initiation of ALIS inhalation was 64.6 years (interquartile range: 60.0-75.1 years). The median time from diagnosis to the initiation of ALIS was 13.7 years (interquartile range: 6.3-15.8 years). All 11 patients had a positive culture at the beginning of ALIS inhalation, with ten (90.9%) having an *M. avium* infection and one (9.1%) having a *Mycobacterium intracellulare* infection. Four patients (36.4%) had at least one cavitory lesion in the lungs. The distribution of MAC types based on HRCT images of patients was 72.7% nodular bronchiectatic (NB) type and 27.3% NB + fibrocavitary (FC) type. All patients were taking at least two GBT drugs at baseline, primarily macrolide (81.8%), ethambutol (90.9%), and rifamycin (72.7%).

Case data summaries

Table 2 summarises the case data for the 11 patients with MAC-LD who received ALIS inhalation therapy. Susceptibility testing showed that the majority of patients (54.5%) had CLA-resistant isolates; all but one of the patients were not using CLA at the time of ALIS initiation. All patients had been priorly treated with at least three different antimicrobial agents. In particular, CLA and ethambutol (EB) were included in the pre-treatment of all patients; rifampicin was also used, except for one patient (case 4). Four patients (cases #5, #6, #8, and #9) had priorly received AMK intravenous drip or inhalation treatment. For two of them (cases #5 and #8), the MIC of AMK was >16 µg/mL. One patient (case #8) underwent surgical resection of MAC lesions. The median duration of total treatment before ALIS introduction was 9.9 years (interquartile range: 6.3-15.8 years). All patients had a sputum-culture-positive at the beginning of ALIS inhalation, but three patients (cases #3, #4, and #6) were culture negative at 1 month; two of them (cases #4 and #6) were culture positive again at subsequent follow-up, while the remaining one (cases #3) achieved culture conversion.

Figure 1 shows the sputum smear results over time and the duration of adverse effects in each case up to 1 month after the introduction of ALIS therapy. Of the six patients (cases #1, #2, #5, #6, #8, and #10) with positive sputum smears at the start of the study, three (cases #1, #6, and #8) achieved negative sputum smear within 1 month. On the other hand, three cases (cases #2, #5, and #10) did not show a decrease in the amount of bacteria; their smear results were all 2+, indicating relatively high bacterial levels. Five patients (cases #3, #4, #7, #9, and #11) were smear-negative at the initiation and none were positive at the 1 month follow-up.

Eight patients (72.7%) completed ALIS inhalation during the first month of treatment, whereas three (cases #1, #4, and #7) discontinued or reduced their dose due to adverse effects. Case #7 discontinued inhalation for about 1 week due to hoarseness from day 7, and then resumed every other day for 1 week. After confirming that hoarseness had improved, daily inhalation was performed from day 21 onwards. After the period shown in Figure 1, a similar treatment schedule was followed for case #1, whose hoarseness appeared relatively late. On the other hand, case #4 had persistent hoarseness for several months, during which time inhalation could not be resumed.

Adverse events after ALIS inhalation

Adverse event profiling related to ALIS is shown in Table 3. Nine patients (81.8%) had some adverse effects due to ALIS inhalation therapy; however, there were no severe systemic adverse events. The most common adverse effect was hoarseness (72.7%), and some patients were found to have laryngitis (e.g., case #1). Hoarseness appeared around 1 week after initiation in most cases, but there was considerable variation in duration. Physicians were instructed to continue or reduce inhalation according to the severity and tolerability of the symptoms, both of which eventually improved. Other notable symptoms were oral discomfort (45.5%) and dysphonia (45.5%), with pharyngolaryngeal symptoms being the most common. There was no appearance of auditory toxicity presumably due to ALIS, and no specific complaints of hearing difficulty.

Clinical symptoms before and after ALIS inhalation

Table 4 presents the percentages of patients who had clinical symptoms, including coughing, sputum, dyspnea, hemoptysis, and fever, before and after ALIS inhalation therapy. Cough and sputum decreased in two patients and blood sputum decreased in one. Conversely, there were no symptoms that increased the number of patients complaining.

Serum AMK concentrations

The peak serum concentrations, measured 1 h after the start of the first ALIS inhalation, were <2.4 µg/mL in all 11 patients (Table 5(A)). Furthermore, the result of the measurement immediately before initiation of the third ALIS inhalation, regarded as the trough serum concentration, was <1.2 µg/mL for all patients (Table 5(B)). However, the peak serum concentration after the third inhalation sparsely ranged from <0.8 to >4.0 µg/mL (Table 5(C)). The third peak concentration was higher than the first for all but two patients (cases #3 and #11). In particular, for case #11, there was no difference in peak and trough concentrations for both the first and third inhalations, suggesting a problem with the inhalation technique.

Discussion

We aimed to identify clinical events that occur mainly in the first month after initiation of ALIS inhalation therapy. This study is a valuable case series reporting on treatment efficacy and adverse effects, with a particular focus on the early-phase of ALIS introduction. Only one studies on real-world data, not clinical trials, of ALIS have been reported,²⁰ the present study is also significant because it is the first to reveal the PK of ALIS in real clinical practice. Eleven patients started ALIS inhalation during their hospitalisation and attended the hospital every 1–2 weeks for a while after discharge. Close follow-up provided an accurate picture of inhalation compliance, treatment efficacy, adverse effects, and serum AMK concentration. A particularly important result was the finding that a certain number of patients exhibited a decrease in the amount of bacteria within the first month of initiation, and that many complained of hoarseness within about a week.

Incidentally, the CONVERT study (INS-212) was a randomised, open-label, international phase III clinical trial designed to evaluate the effect of ALIS on culture conversion in patients with refractory lung disease due to MAC.¹⁹ This trial was conducted at more than 125 sites in 18 countries. A comparison of the present study and CONVERT shows that the median patient age in both is about the same, at approximately 65 years. On the other hand, the patients analysed in our study exhibited several factors that made them more difficult to treat compared to those in the CONVERT study, e.g., low BMI (19.8 vs 21.3 kg/m²), long disease duration (13.7 vs 4.6 years), and high CLA resistance rates (54.5% vs 22.9%). This was presumably because many patients were referred to our hospital after no improvement upon GBT at other hospitals.

Eight patients (72.7%) completed ALIS inhalation during the first month of treatment without interruption. The remaining three cases discontinued after consultation with a physician, indicating good inhalation compliance. Three of the six patients (50.0%) with positive sputum smears at the initiation of ALIS treatment were confirmed to be sputum-smear-negative within 1 month. In the CONVERT study, the sputum culture conversion rate at 6 months of ALIS inhalation was 29.0%, of which about half was achieved within 1 month of initiation. These results suggest that some patients may benefit from treatment as early as 1 month after initiation. There were two cases with MIC of AMK > 16 µg/mL, both of which had previously received therapy with intravenous or inhaled AMK. It has been reported that these prior treatments can lead to the acquisition of AMK resistance.²³ However, CLSI recently set the decision breakpoint for the use of ALIS for MAC treatment at 128 µg/mL or higher.²⁴ It is not clear whether the aforementioned two cases had resistant strains or not, but there was at least no increase in the amount of bacteria in the early-phase of ALIS treatment.

We observed no serious systemic adverse effects within 1 month in all patients who inhaled ALIS. On the other hand, localised adverse effects, such as disorders of the pharyngolarynx in particular, appeared in most patients (72.7%). Many patients complained of hoarseness or dysphonia within a week; however, such symptoms may also be present several weeks after initiation, as we have previously reported (case #1).²⁵ If laryngitis is confirmed by an otolaryngologist, consideration should be given to reducing the frequency of ALIS inhalation. In such cases, resuming intermittent bi-daily dosing after primary interruption is a viable option.^{20,25} These adverse effects were reversible, and patients were often able to safely resume treatment after a temporary ALIS dose reduction. Laryngitis can also be prevented by gargling with warm water or glycerin post-dosing, rinsing the mouth after completion of nebuliser treatment, and changing the time of ALIS inhalation to the evening.²⁰ ALIS-induced hypersensitivity pneumonitis after induction has also been reported;²⁶ it occurred at a rate of 3.1% in the CONVERT study. Non-airway adverse effects are infrequent but occur at a constant rate. Diarrhoea, nausea, and fatigue seem to be the most common among them. ALIS can cause respiratory and gastrointestinal adverse effects, most of which appear in the first month of treatment. Nevertheless, considering the aforementioned therapeutic effects, it is advisable to continue inhalation during this period. It is important for ALIS prescribers to closely follow symptoms, oxygen saturation, X-rays, and not hesitate to consult an otolaryngologist if necessary. Serum Krebs von den Lungen-6 (KL-6) level is also considered a useful biomarker related to disease progression and treatment response of MAC-LD or reflect the clinical activity of drug-induced pneumonia.^{27,28} Furthermore, it would be effective to share patient information in advance among physicians, nurses, and pharmacists in order to explain possible adverse effects and how to deal with them. The indication for ALIS may expand to other diseases in the future, because there are reports of its efficacy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection;²⁹ clinical trials have been proposed for the treatment of *Mycobacterium abscessus* infections using ALIS.³⁰ In this context, this report summarising events that occur early in treatment is valuable.

When inhaled using the dedicated eFlow® nebuliser system, ALIS is efficiently distributed to the alveoli in the peripheral lungs, and liposome technology facilitates its uptake by macrophages, the major infected cells.³¹ More specifically, 73.9% of the ALIS aerosol particles produced by

eFlow[®] are in the 1–5 µm particle size range, which is considered optimal for delivery to the alveolar region.^{32,33} Liposomal AMK exhibits better uptake into macrophages than free AMK because of its non-polarity, and kills more intracellular mycobacteria under *in vitro* conditions.^{34,35} In the CONVERT study, the maximum serum concentration (C_{max}) and area under the curve from 0 to 24 h (AUC₂₄) of AMK were similar on day 1 and at steady state, indicating little or no serum accumulation of AMK upon ALIS inhalation. The medians of the first and third peak concentrations in the present study were 1.4 µg/mL (interquartile range: 1.2–1.6 µg/mL) and 2.3 µg/mL (interquartile range: 1.7–3.2 µg/mL), respectively, with a difference. This may have been because the patients were still unfamiliar with the inhalation technique. In any case, these levels are much lower than the serum AMK level following intravenous therapy,¹⁵ and lead to a lower incidence of systemic adverse events such as hearing loss and renal function abnormalities.

This study has several limitations. Firstly, the treatment efficacy was not determined based on sputum culture, which is the golden standard because of the short observation period. It may not be accurate to consider improvement or exacerbation with sputum smear results. However, the CONVERT study has shown that ALIS can produce sputum conversion for as long as several months. Secondly, differences in blood levels and therapeutic effects of ALIS due to patient mastery of the inhalation technique cannot be ignored. To minimise this factor as much as possible, cognitive function and hand dexterity of the patients were checked by a multidisciplinary medical team before admission, and close follow-up was conducted in the outpatient clinic after discharge.

Conclusions

ALIS may reduce the amount of MAC bacteria in sputum within a month, but adverse effects such as hoarseness often appear within a few weeks. Therefore, it is important to not interrupt treatment completely but employ a multifaceted approach through multidisciplinary collaboration in the early-phase of induction.

List Of Abbreviations

ALIS amikacin liposome inhalation suspension, AMK amikacin, AZM azithromycin, CLA clarithromycin, CPFX ciprofloxacin, CZM clofazimine, EB ethambutol, EM erythromycin, FC fibrocavitary type, GBT guideline-based therapy, KL-6 Krebs von den Lungen-6, KM kanamycin, LVFX levofloxacin, MAC *Mycobacterium avium* complex, MIC minimum inhibitory concentration, NB nodular bronchiectatic type, NTM nontuberculous mycobacterial, PD pharmacodynamics, PK pharmacokinetics, RFB rifabutin, RFP rifampicin, SM streptomycin, SPFX sparfloxacin, STFX sitafloxacin.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by the ethics committees of Keio University School of Medicine (20110267) and related research institutions. All adult patients provided written informed consent to participate in this study.

Consent for publication

The patients provided written informed consent for publication of individual clinical details and all the accompanying images.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AM, HN, and KY contributed study design, data collection, writing and reviewing of the manuscript. HT, HL, TO, TK, SA, and KN contributed to the interpretation of the results. MH and HO were involved in planning and supervised the otorhinolaryngology field. TA, HK, MI, and KF conceived

the study and were in charge of overall direction and planning. NH supervised the project. All authors read and approved the final manuscript.

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Tables

Table 1 Patient background data (n=11)

Backgrounds	median [interquartile range] or number (%)
Age, years	64.6 [60.0-75.1]
Sex, Male / Female	2 (18.2) / 9 (81.8)
Time from diagnosis until the initiation of treatment, years	13.7 [6.3-15.8]
Weight, kg	49.4 [44.7-51.5]
BMI, kg/m ²	19.8 [16.4-22.4]
Smoking history	2 (18.2)
Medical history	
Bronchial asthma	2 (18.2)
Malignancy	2 (18.2)
Diabetes mellitus	1 (9.1)
Mycobacterium species	
<i>M. avium</i>	10 (90.9)
<i>M. intracellulare</i>	1 (9.1)
Presence of cavitory lung lesions	4 (36.4)
Radiological pattern	
NB / FC / NB+FC / unclassified	8 (72.7) / 0 (0) / 3(27.3) / 0 (0)
Number of GBT drugs in regimen (at baseline)	
0 / 1 / 2 / 3 / 4 or more	0 (0) / 0 (0) / 5 (45.5) / 4 (36.4) / 2 (18.2)
Drug class (at baseline)	
Macrolide	9 (81.8)
Ethambutol	10 (90.9)
Rifamycin	8 (72.7)
Fluoroquinolone	3 (27.3)
Others	0 (0)
Generic name of drug (at baseline)	
Clarithromycin	3 (27.3)
Azithromycin	3 (27.3)
Erythromycin	3 (27.3)
Ethambutol	10 (90.9)
Rifampicin	8 (72.7)
Sitafloxacin	3 (27.3)

FC fibrocavitary type, GBT guideline-based therapy, NB nodular bronchiectatic type

Table 2 Clinical characteristics of patients with *Mycobacterium avium* complex receiving ALIS

Case	Sex	Age	Species	MIC of CLA (µg/ml)	MIC of AMK (µg/ml)	Radiological pattern	Prior Treatment	Total treatment duration before ALIS (year)	Drugs at ALIS initiation	Sputum culture results before ALIS initiation	Sputum culture results 1 month after ALIS initiation
#1	F	56	<i>M.avium</i>	>32	4	NB	CLA, EB, RFP, RFB, EM, STFX	4.5	EB, RFP	+	+
#2	F	69	<i>M.avium</i>	4	1	NB+FC	CLA, EB, RFP, KM	19.8	CLA, EB, RFP	+	+
#3	M	76	<i>M.avium</i>	>32	16	NB	CLA, EB, RFP, EM	13.7	EB, RFP, EM	+	-
#4	F	69	<i>M.avium</i>	0.5	2	NB	CLA, EB, AZM	3.9	EB, AZM	+	-
#5	F	63	<i>M.avium</i>	>32	>16	NB+FC	CLA, EB, RFP, AMK div, AMK inh, STFX, LVFX	15.8	EB, RFP, STFX	+	+
#6	F	75	<i>M.avium</i>	0.5	16	NB	CLA, EB, RFP, RFB, AZM, AMK div, AMK inh	9.9	EB, AZM	+	-
#7	F	79	<i>M.avium</i>	>32	4	NB	CLA, EB, RFP	13.9	CLA, RFP	+	+
#8	F	64	<i>M.avium</i>	>32	>16	NB	CLA, EB, RFP, EM, SM, AMK div, AMK inh, STFX, SPFX, ope	21.3	EB, RFP, EM, STFX	+	+
#9	M	61	<i>M.avium</i>	>32	8	NB	CLA, EB, RFP, EM, AMK div, STFX	7.3	EB, RFP, EM, STFX	+	+
#10	F	60	<i>M.avium</i>	2	8	NB+FC	CLA, EB, RFP, AZM, SM, CZM, LVFX	8.4	CLA, EB, RFP	+	+
#11	F	56	<i>M.intracellulare</i>	0.25	4	NB	CLA, EB, RFP, AZM	6.3	EB, AZM	+	+

ALIS amikacin liposome inhalation suspension, MIC minimum inhibitory concentration.

M male, *F* female, *div* intravenous drip *inh* inhalation (non-liposomal), *ope* operation.

CLA clarithromycin, EB ethambutol, RFP rifampicin, RFB rifabutin, EM erythromycin, STFX sitafloxacin, KM kanamycin, AZM azithromycin, AMK amikacin, LVFX levofloxacin, SM streptomycin, SPFX sparfloxacin, CPFX ciprofloxacin, CZM clofazimine, NB nodular bronchiectatic type, FC fibrocavitary type

Sputum culture "+" denotes positive and "-" denotes negative

Table 3 Adverse event profiling of ALIS (n=11)

Adverse event	n (%)
Uncomfortable feeling in the oral cavity	5 (45.5)
Hoarseness	8 (72.7)
Dysphonia	5 (45.5)
Hemoptysis	1 (9.1)
Digestive symptom	1 (9.1)
Vertigo	1 (9.1)
Renal toxicity	0 (0)
Auditory toxicity	0 (0)

ALIS amikacin liposome inhalation suspension

Table 4 Clinical symptoms before and after ALIS (Number [%])

Clinical symptom	Before treatment (n=11)	After treatment (n=11)
Cough	9 (81.8)	7 (63.6)
Sputum	10 (90.9)	8 (72.7)
Dyspnea	3 (27.3)	3 (27.3)
Hemoptysis	3 (27.3)	2 (18.2)
Fever	1 (9.1)	1 (9.1)

ALIS amikacin liposome inhalation suspension

Table 5 Serum amikacin concentrations (n=11)

Serum amikacin concentrations (µg/ml)	n (%)
(A) Serum amikacin concentrations 1 h after the start of the first ALIS inhalation (peak concentration)	
< 0.8	0 (0)
0.8 to <1.6	8 (72.7)
1.6 to <2.4	3 (27.3)
2.4 to <3.2	0 (0)
3.2 to <4.0	0 (0)
≥ 4.0	0 (0)
(B) Serum amikacin concentrations just before the start of the third ALIS inhalation (trough concentrations)	
< 0.8	9 (81.8)
0.8 to <1.2	2 (18.2)
≥ 1.2	0 (0)
(C) Serum amikacin concentrations 1 h after the start of the third ALIS inhalation (peak concentration)	
< 0.8	1 (9.1)
0.8 to <1.6	1 (9.1)
1.6 to <2.4	4 (36.4)
2.4 to <3.2	2 (18.2)
3.2 to <4.0	2 (18.2)
≥ 4.0	1 (9.1)

ALIS amikacin liposome inhalation suspension

Figures

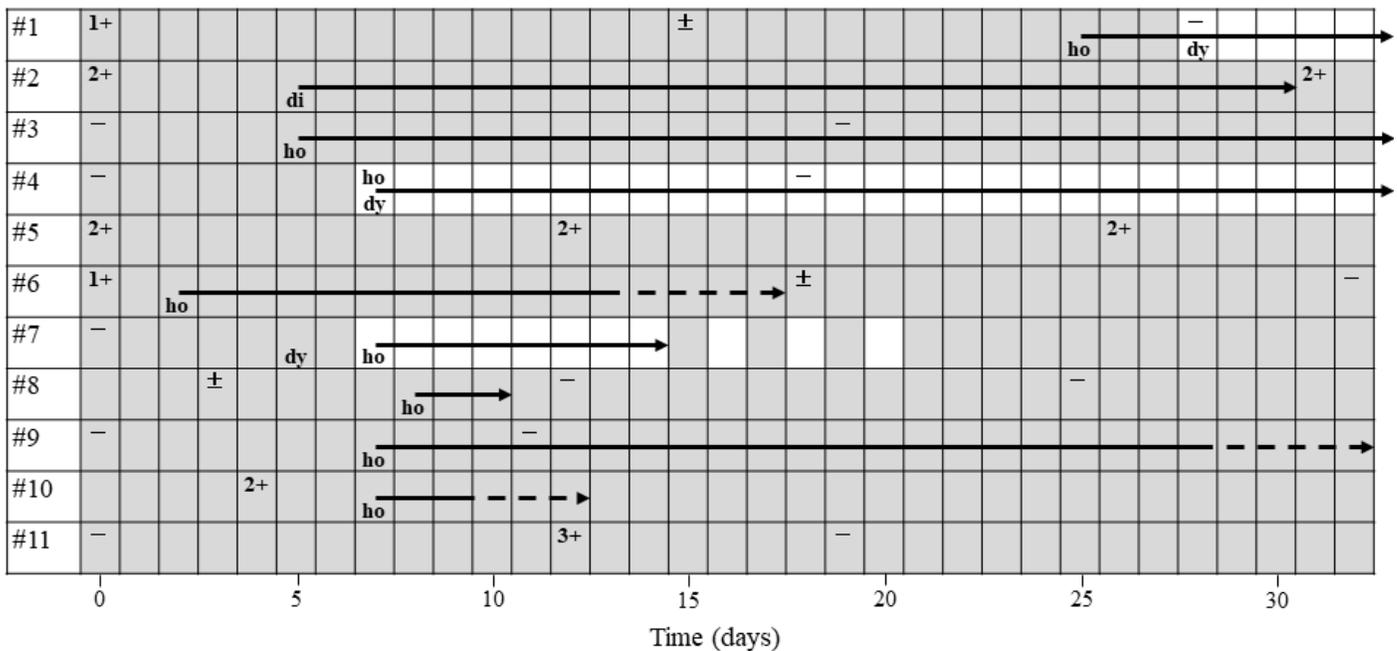


Figure 1

Sputum smear results over time and duration of adverse effects in each case. Halftone pattern indicates the period during ALIS treatment. Smear results are shown as (-) to (3+) depending on the amount of bacteria based on the bacterial collection method.

The end point of the solid arrow indicates the day when the side effect disappeared, and the end point of the dotted arrow indicates a state of general improvement.

ho: hoarseness; dy: dysphonia; di: digestive symptom