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Amikacin Liposomal Inhalation Suspension in the Treatment of Mycobacterium abscessus Lung Infection: A French Observational Experience

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Background. Mycobacterium abscessus infections remain difficult to manage in both cystic fibrosis (CF) and non-CF patients and reported clinical outcomes are largely unsatisfactory. Clinical trial data are limited and no approved therapies are currently available for the management of M. abscessus lung diseases. As an alternative, cohort studies may provide insightful information into the management of M. abscessus pulmonary disease.

Methods. Based on a retrospective observational cohort study, we investigated the safety and efficacy of amikacin liposome inhaled suspension (ALIS) as an adjunct to a standard antibiotic regimen for M. abscessus lung infection in both CF and non-CF patients. We also assessed the association of patient drug compliance with culture conversion and clinical outcomes.

Results. Twenty-six patients had long-term follow-up data available. Culture conversion was achieved in 54% (14/26) of the patients with no difference between CF and non-CF patients after an average treatment duration of 10 months. Patient treatment compliance was significantly better in the converter group compared to nonconverters with an odds ratio of 44.78 associated with good compared to poor patient compliance. Overall, 9 patients (35%) experienced an adverse event that led to treatment discontinuation.

Conclusions. ALIS appears beneficial in both CF and non-CF populations with M. abscessus lung disease.

Keywords. amikacin liposomal inhalation suspension; cystic fibrosis; Mycobacterium abscessus; nontuberculous mycobacteria; treatment.

Nontuberculous mycobacteria pulmonary disease (NTM-PD) is emerging as a global threat to individuals with chronic lung diseases [1]. Mycobacterium abscessus is the most frequently encountered agent of NTM-PD in patients with cystic fibrosis (CF) in most areas [2–4] and is the second most common of NTM in non-CF patients. NTM-PD due to M. abscessus is often associated with poor clinical outcome and accelerated loss of lung function [5, 6]. Furthermore, M. abscessus is refractory to most chemotherapeutic treatments. It demonstrates intrinsic resistance to most antibiotic classes due to the presence of an impermeable waxy cell envelope, the expression of a wide range of antibiotic-modifying/inactivating enzymes, and efflux pumps and genetic polymorphisms in antibiotic target genes [7, 8]. Guidelines for the management of M. abscessus lung disease (MAB-LD) in CF patients recommend a multidrug regimen that includes 3 active drugs during the initial phase of treatment; macrolides are only counted as active if there is no mutational or inducible resistance. For
the continuation phase of therapy (following the parenteral component), the recommendations include at least 2–3 drugs with inhaled amikacin for >12 months [9]. Despite these recommendations, treatment outcomes for MAB-LD remain unsatisfactory and a recent meta-analysis reported a pooled treatment success rate of 41.5% [6]. This emphasizes the necessity for rapid development of new drugs and/or new drug regimens to achieve an unmet medical need and to improve the clinical outcome in patients with MAB-LD.

Amikacin liposomal inhalation suspension (ALIS) is composed of liposome-encapsulated amikacin. It is delivered to the patient by oral inhalation and taken up by alveolar macrophages, which represent an intracellular niche where NTM can reside [10, 11]. In a previous phase 2 study including 32 MAB-LD patients, sputum culture conversion (SCC) was observed in 4 of 15 treated patients (27%), whereas 1 of 17 patients converted in the placebo group (6%) [12]. Another investigator-initiated study assessing the efficacy and safety of ALIS in the treatment of 3 MAB-LD patients is currently ongoing (ClinicalTrials.gov identifier NCT03038178). We recently reported the successful treatment of 3 MAB-LD in CF patients [13].

Herein, we present a retrospective observational cohort study and report on the outcomes of addition of ALIS to a multidrug regimen for the treatment of MAB-LD in both CF and non-CF populations in a real-world setting and investigated the influence of patient compliance on clinical outcomes.

### STUDY DESIGN, METHODS, AND TREATMENT

We present here a retrospective observational cohort study conducted in France (including French overseas territories) in 28 patients treated with ALIS and *M. abscessus* in their sputum, based on at least 2 positive cultures, and who met the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2007 criteria for mycobacterial pulmonary disease. Patients received at least 3 weeks of treatment with ALIS in addition to multidrug therapy for *M. abscessus* lung infection between March 2016 and February 2020. Patients were included if (i) the ATS/IDSA diagnostic criteria for *M. abscessus* lung disease were fulfilled, (ii) they were aged >12 years, and (iii) they could receive a minimum of 3 weeks of treatment with ALIS. Patients with extrapulmonary or disseminated disease were not eligible for inclusion.

ALIS is not available yet in France for the treatment of *M. abscessus* lung infection through a market authorization. However, a Temporary Authorization for Use (ATU) allowing early access to ALIS has been available in France since 2014. ALIS was administered once daily at a concentration of 590 mg/8.4 mL by oral inhalation using the Lamira Nebulizer System continuously.

Participating healthcare professionals were sent a case report form by email to record clinical and laboratory data of interest (comprising body mass index [BMI], pulmonary function, radiology, co-pathogens, concomitant and previous antibiotic therapy [oral or intravenous], and adverse events) after obtaining the patient consent. Spirometry and radiographic imaging results were collected prior to and at least 6 months after starting ALIS treatment.

Mycobacterial cultures, species identification, and drug susceptibility testing and interpretation were performed according to the recommendations of the French Society for Microbiology and the National Reference Center for mycobacteria, Paris (https://www.sfm-microbiologie.org/wp-content/uploads/2019/07/NTM_AZAY_antibiogramme_FINAL_27-05-19_FM.pdf). In brief, mycobacterial isolates were identified by...

### Table 1. Baseline Characteristics in Participants With or Without Cystic Fibrosis

| Characteristic                          | Total Population (N = 26) | CF (n = 13) | Non-CF (n = 13) |
|----------------------------------------|---------------------------|-------------|-----------------|
| Sex, male/female, No.                  | 17/9                      | 11/2        | 6/7             |
| Age, y, median                         | 42.5                      | 22          | 63              |
| CFTR genotype, No.                     |                           |             |                 |
| F508del/F508del                        | ...                       | 3           |                 |
| F508del/other                          | ...                       | 6           |                 |
| Other/other                            | ...                       | 3           |                 |
| Nd/Nd                                  | ...                       | 1           |                 |
| Etiology of Non CF bronchiectasis, No. |                           |             |                 |
| Idiopathic                             | ...                       | 4           |                 |
| Post-TB                                | ...                       | 5           |                 |
| Marfan                                 | ...                       | 1           |                 |
| Primary Ciliary Dyskinesia             | ...                       | 2           |                 |
| Asthma                                 | ...                       | 1           |                 |
| BMI, kg/m²                             | 19.8                      | 19.4        | 21              |
| FEV₁, % (min–max)                      | 52 (11–110)               | 51.7 (11–110)| 52.3 (19–88)   |
| Radiological features, No. (%)         |                           |             |                 |
| Bronchiectasis                         | 23 (88)                   | 13/13       | 10/13           |
| Nodules, consolidations                | 15 (57)                   | 5/13        | 10/13           |
| Cavity                                 | 7 (27)                    | 0/13        | 7/13            |
| Co-pathogens, No. (%)                  |                           |             |                 |
| Aii                                     | 21 (81)                   | 16          | 5               |
| Pseudomonas aeruginosa                 | 10 (38)                   | 8           | 2               |
| Staphylococcus aureus                  | 8 (31)                    | 8           | 0               |
| Aspergillus fumigatus                  | 7 (27)                    | 4           | 3               |
| *Mycobacterium abscessus* species      |                           |             |                 |
| bolletii                               | 2                         | 1           | 1               |
| abscessus                              | 21                        | 11          | 10              |
| massilense                             | 1                         | 1           | 0               |
| Not available                           | 2                         | 0           | 2               |
| Prior anti-TB regimen                  |                           |             |                 |
| IV amikacin                            | 25                        | 12          | 13              |
| Penem                                  | 19                        | 12          | 7               |
| Macrolide                              | 23                        | 12          | 11              |
| Linezolid                              | 10                        | 6           | 4               |
| Clofazamine                            | 6                         | 2           | 4               |

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; F, female; FEV₁, forced expiratory volume in 1 second; IV, intravenous; M, male; Nd, not done; PCD, primary ciliary dyskinesia; TB, tuberculosis.
the DNA strip assay GenoType Mycobacterium CM test (Hain Lifescience, Nehren, Germany). For strains belonging to *M. abscessus*, the GenoType NTM-DR kit was used to identify the isolate subspecies and to detect *erm*41 genotypes involved in intrinsic resistance to clarithromycin and azithromycin, mutations in the *rrl* gene in acquired resistance to clarithromycin and azithromycin, and mutations in the *rrs* gene in acquired resistance to amikacin and tobramycin.

The Institutional Review Board (IRB) at Montpellier University Hospital approved the study (IRB number 2019_IRB-MTP811-16). All patients provided consent.

**Efficacy and Safety Measures**

We applied the NTM-NET treatment outcome definitions and defined culture conversion as resulting from at least 3 consecutive negative microbiological cultures from respiratory samples taken at least 4 weeks apart during antimycobacterial treatment [14]. Patient drug compliance was defined as compliance with therapy by counting the months of treatment during which ALIS was dispensed. This was based on the assumption that patients who made the effort to retrieve their medication from the hospital pharmacy (the only possibility to have access to the ATU-approved therapy) were presumed to take their treatment on a regular basis compared with those who collected their treatment infrequently or not at all. We interpreted the level of compliance by determining the ratio between the duration (in months) ALIS was dispensed and the duration of the prescribed treatment: 100% ALIS dispensed by pharmacies translated arbitrarily as a good level of compliance.

Patients who demonstrated culture conversion (converters) were compared with those who were considered nonconverters for association with patient drug compliance and baseline characteristics. In addition, clinical outcomes were compared between converters and nonconverters.

Adverse events were documented, notably those that resulted in discontinuation of the ALIS treatment.

The retrospective observational design and the small sample size of the present study limits statistical analysis potential and only odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the presence of co-pathogens and patient treatment compliance in relation to sputum conversion.

**RESULTS**

**Patients and Baseline Characteristics**

Twenty-eight patients with *M. abscessus* in their sputum were originally treated with ALIS in France (Montpellier, Paris, Amiens, Rouen, Lille, Guadeloupe) from March 2016 to February 2020. Finally, 2 patients were excluded. One patient was excluded after being lost to follow-up and another patient died due to a general deterioration (the patient had taken ALIS 3 weeks during the decline and ALIS was not imputable according to the investigator). Most patients were male (17/26 [65%]) with a median and mean age of 42.5 years and 44.7 years, respectively. Among the patients, 50% had CF (Tables 1 and 2).

MAB-LD patients with CF were younger but did not show significant differences in BMI and lung function. Patients had radiographic evidence of bronchiectasis, nodular infiltrates, and/or cavitary disease, as outlined in Tables 1 and 2. The majority of cases were considered to be refractory to treatment and/or difficult to treat, according to the persistence of *M. abscessus* despite intravenous and oral therapy.

The most frequently isolated *M. abscessus* subspecies was *M. abscessus* subsp *abscessus* (*n* = 19), followed by *M. abscessus* subsp *massiliense* (*n* = 3) and *M. abscessus* subsp *boletii* (*n* = 2). Data on the subspecies were unavailable for 2 patients.

Genetic drug susceptibility test results were established for isolates of 20 patients. Isolates of 17 patients harbored the inducible clarithromycin resistance gene *erm*41 (minimum inhibitory concentrations ≥16 µg/mL) carrying the T28C substitution genotype while patient had C28 genotype. Phenotypic drug susceptibility testing data are not available for most of the isolates. No patient harbored the *rrs* gene mutation.

The most commonly detected co-pathogens were *Pseudomonas aeruginosa* (*n* = 10 [38%]), *Staphylococcus aureus* (*n* = 8 [31%]), and *Aspergillus fumigatus* (*n* = 7 [27%]), while 1 patient had a NTM coinfection with *Mycobacterium avium*. Prior antibiotic regimens are listed in Table 2 and at baseline all patients underwent either a 2-week or 3-week treatment of intravenous antibiotics most often comprising imipenem or meropenem and amikacin.

**On-Study Treatment and Sputum Culture Conversion**

The total patient population, including CF and non-CF patients, received ALIS for a minimum of 1 month and on average, patients received treatment for 10 months (range, 1–43 months). Accompanying antibiotics included clarithromycin, intravenous imipenem, and amikacin in the majority of cases and no other inhaled antibiotic therapy was used during the study period. The most common regimen was intravenous imipenem, amikacin, and oral clarithromycin (*n* = 10/26 [38%]), followed by intravenous meropenem, amikacin, clarithromycin, and linezolid (*n* = 5/26 [19%]). Twenty-four of 26 patients had at least a macrolide, most of them clarithromycin. No difference was observed in term of sputum correction and regarding the presence of the *erm*41 gene mutation.

Sputum culture conversion was observed in 14 cases at 6 months and 14 at 12 months, with similar rates between CF (*n* = 7) and non-CF patients (*n* = 7) (Tables 3 and 4). Eight patients did not convert and no microbiological data were available for 4 patients (unclassifiable patients) (Tables 4 and 5, Figure 1). At 6 months, SCC was observed in 10 of the
| Patient ID | Sex | Age, y | Etiology (CFTR Genotype) | Mycobacterium abscessus Subspecies | Prior Antibiotic Regimen | Radiological Features | Spirometry (FEV₁ Predicted) | BMI, kg/m² |
|-----------|-----|--------|--------------------------|-----------------------------------|-------------------------|----------------------|------------------------|-----------|
| 1         | M   | 21     | CF (ΔF508/ΔF508)         | abscessus                         | Imipenem, IV amikacin, clarithromycin | Bronchiectasis       | 81                     | 18         |
| 2         | M   | 24     | CF (S364P/S364P)         | abscessus                         | Meropenem, IH amikacin, clarithromycin, linezolid | Bronchiectasis, nodules | 63                     | 17.95      |
| 3         | M   | 36     | CF (ΔF508/R347P)         | abscessus                         | Meropenem, IH amikacin, clarithromycin, linezolid | Bronchiectasis       | 23                     | 18         |
| 4         | M   | 28     | CF (G542X/1717-G > A)    | massiliense                       | Imipenem, IV amikacin, clarithromycin | Bronchiectasis       | 34                     | 20         |
| 5         | F   | 56     | CF (ΔF508/3272 - 26 A > G) | massiliense                       | Imipenem, IV amikacin, clarithromycin | Bronchiectasis       | 37                     | 21.7       |
| 6         | M   | 19     | CF (ΔF508/W846)          | abscessus                         | Meropenem, IH amikacin, clarithromycin, linezolid | Bronchiectasis       | 52                     | 17         |
| 7         | M   | 14     | CF (ΔF508/ΔF608)         | abscessus                         | Meropenem, IV amikacin, clarithromycin, linezolid | Bronchiectasis       | 74                     | 14.7       |
| 8         | M   | 60     | CF (G542X/3849)          | abscessus                         | Meropenem, IV amikacin, clarithromycin, linezolid | Bronchiectasis       | 36                     | 19.88      |
| 9         | M   | 13     | CF (ΔF508/2183AA > G)    | boletii                           | Imipenem, IV amikacin, clarithromycin | Bronchiectasis       | 110                    | 16         |
| 10        | M   | 22     | CF (ΔF508/Y122X)         | abscessus                         | Unavailable             | Bronchiectasis, nodules, consolidation | NA                     | 26         |
| 11        | M   | 20     | CF (ΔF508/394delITT)     | abscessus                         | Ethambutol, rifadin, IV amikacin, azithromycin, clarithromycin, linezolid | Bronchiectasis, nodules | 59                     | 22         |
| 12        | M   | 25     | CF (ΔF508/ΔF508)         | massiliense                       | Azithromycin, cefoxitin, IV amikacin, clofazamine, tigecycline, rifabutin, imipenem | Bronchiectasis, nodules | 11                     | 19         |
| 13        | F   | 20     | CF (genotype unknown)    | abscessus                         | IV amikacin, linezolid, clofazamine, azithromycin, imipenem | Bronchiectasis, nodules | 48                     | 19         |
| 14        | F   | 60     | Idiopathic/asthma        | abscessus                         | Rifadin, clarithromycin, ethambutol, clofazamine, cefoxitin, IV amikacin, azithromycin | Bronchiectasis, nodules | 88                     | 16.8       |
| 15        | F   | 55     | Idiopathic               | abscessus                         | Cefoxitin, IV amikacin, tigecycline | Cavity, nodules, bronchiectasis, consolidation | 80                     | 17.53      |
| 16        | M   | 87     | Post-TB                  | Unavailable                       | Azithromycin, cefoxitin, IV amikacin, clofazamine, tigecycline | Bronchiectasis, consolidation, nodules, cavity | 84                     | 24.9       |
| 17        | F   | 73     | Post-TB                  | abscessus                         | Tigecycline, IV amikacin, cefoxitin | Consolidation, nodules, bronchiectasis | 93                     | 18.31      |
| 18        | M   | 49     | Marfan syndrome          | abscessus                         | Imipenem, IV amikacin, azithromycin, linezolid | Cavity, consolidation | 48                     | 22         |
| 19        | M   | 86     | Post-TB                  | Unavailable                       | Rifadin, ethambutol, clarithromycin, IV amikacin, cefoxitin, azithromycin | Bronchiectasis       | 44                     | 18.31      |
| 20        | M   | 30     | PCD                      | abscessus                         | Imipenem, amikacin, clarithromycin | Bronchiectasis, consolidation | 20                     | 22.9       |
| 21        | F   | 28     | PCD                      | bolletii                          | Imipenem, IV amikacin, clarithromycin, linezolid, cefoxitin, cefotaxime, meropenem | Bronchiectasis, nodules, cavity | 22                     | 23.2       |
| 22        | F   | 75     | Post-TB                  | abscessus                         | Imipenem, amikacin, clarithromycin | Bronchiectasis       | 19                     | 18         |
| 23        | F   | 67     | Post-TB, postlobectomy, rheumatoid arthritis | abscessus                         | IV amikacin, azithromycin, linezolid, cefotaxime | Nodules, consolidation, cavity | 50                     | 21.3       |
| 24        | F   | 74     | Idiopathic               | abscessus                         | IV amikacin, clarithromycin, imipenem, tigecycline, clofazamine | Bronchiectasis, nodules | 75                     | 16.9       |
| 25        | M   | 63     | Idiopathic               | abscessus                         | Clarithromycin, IV amikacin, imipenem | Bronchiectasis, nodules, cavity | 32                     | 20.17      |
| 26        | M   | 57     | Asthma                   | abscessus                         | Clarithromycin, IV amikacin, imipenem, moxifloxacin, linezolid, clofazamine, tigecycline | Nodules, cavity | 25                     | 18.42      |

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transregulator gene; F, female; FEV₁, forced expiratory volume in 1 second; IH, Inhaled; IV, intravenous; M, male; NA, non available; PCD, primary ciliary dyskinesia; TB, tuberculosis.
| Patient ID | Converter | Antibiotic Regimen During ALIS | ALIS Treatment Duration, mo | Compliance | Radiological Follow-up | Spirometry (FEV₁, % Predicted) Follow-up | BMI Post-ALIS, kg/m² |
|------------|-----------|--------------------------------|-----------------------------|------------|-----------------------|------------------------------------------|---------------------|
| 1          | No        | Clarithromycin                  | 2                           | Poor       | Stable                | 83 (+2%)                                 | 19.0 (+5%)          |
| 2          | No        | Clarithromycin                  | 1                           | Poor       | Deterioration         | 56 (−11%)                               | 17.0 (−5%)          |
| 3          | No        | Clarithromycin                  | 6                           | Poor       | Stable                | 23 (0%)                                 | 17.0 (−5%)          |
| 4          | NA at month 6, no at month 12 | Clarithromycin | 3                           | NA         | NA                    | 40 (+18%)                               | 20.0 (0%)           |
| 5          | Yes       | Clarithromycin                  | 3                           | Good       | Improved              | 32 (−14%)                               | 21.0 (−3%)          |
| 6          | Yes       | Meropenem, clarithromycin       | 43                          | Good       | Stable                | 72 (+38%)                               | 19.0 (+12%)         |
| 7          | Yes       | Meropenem, clarithromycin       | 10                          | Good       | Improved              | 71 (−4%)                                | 16.0 (+9%)          |
| 8          | Yes       | Imipenem, clarithromycin, linezolid, ciprofloxacin | 16 | Good | Improved | 37 (+3%) | 20.0 (+1%) |
| 9          | Yes       | Clarithromycin                  | 9                           | Good       | Improved              | 99 (−10%)                               | 17.0 (+6%)          |
| 10         | Yes       | Tigecycline, linezolid, clofazimine | 12 | Good | Improved | 71 (pre-FEV₁ unavailable) | 27.0 (+4%) |
| 11         | Yes       | Clofazimine, rifampin, tedizolid | 6                           | Good       | NA                    | NA                                      | 23.0 (+5%)          |
| 12         | No        | Rifabutin, tigecycline, ceftazidime-avibactam, imipenem | 35 | Good | Deterioration | NA | NA |
| 13         | No        | Linezolid, clofazimine, azithromycin, imipenem, rifabutin | 4 | Good | NA | 53 (+10%) | 20.2 (+6%) |
| 14         | Yes       | Imipenem, tigecycline           | 6                           | Good       | Improved              | 83 (−6%)                                | 16.5 (−2%)          |
| 15         | No        | Cefoxitin, tigecycline          | 3                           | Poor       | Improved              | NA                                      | NA |
| 16         | NA        | Azithromycin, linezolid         | 1                           | Good       | Improved              | 77 (−8%)                                | 23.7 (−5%)          |
| 17         | Yes       | Azithromycin, clofazimine, tedizolid, rifabutin | 13 | Good | Deterioration | NA | NA |
| 18         | Yes at month 12, NA at month 6 | Imipenem, tigecycline, rifabutin | 8 | Good | NA | 52 (+8%) | 21.0 (−5%) |
| 19         | Yes       | Linezolid, azithromycin, tigecycline | 7 | Good | Improved | 43 (−2%) | 17.7 (−3%) |
| 20         | Yes       | Clarithromycin                  | 11                          | Good       | Improved              | 22 (+10%)                               | 22.9 (0%)           |
| 21         | Yes       | Clarithromycin                  | 6                           | Good       | Stable                | 21 (−4.5%)                               | 21.2 (−9.4%)        |
| 22         | NA        | Clarithromycin                  | 1                           | Good       | Stable                | 18 (−5%)                                 | 18.0 (0%)           |
| 23         | No        | ...                              | 17                          | Poor       | Deterioration         | 39 (−22%)                               | 19.0 (−10%)         |
| 24         | Yes       | Clarithromycin, imipenem, tigecycline, clofazimine | 10 | Good | Improved | 97 (+29%) | 18.8 (10.7%) |
| 25         | No        | Linezolid, minocycline          | 5                           | Good × 5 mo then poorly compliant | Improved | NA | NA |
| 26         | Yes       | Clarithromycin, moxifloxacin    | 22                          | Good       | Improved              | 16 (−34%)                               | 18.1 (−2%)          |

Changes in FEV₁ and BMI were not significantly different between converters and nonconverters: odds ratios, 0.89 (nonsignificant) and 2.62 (nonsignificant), respectively.

Abbreviations: ALIS, amikacin liposome inhaled suspension; BMI, body mass index; FEV₁, forced expiratory volume in 1 second; M, male; NA, not applicable.
| Patient ID | Start Date of ALIS | Total ALIS Duration, mo | Culture at 3 mo | Culture at 6 mo | Culture at 12 mo |
|------------|--------------------|-------------------------|----------------|----------------|-----------------|
| 1          | 21 Dec 2018        | 2                       | Positive       | Positive       | Positive        |
| 2          | 10 Nov 2016        | 1                       | Positive       | Positive       | Positive        |
| 3          | 12 Apr 2016        | 6                       | Positive       | Positive       | Positive (still positive at 24 and 36 mo) |
| 4          | 1 Nov 2019         | 3                       | NA             | NA             | Positive        |
| 5          | 1 Nov 2019         | 10                      | Negative       | Negative       | Negative        |
| 6          | 24 Mar 2016        | 43                      | Negative       | Negative       | Negative        |
| 7          | 30 Sep 2016        | 10                      | Negative       | Negative       | Negative        |
| 8          | 5 Apr 2016         | 16                      | Negative       | Negative       | Negative        |
| 9          | 7 Nov 2019         | 9                       | Negative       | Negative       | Negative        |
| 10         | 29 Nov 2018        | 12                      | Positive       | Negative       | Negative        |
| 11         | 18 Dec 2019        | 6                       | Negative       | Negative       | Negative        |
| 12         | 22 May 2017        | 35                      | Positive       | Positive       | Positive        |
| 13         | 2 Feb 2018         | 4                       | Positive       | Positive       | Negative at 10 mo (no follow-up available as stopped therapy at 4 mo) |
| 14         | 24 Mar 2016        | 6                       | Positive       | Negative       | Negative        |
| 15         | 15 May 2019        | 3                       | Positive (stopped treatment) | Positive | NA |
| 16         | 22 Mar 2016        | 1                       | Positive (no further cultures available; patient deceased) | NA | NA |
| 17         | 13 May 2019        | 12                      | NA             | Negative       | Positive        |
| 18         | 12 Oct 2018        | 6                       | NA             | Negative       | Negative        |
| 19         | 29 Aug 2017        | 4                       | Negative       | Negative       | Negative        |
| 20         | 31 Jul 2019        | 10                      | Negative       | Negative       | Negative        |
| 21         | 25 Sep 2019        | 6                       | Negative       | Negative       | Negative        |
| 22         | 22 Nov 2019        | 1                       | Positive (stopped ALIS after 1 mo) | NA | NA |
| 23         | 27 Oct 2017        | 11                      | Positive       | Positive       | Positive at 24 mo |
| 24         | 20 Aug 2018        | 10                      | Negative       | Therapy stopped 15 Jun 2019 | Positive |
| 25         | 22 Aug 2018        | 5                       | Positive       | Positive       | Positive        |
| 26         | 22 Nov 2017        | 22                      | NA             | Negative       | Negative        |

Abbreviations: ALIS, amikacin liposome inhaled suspension; NA, not applicable.

*Patient with lung transplant excluded in analysis (forced expiratory volume in 1 second data available for 12 converters and 8 nonconverters).

19 patients with *M. abscessus* subsp *abscessus* and in both patients with *M. abscessus* subsp *bolletii*. Only 1 of the 3 *M. abscessus* subsp *massiliense*-infected patients and 1 of the 2 patients with the unidentified *M. abscessus* subspecies converted during all 3 culture analysis time points of 3, 6, and 12 months (Table 4). In 20 patients for whom genetic drug susceptibility test results were available, 9 were converters and 8 were nonconverters. Presence of the erm41 gene mutation was similar between converters (n = 8/14) and nonconverters or unclassifiables (n = 9/14).

SCC was more frequent among patients who had other copathogens cultured at the start of *M. abscessus* treatment, in particular those with *P. aeruginosa* (7/14 [50%] versus 2/8 [25%]) (Table 5). Although not statistically significant, the presence of *P. aeruginosa* coinfection may be associated with the likelihood of SCC for MAB (OR, 3.0 [95% CI, 1.6–15.6]; P = .3671).

### Clinical and Radiographic Outcomes

A follow-up computed tomography scan was performed 6 months after initiation of therapy with the ALIS-containing regimen, and data were available for 22 patients as part of their follow-up.

Three of 8 nonconverters demonstrated radiographic deterioration (Tables 3 and 5). Stable or improved radiological evolution was observed for 18 patients (12 [86%] of whom showed culture conversion) (Table 5). Radiological deterioration was observed in 1 converter and 3 nonconverters (OR, 4; nonsignificant). No overall differences were observed between the converter and nonconverter groups due to a too small number of patients and, in particular, there was no significant difference in patients with or without cavitary lesions associated with condensations or bronchiectasis.

Changes in forced expiratory volume in 1 second (FEV₁) and BMI were not significantly different between converters and nonconverters (OR, 0.89 [nonsignificant] and OR, 2.62 [nonsignificant], respectively) (Table 3). A slight increase in BMI was noted in the entire population (+0.44%). Patients with CF showed a 2.9% increase in BMI whereas non-CF patients showed a mean 2.63% decrease in BMI post-ALIS. Converters demonstrated a 1.14% increase in BMI (data available for 13/14 patients) and nonconverters had a 1.8% decrease in BMI (data for 6/8 patients) (Table 5). Posttreatment spirometry data were available for 11 CF patients. Overall, a 2.44% increase in FEV₁ was observed in this group (excluding 1 patient who
underwent lung transplant). In the non-CF group (data available for n = 10), FEV₁ remained unchanged (Table 3). The entire cohort (CF and non-CF patients) did not show any change in FEV₁. Nevertheless, we observed an increasing trend in converters (+0.5%) while the nonconverter group has a FEV₁ trend of −4.2% posttreatment with ALIS (Table 5).

Two patients (6 and 8, Table 4) demonstrated conversion after 3 months of therapy. However, they both cultured Pseudomonas aeruginosa and continued to receive ALIS in order to eradicate this pathogen.

**ALIS Duration Treatment, Compliance, and Adverse Events**

Patients received treatment for an average of 10 months (range, 1–43 months). The average treatment duration of ALIS in patients who converted was 12.4 [range, 3–43] months (Table 3) and 9.1 [range, 1–35] months in patients who did not convert.

All patients who converted their sputum culture had a good compliance of ALIS. Good compliance was noted in 20 of 26 (77%) patients. SCC was achieved in 14 of 20 (70%) patients with good compliance when none of the poorly compliant patients converted their sputum culture at 6 months. Compliance data were not available for 1 patient (Tables 3 and 5). The OR of SCC was 44.78 comparing good compliance with poor compliance and was statistically significant (95% CI, 4.6–440.4; P = .049).

Adverse events were reported in 13 patients. The most commonly reported effects was cough followed by bronchospasm, dysphonia, hearing loss, and tinnitus. Nine patients stopped treatment due to side effects (Table 6). Discontinuations driven by adverse events were more common in nonconverters (50%) compared to converters (21%) (Table 5). Globally, secondary effects led to discontinuation of treatment in 7 of 20 compliant patients and 2 of 6 noncompliant patients.

**DISCUSSION**

The addition of ALIS to standard multidrug regimens for MAB-LD may lead to improved microbiological outcomes in both CF and non-CF patients. In a previous placebo-controlled trial with ALIS, SCC was reported in MAB-LD [15]. A larger open-label investigator-initiated trial is currently in the United States to assess the contribution of ALIS to a guideline-based therapy for MAB-LD [16]. In our study, the achieved SCC rate was 53.8% (n = 14/26), a higher value than the pooled estimation (34% when adjunctive surgery was excluded) reported in the meta-analysis by Diel and colleagues or in the study by Siegel and colleagues (27.3%) but comparable to the findings by Kwak and colleagues [6, 16, 17]. In addition, we observed similar SCC rates between CF and non-CF patients while the SCC was slightly better in non-CF patients as compared to CF patients in the Siegel et al study [16]. When considering the microbiological outcomes with the M abscessus subspecies, more than half of the patients with M abscessus subsp abscessus converted. Of the 17 patients with M abscessus isolates harboring the macrolide-inducible resistance gene, 9 patients culture-converted, suggesting that

![Figure 1](image-url)  
**Figure 1.** Relative proportion of patients (number) with positive (black) and negative (white) cultures for *Mycobacterium abscessus* after 3, 6, and 10–12 months of amikacin liposome inhaled suspension (ALIS) treatment. Microbiological data were available for 22 of the 26 study patients at 3 and 6 months of ALIS treatment and for 22 patients after 10–12 months of ALIS therapy. Abbreviation: M, month.

Table 5. Clinical Characteristics of Converters and Nonconverters at 6 Months of Amikacin Liposome Inhaled Suspension Treatment

| Characteristic                     | All Patients (N = 26) | Converters (n = 14) | Nonconverters (n = 8) | Unclassifiable (n = 4) |
|-----------------------------------|-----------------------|---------------------|-----------------------|------------------------|
| Mean ALIS treatment duration, mo (min–max) | 10 (1–43)             | 12.4 (3–43)         | 9.1 (1–35)            | 2.8 (1–6)              |
| Poor compliance with ALIS         | 6 (23)                | 0 (0)               | 5 (63)                | 1 (25)                 |
| Adverse event                     | 13/26 (50)            | 6 (43)              | 5 (63)                | 2 (50)                 |
| Discontinuation due to adverse event | 9/26 (35)             | 3 (21)              | 4 (50)                | 2 (50)                 |
| Radiographic signs stable/improved | 14 (54)               | 12 (86)             | 4 (50)                | 2 (50)                 |
| Mean change in FEV₁, %            | 0                     | 0.5                 | −4.2                  | 3.2                    |
| Mean change in BMI, %             | 0.44                  | 1.1                 | −1.8                  | 0                      |
| Co-pathogens at baseline (all)    | 21/26 (81)            | 13 (93)             | 6 (75)                | 2 (50)                 |
| *Pseudomonas aeruginosa*          | 10/26 (38)            | 7 (50)              | 2 (25)                | 1 (25)                 |
| *Staphylococcus aureus*           | 8/26 (31)             | 5 (36)              | 2 (25)                | 1 (25)                 |
| *Aspergillus fumigatus*           | 7/26 (27)             | 5 (36)              | 2 (25)                | 0 (0)                  |

Data are presented as No. (%) unless otherwise indicated. Abbreviations: ALIS, amikacin liposome inhaled suspension; BMI, body mass index; FEV₁, forced expiratory volume in 1 second.
| Patient ID | Adverse Event          | ALIS Discontinuation due to Adverse Event |
|-----------|------------------------|------------------------------------------|
| 3         | Bronchospasm           | Yes                                      |
| 5         | Bronchospasm           | Yes                                      |
| 12        | Hearing loss, tinnitus| No                                       |
| 13        | Hearing loss           | Yes                                      |
| 14        | Cough                  | Yes                                      |
| 15        | Cough                  | Yes                                      |
| 16        | Hearing loss, cough    | Yes                                      |
| 17        | Cough, dysgeusia       | No                                       |
| 19        | Cough                  | Yes                                      |
| 21        | Cough                  | No                                       |
| 22        | Mycosis, dysphonia     | Yes                                      |
| 23        | Cough, tinnitus        | Yes                                      |
| 26        | Cough                  | No                                       |

Abbreviation: ALIS, amikacin liposome inhaled suspension.

Recently, we have reported on a cohort of 5 CF patients with MAB-LD who were prescribed ALIS as part of a multidrug regimen. The 3 patients who were drug-compliant and completed treatment had negative cultures for *M abscessus*, did not experience pulmonary exacerbations, and lung function stabilized, while the other 2 remaining patients terminated ALIS due to poor compliance [13]. In the present larger retrospective cohort from real-world experience with ALIS in France, we assessed the association of drug compliance with ALIS as part of a multidrug regimen for MAB-LD in CF and non-CF patients with SCC and clinical outcomes and we found a strong correlation between drug compliance and SCC. SCC was achieved in 70% of patients with good compliance when none of the poorly compliant patients converted their sputum culture at 6 months. The OR of SCC was particularly high (44.78) comparing good compliance with poor compliance. Adverse events were observed in 13 patients and the types of adverse events were consistent with those reported in previous ALIS studies [12, 26]. Discontinuation due to adverse events occurred in 9 patients, predominantly in those who failed to convert. Ototoxicity was reported in 5 patients, all of whom had a previous history of intravenous amikacin treatment. Compliance with prescribed nebulizer treatment in CF in the real-world setting has been reported to be suboptimal due to treatment burden or side effect, and poor compliance was associated with unsatisfactory outcomes [27]. We found that treatment compliance was influenced by the occurrence of adverse events and that good compliance was associated with culture conversion. This emphasizes the crucial role of educating patients regarding the management of adverse events and the potential risks of premature treatment termination. Finally, patient selection for ALIS treatment, taking into consideration risk factors for potential ototoxicity and bronchospasm and regular follow-up of these, may be important to further optimize ALIS treatment.

Some limitations of this study are related to the small sample size, the retrospective design, and the heterogeneity of the cohort, including underlying and coexisting conditions as well as differences in accompanying drug regimens combined with ALIS. Furthermore, only patients from France and French overseas territories were included. Therefore, the results reported here may not reflect other regions/countries due to regional differences in healthcare systems, distinct spread of different types of *M abscessus* strains (subspecies), antimicrobial susceptibility patterns, and clinical management of NTM-PD.

**CONCLUSIONS**

This study shows a 54% SCC rate with an ALIS-containing multidrug regimen for treatment of MAB-LD in both CF and non-CF patients, which was associated with an acceptable safety profile. Efficacy of ALIS was observed for all 3 *M abscessus*
subspecies as well as in patients infected with isolates displaying macrolide-inducible resistance. Importantly, beyond SCC, radiological and lung function stabilization/ improvement were achieved in 19 of 26 (73%) and 10 of 20 (50%) patients, respectively. Adverse events and ALIS termination due to side effects were more limited in this real-world setting as compared with published data, and drug compliance was correlated with a higher SCC. Future randomized trials of ALIS-containing regimens are now warranted to support these findings for a better management of MAB-LD.

Notes
Potential conflicts of interest. The authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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