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BRIEF REPORT

# Positive Effect of Liposomal Amikacin for Inhalation on *Mycobacterium abcessus* in Cystic Fibrosis Patients

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*Mycobacterium abscessus* is difficult to eradicate. At the Montpellier CF Center, we prescribed liposomal amikacin for inhalation to 5 patients with *M abscessus* infection. The 3 patients who completed the treatment did not have any respiratory exacerbation, showed negative cultures for *M abscessus* in their sputum, and stabilized their spirometric functions.

**Keywords:** cystic fibrosis; liposomal amikacin; *Mycobacterium abscessus*; nontuberculous mycobacteria; treatment.

Cystic fibrosis (CF) is the most common, potentially lethal, autosomal recessive disease in whites [1]. It is mainly characterized by recurrent cycles of airway infections and chronic inflammation, eventually leading to permanent lung damage [1, 2]. Lung infections with nontuberculous mycobacteria (NTM) are emerging as a global threat to individuals with chronic lung diseases [3, 4]. The increase of NTM infection diagnosis in CF subjects is probably due to greater surveillance, better detection techniques, and/or shifts in the lung microbiome due to widespread antibiotic use [2].

Nontuberculous mycobacteria may infect CF patients at all ages, but mycobacterial lung disease most often occurs in patients older than 15 years, with an estimated incidence of 13%–20% [5, 6]. Infection is mostly indolent and generally progresses slowly [5]. However, a serious, life-threatening lung disease may develop in some patients, and fatal disseminated infections have been reported after lung transplantation [5]. The source of these infections is still unclear, but NTM, which are ubiquitous in water and soil, may frequently be isolated from residential sources, including showerheads and other home water sources [6–8]. In addition, a few studies suggested transmission from tap water and from person-to-person [6–8].

The genus *Mycobacterium* was introduced in 1896, and a total of 169 species and 13 subspecies have been assigned to it [9]. Although in the United States, *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus* are the most frequent pathogens, in Europe, *M abscessus* seems to be the main NTM in CF patients [2, 6, 10]. Infections due to *M abscessus* are associated with poor clinical outcomes and accelerated loss of lung function [2, 6].

Unfortunately, *M abscessus* is notoriously difficult to treat because it shows a high level of intrinsic drug resistance to many antibiotics, due to the presence of an impermeable cell wall, antibiotic-modifying/inactivating enzymes, biofilms, efflux pumps, and genetic polymorphisms in target genes [2, 3, 7]. Recent guidelines for the management of *M abscessus* infection in CF patients recommend a combined treatment with a macrolide, an aminoglycoside, and at least 1 other antibiotic [7]. Many guidelines recommend to prescribe inhaled amikacin, an aminoglycoside active against Pseudomonas *aeruginosa* as well [11]. Amikacin is available for intravenous (i.v.) administration only, and therefore clinicians prescribe the i.v. form as inhaled treatment, which is often not well tolerated by patients. Liposomal amikacin for inhalation (LAI) is delivered using an optimized nebulizer, once a day, which allows a rapid delivery of the drug throughout the respiratory tree [11]. Pharmacological studies on humans focused on the use of such a drug against *P aeruginosa* infection, but mouse models showed that LAI is also effective against NTM, as much as higher concentrations of free amikacin [2, 12]. In addition, LAI may reach high levels in alveolar macrophages, and it is associated with macrophage defects in cytokine signaling or pathogen-killing functions [11].

## METHODS

Two hundred fifteen patients (median age 19.6 years) attend our pediatric and adult CF center in Montpellier (France). Patients are regularly investigated for microbiological analysis during their follow-up according to recommendations [8]. Currently, 11 patients are chronically colonized with *M abscessus*. We decided to treat 5 of them with LAI because they recently underwent a severe rapid deterioration of their clinical status and respiratory functions. In addition, all 5 of these patients showed radiological findings compatible with *M abscessus* disease, and other diseases (such as tuberculosis) had already been ruled out. All *M abscessus* strains were genetically determined without rrs or erm 41 mutation, demonstrating no resistance

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against aminoglycosides, with a minimum inhibitory concentration (MIC) <64 μg/mL. All 5 patients were also chronically colonized by *P aeruginosa* and *S aureus*. Antibiotic prescription, based on bacteria susceptibility, seemed no longer effective for these patients. In addition, they did not tolerate inhaled amikacin (i.v. form). To prescribe LAI for *M abscessus* treatment, we obtained a Temporary Use Authorization, which is an exceptional permission to prescribe an innovative therapy before marketing authorization in France. Patients (or their parents, if minors) signed an informed consent before starting the prescribed therapy.

All evaluated patients presented with *Mycobacterium abscessus* in their sputum with at least 5 positive cultures, before LAI treatment (Table 1). At inclusion, they all underwent either a 2-week or 3-week treatment of i.v. meropenem at high doses.

We administered 590 mg of LAI (70 mg/mL), at 1 daily dose (according to a previous pharmacokinetic/pharmacodynamic study [12]), every day for 3 months and then every other month. Each patient received clarithromycin as well, as a continuous treatment, during the entire evaluation period. Patients 1, 2, and 4 showed an inducible clarithromycin resistance (MICs ≥16 μg/mL) associated with T28C substitution. Patients 3 and 5 were not resistant to clarithromycin. Patients received no other inhaled therapy during the month when they were not treated with LAI.

## RESULTS

None of the 5 patients showed any side effect related to the treatment. The prescribed inhaled drug was taken regularly by only 3 of them (ie, patients 1, 3, and 5), whereas the other 2 were not compliant and the prescription was interrupted after the first 3 months of treatment (use of LAI inferior to 4 days per week). The 3 compliant patients did not receive any i.v. antibiotic therapy, during the observational period, besides the meropenem treatment, at inclusion. The clinical evolution and sputum cultures are shown in Table 1. Two to six months after they started the treatment, all 3 compliant patients no longer showed presence of *M abscessus* in their sputum. No significant modification was detected on high-resolution computed tomography. Finally, the 3 treated patients showed stabilization or improvement of their pulmonary function test values, and their clinical symptoms improved after treatment.

## DISCUSSION

*Mycobacterium abscessus* is a rapidly growing, multidrug-resistant organism that accounts for more than half of all NTM infection in CF patients [7]. The diagnosis of NTM lung disease is based on the American Thoracic Society's guidelines, which include a combination of clinical, radiographic, and microbiologic elements, associated with a longitudinal follow-up of the patient and detection of multiple positive sputum cultures [6, 13]. Once the disease is diagnosed, a specific treatment should be prescribed. In a randomized placebo controlled trial, proposed

**Table 1. Characteristics of the 5 Patients Treated With Liposomal Amikacin for Inhalation**

| Patient ID | Year of Birth | Genetic Mutations | First MAB Infection | Number of Positive MAB Cultures Before Treatment | First LAI Prescription | Treatment Compliance | Before LAI | | | After LAI (Most Recent Visit) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Body Mass Index (kg/m$^2$) | VEMS (% of Predicted Value) | FVC (% of Predicted Value) | Most Recent Visit at CF Center | Body Mass Index (kg/m$^2$) | VEMS (% of Predicted Value) | FVC (% of Predicted Value) | Positive MAB Cultures | Negative MAB Cultures |
| 1* | 2000 | DF508/W846 | 12/2013 | 7 | 03/2016 | Good | 15.9 | 52% | 71% | 07/2017 | 17.4 (+1.5) | 71% (+19%) | 79% (+8%) | 1 since 03/2016<br>0 after 09/2016 | 4 since 09/2016 (6 months treatment) |
| 2 | 1983 | DF508/R347P | 05/2008 | 26 | 03/2016 | Drop out after 2 months | 17.4 | 27% | 56% | 06/2017 | 17.5 (+0.1) | 25% (−2%) | 51% (−5%) | 9 since 03/2016 | 0 |
| 3* | 1959 | G542X/3849 + 10kb C > T | 02/2011 | 11 | 04/2016 | Good | 18.6 | 33% | 64% | 05/2017 | 20.6 (+2.0) | 34% (+1%) | 66% (+2%) | 1 since 04/2016<br>0 after 08/2016 | 3 since 08/2016 (4 months treatment) |
| 4 | 1995 | S364P/S364P | 05/2016 | 14 | 12/2016 | Drop out after 1 month | 17.1 | 61% | 83% | 07/2017 | 16.8 (−0.3) | 56% (−5%) | 69% (−14%) | 2 since 12/2016 | 0 |
| 5* | 2005 | DF508/DF508 | 05/2016 | 5 | 12/2016 | Good | 14.0 | 60% | 65% | 06/2017 | 16.0 (+2.0) | 75% (+15%) | 83% (+18%) | 1 since 12/2016<br>0 after 01/2017 | 3 since 01/2017 (2 months treatment) |

Abreviations: CF, cystic fibrosis; FVC, forced expiratory volume in 1 second; ID, indentification; LAI, liposomal amikacin for inhalation; MAB, *Mycobacterium abscessus*; VEMS, maximum expiratory volume per second.
*Patients still under LAI treatment.

in a poster at the American Thoracic Society Conference of 2015, CF subjects with NTM lung disease were assigned to inhaled liposomal amikacin or placebo (64% *M avium* complex and 36% *M abscessus* complex), in addition to their ongoing NTM therapy [14]. At the end of the 6-month treatment period, there was a statistically significant increase in culture negativity overall and for the MAC group [2, 14].

As survival in cystic fibrosis increases, the emergence of new and resistant bacterial infections, including NTM, is an increasing concern [10]. To assure active and healthy aging for these subjects, we should (1) assess new ways to improve patients' compliance and reduce pulmonary infections and (2) decelerate the progression of the lung disease. Considering all of the above recommendations, we prescribed the new LAI in 5 of our patients who suffered from *M abscessus* infection. We hoped that the prescription of a single daily dose of nebulized therapy would improve patients' compliance. This was true for only 3 of our 5 patients. In this group, we recorded general improvement in patients' general status, a stabilization of their pulmonary function tests, an improvement of their body mass index, and the disappearance of *M abscessus* in their sputum.

A limit of our results may be that patients' improvement could be due to the activity of LAI against *P aeruginosa*. Nevertheless, *M abscessus* negative cultures support the fact that the treatment acted on this germ as well. Another limit of our findings is that our patients are still taking the drug; therefore, we have no information on possible culture conversion at the end of the therapy with LAI, as highlighted by other authors [15]. Moreover, our results are not in line with those published by Olivier et al [15]. In their study of six CF patients with *M abscessus* infection, only one showed negative cultures after treatment with LAI. We found no significant reason that could explain such discrepancy.

## CONCLUSIONS

The possibility of using a single-dose inhaled antibiotic could be associated to a better patients' compliance. Also, the fact that LAI is active on both *P. aeruginosa* and *M abscessus* could make this drug of even greater interest, and allow to modify existing guidelines. The present communication highlight the possibility of reaching a good control of *M abscessus* infection in CF patients, with a single daily dose inhaled therapy with liposomal amikacin. Further studies are needed to assess the clinical, microbiological and spirometric evolution of these patients, and to propose new guidelines.


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