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LETTER TO THE EDITOR



## Efficacy of nebulized liposomal amphotericin B in the treatment of ABPA in an HIV/HBV co-infected man: Case report and literature review

Magali Garcia, MD, PhD<sup>a,b,c</sup>, Gwénaél Le Moal, MD<sup>d</sup>, Jacques Cadranet, MD, PhD<sup>e,f</sup>, France Roblot, MD<sup>b,d,g</sup>, and Cendrine Godet, MD<sup>d</sup>

<sup>a</sup>Laboratoire de Virologie et Mycobactériologie, CHU Poitiers, Poitiers, France; <sup>b</sup>Faculté de Médecine et Pharmacie, Université de Poitiers, Poitiers, France; <sup>c</sup>EA 4331, LITEC, Université de Poitiers, Poitiers, France; <sup>d</sup>Service de Maladies Infectieuses et Tropicales, CHU Poitiers, Poitiers, France; <sup>e</sup>Service de Pneumologie, AP-HP, Hôpital Tenon, Paris, France; <sup>f</sup>Sorbonne Université, UPMC Université Paris, Paris, France; <sup>g</sup>Inserm, Poitiers, France

A 56-year-old HIV1/HBV co-infected Caucasian man with medical history of asthma and chronic obstructive pulmonary disease (COPD) presented with cough, increasing dyspnea, and general weakness. He had been diagnosed with HIV1/HBV positive 20 years before and treated since 1997. He had a recent CD4 count of 483 cells.mm<sup>-3</sup> (17%) and an HIV-1 viral load <50 copies mL<sup>-1</sup> under Highly Active Anti Retroviral Therapy (HAART) regimen (darunavir/ritonavir 600/100 mg twice a day, etravirine 200 mg twice a day). He had not been suffering from any opportunistic infection. Laboratory investigations showed an elevated peripheral blood eosinophil count (1.222 cells µL<sup>-1</sup>), total immunoglobulin (Ig)E (749 IU mL<sup>-1</sup>), specific anti-*Aspergillus fumigatus* IgE levels at 28.1 kU.L<sup>-1</sup>, and the presence of specific anti-*A. fumigatus* precipitins in the serum (two lines). A thoracic computed tomography (CT) scan revealed left apical condensation with right bronchiectasis associated with bronchocele (Figure 1A). The association of poorly controlled asthma, COPD, and clinical, biological and radiological presentations supported the diagnosis of allergic bronchopulmonary aspergillosis (ABPA).

Nebulized LAmB (25 mg twice per week) administered with a PARI TurboBOY nebulizer (PARI GmbH, Munchen, Germany) in association with nebulized budesonide (1 mg twice a day) plus budesonide and formoterol (400/12 µg, 2 inhalations, twice a day) were proposed as nebulized amphotericin B was an alternative regimen in ABPA management that is now integrated to recommended strategies (3) and because of severe comorbidities and high risk of drug interactions in this case. According to the ABPA guidelines, after four months of attack treatment, the patient presented immunological criteria for medication response (clinical and radiological (Figure 1B) response associated with a decline of total

IgE ≥20% (518 IU mL<sup>-1</sup>) (1), allowing maintenance treatment consisting of one nebulization of LAmB (25 mg) per week associated with nebulized budesonide (1 mg twice a day) plus budesonide and formoterol (400/12 µg, 2 inhalations, twice a day). Finally, after 16 months, treatment was reduced to only two nebulizations of LAmB (25 mg) per month associated with budesonide and formoterol (400/12 µg, 2 inhalations, twice a day), leading to persistent improvement of symptoms, total IgE concentration (276 IU mL<sup>-1</sup>), and radiological findings. No adverse effect in relation with nebulized LAmB was noted. After two years of follow-up, his clinical, biological, and radiological presentation, as well as his pulmonary function tests, are stable.

*Aspergillus spp.* is an ubiquitous filamentous and spore-forming fungus found in the environment and involved in several lung diseases in humans such as ABPA, *Aspergillus* bronchitis, invasive pulmonary aspergillosis, and aspergilloma. ABPA, which is a chronic hypersensitivity disease due *A. fumigatus* antigens occurring mainly in asthma, cystic fibrosis, or COPD and in genetically susceptible patients, can be complicated by exacerbations that are potentially destructive to the lungs (2) and which often necessitate prolonged treatment. Usual ABPA treatment associates systemic steroids to suppress immune hyper reactivity with anti-fungal agents (systemic triazoles) to decrease the fungal burden (3). Unfortunately, steroid-based medications are not devoid of side effects such as immunosuppression, diabetes mellitus, skin atrophy, dyslipidemia, osteopenia, hypertension, or ABPA progression to chronic pulmonary aspergillosis (4). Moreover, Azoles and Itraconazole are often poorly tolerated, and the capsule's problematic bioavailability can limit its clinical usefulness. Chishimba et al. reported up to 40% of adverse effects or therapeutic failure associated with the

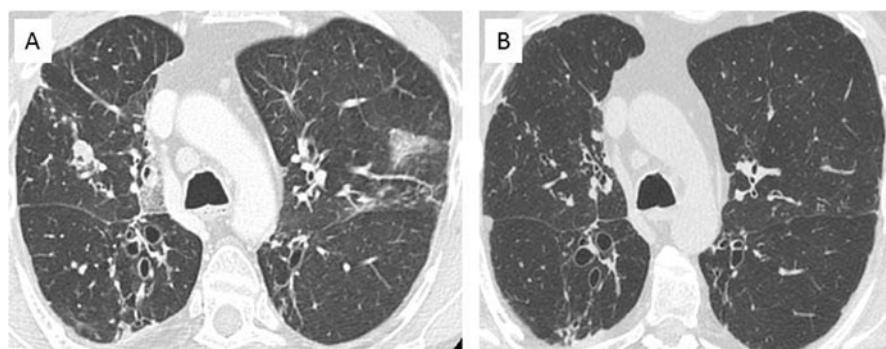


**Figure 1.** (A) Computed tomography (CT) chest images at allergic bronchopulmonary aspergillosis exacerbation. Section through the upper zones: left apical condensation with right bronchiectasis associated with bronchocele. (B) CT chest images 4 months after initiation of nebulized liposomal amphotericin B. Note resolution of consolidation and bronchocele (residual bronchiectasis).

use of itraconazole. In this study, in which treatment was second or third line with voriconazole or posaconazole, the authors described up to 55 and 22% of adverse events, respectively (5). Another treatment option for fungal infections can be nebulized liposomal amphotericin in solid transplant organs: in a cohort study of 27 lung transplant patients, a single weekly administration of nebulized LAmB (25 mg) yielded levels of amphotericin B in patients' bronchoalveolar lavage that were high enough to inhibit growth of *Aspergillus spp.* ( $2 \mu\text{g mL}^{-1}$ ) persisting for 2 weeks (6). Nebulized LAmB has also been shown to represent an effective alternative to conventional ABPA drugs, providing *in situ* heightening of antifungal lung tissue concentration, particularly in devascularized sites. At the same time, given that serum concentration of amphotericin B is negligible (6), it circumvents drug interactions, decreases the potential toxicity of systemic antifungal treatments due to the lack of plasmatic efflux, and improves eradication of *Aspergillus*. Use of a fungicide, such as nebulized liposomal amphotericin, could be of interest in limiting the risks of emerging azole-resistant strains and subsequent failure to respond to therapy (7). Furthermore, nebulized LAmB tolerance has been reported as being quite effective, particularly using lipid formulations, which contain phospholipids and cholesterol with properties similar to those of the natural surfactant (8). More recently, a cohort study (9) and a randomized prospective study (10) reported the efficacy and safety of nebulized amphotericin B in patients with ABPA, which not only allows control of the respiratory disease, but also decrease of steroid dose administrations during treatment. A randomized prospective study, presently in the inclusion phase, is likely to confirm the benefit of this strategy by leading to reduced exacerbation of clinical ABPA symptoms (NCT02273661). Preliminary results of 108 patients, enrolled and treated with nebulized LAmB, show no adverse effects secondary to nebulization, no refusal of participation, and perfect patient compliance.

In our case, because of a replicative chronic HBV infection, an HIV-1 infection, and previous HAART toxicity (Fanconi syndrome, osteoporosis and left femoral head osteonecrosis), there were a number of limitations to the usual ABPA treatment; due to drug interactions and potential side effects, triazoles and systemic steroids could not be prescribed. As a consequence, and because nebulized LAmB has been shown to represent an interesting, safe, and efficient alternative to conventional ABPA drugs, this drug was chosen to treat this patient.

ABPA is rare in HIV patients; only three cases have been reported in the literature so far (11–13). The median age in the four patients was 36 years (33–56); sex ratio was 1:1. In each case, the patients had a medical history of asthma, a CD4 count  $\geq 300 \text{ cells mm}^{-3}$  under HAART, including protease inhibitor and reverse transcriptase inhibitor. There is no guideline concerning ABPA management in HIV-patients, and due to potential immunosuppression of these patients and drug interactions with HAART, treatment of an ABPA can be challenging. In the first report, the patient was administered prednisone (1 mg/kg/day for 3 months) alone (11), whereas in the second he received itraconazole alone for 12 months (12) and in the last, the patient took both (prednisone 0.2 mg/kg/day plus itraconazole 200 mg daily for 4 months) (13). Moreover, as a substrate and strong inhibitor of cytochrome P450, triazole medication exposed the patient to many drug interactions, especially with HAART, which can lead to decreased (with reverse transcriptase inhibitor) or increased (with protease inhibitor) triazole concentrations, which entail emergence of resistant *Aspergillus* or noteworthy side effects, such as adrenal suppression, which are reinforced when combined with steroids (5,12,14,15). Indeed, itraconazole inhibiting the metabolism of several steroids can lead to hypercorticism and failure of the hypothalamo-pituitary axis.

The present case highlighted, for the first time, the efficacy of LAmB not only in controlling ABPA

exacerbation in an HIV/HBV patient, but also in preventing relapse during maintenance therapy while minimizing the toxicity of standard treatment. This regimen led to the successful treatment of our patient who had severe comorbidities and high risk of drug interactions leading to complications. Strategies using nebulized LAMB would be worth evaluating in cases refractory to standard treatment or when the reference treatment may not be extended due to interactions or side effects.

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## Declaration of interest

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