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Nebulised liposomal amphotericin-B as maintenance therapy in allergic bronchopulmonary aspergillosis: a randomised, multicentre trial

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Abstract

Background In allergic bronchopulmonary aspergillosis (ABPA), prolonged nebulised antifungal treatment may be a strategy for maintaining remission.

Methods We performed a randomised, single-blind, clinical trial in 30 centres. Patients with controlled ABPA after 4-month attack treatment (corticosteroids and itraconazole) were randomly assigned to nebulised liposomal amphotericin-B or placebo for 6 months. The primary outcome was occurrence of a first severe clinical exacerbation within 24 months following randomisation. Secondary outcomes included the median time to first severe clinical exacerbation, number of severe clinical exacerbations per patient, ABPA-related biological parameters.

Results Among 174 enrolled patients with ABPA from March 2015 through July 2017, 139 were controlled after 4-month attack treatment and were randomised. The primary outcome occurred in 33 (50.8%) out of 65 patients in the nebulised liposomal amphotericin-B group and 38 (51.3%) out of 74 in the placebo group (absolute difference -0.6% , 95% CI $-16.8-+15.6\%$; OR 0.98, 95% CI 0.50–1.90; $p=0.95$). The median (interquartile range) time to first severe clinical exacerbation was longer in the liposomal amphotericin-B group: 337 days (168–476 days) versus 177 days (64–288 days). At the end of maintenance therapy, total immunoglobulin-E and *Aspergillus* precipitins were significantly decreased in the nebulised liposomal amphotericin-B group.

Conclusions In ABPA, maintenance therapy using nebulised liposomal amphotericin-B did not reduce the risk of severe clinical exacerbation. The presence of some positive secondary outcomes creates clinical equipoise for further research.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a complex bronchopulmonary disease resulting from immunological reactions mediated against *Aspergillus fumigatus*. It occurs in approximately 0.7–13% of patients with asthma and 6–10% of those with cystic fibrosis [1–3]. ABPA is clinically characterised by the occurrence of recurrent acute episodes of exacerbations [4]. Untreated and recurrent severe exacerbations increase the risk of hospitalisation, development of bronchiectasis, permanent obstructive ventilation defect and fibrotic lung lesions [4, 5]. ABPA treatment should be started early to prevent and control exacerbations before irreversible sequelae set in [6].

The most recent expert consensus recommended a therapeutic strategy of ABPA exacerbation including systemic glucocorticoids to reduce the inflammatory component and antifungal azoles to prevent mycelium proliferation [4]. In patients with recurrent exacerbations, long-term preventive therapy may necessitate oral azoles, low-dose glucocorticoids for a nonestablished optimal duration [7]. However, multiple adverse events are common with glucocorticoids and azoles, ranging from mild to severe and persistent or life-threatening adverse events [8]. The other issue with azoles is the emergence of azole-resistant *Aspergillus* spp., which precludes long-term use [9]. As most patients require prolonged therapy, treatment goals should be met with minimal adverse reactions.

Nebulisation of amphotericin-B deoxycholate has been proposed as an alternative to itraconazole [4] with potential efficacy in maintaining remission of ABPA [10, 11]. However, the safety of this treatment is challenging, as bronchospasm may occur [11]. The lipid formulation of amphotericin-B, *i.e.* liposomal amphotericin-B (L-amphotericin-B), containing phospholipids and cholesterol with properties similar to those of the natural surfactant, are likely to be better tolerated than nonlipid formulations [12], with long-term efficacy and safety [13, 14]. A few cases of difficult-to-treat ABPA have shown durable improvement, *i.e.* reduction of exacerbations, following nebulisation of L-amphotericin-B [15, 16]. However, these observations have yet to be confirmed in a dedicated trial.

Consequently, we conducted a multicentre randomised controlled trial to determine, in patients with controlled ABPA, the impact of an additional 6-month nebulised L-amphotericin-B as maintenance therapy on the rate of severe clinical exacerbation during 24-month follow-up.

Materials and methods

Study design and oversight

The NebuLamB trial is a randomised, single-blind, placebo-controlled trial. Patients with ABPA from 30 French hospitals were randomly assigned to receive either 6 months of nebulised L-amphotericin-B or nebulised placebo as maintenance therapy after an initial 4-month attack treatment. The study was registered at clinicaltrials.gov (NCT02273661).

The study protocol (supplementary material) was approved by the ethics committee at Centre Hospitalier Universitaire de Poitiers, France (2014-000872-24). Written informed consent was obtained from all patients. The trial was overseen by a steering committee that presented information regarding the progression and monitoring of the study to the Groupe pour la Recherche et l'Enseignement en Pneumo-Infectiologie network every 4 months. An independent adjudication committee blinded to the allocated treatment was responsible for assessing all severe clinical exacerbations. An independent safety monitoring board was set up.

Research assistants regularly monitored all the centres on site to check adherence to the protocol and the accuracy of recorded data in accordance with good clinical practice guidelines. An investigator at each centre was responsible for patient screening and recruitment, adherence to the protocol, and completion of electronic case-report forms.

Participants

Adult with newly diagnosed ABPA or with previous uncontrolled ABPA during the past 2 years and presenting with exacerbation requiring attack treatment with glucocorticoids and itraconazole were eligible. ABPA was defined as follows: atopy or history of asthma; elevated serum total immunoglobulin (Ig)E level ($>417 \text{ IU}\cdot\text{mL}^{-1}$); elevated *A. fumigatus*-specific IgE level ($>0.35 \text{ kUA}\cdot\text{L}^{-1}$) or immediate cutaneous hypersensitivity to *Aspergillus* antigen; associated with two of the following criteria, documented precipitating antibodies or positive *A. fumigatus*-specific IgG, total eosinophil count $>500 \text{ cells}\cdot\mu\text{L}^{-1}$, documented radiological infiltrates consistent with ABPA.

The main exclusion criteria were cystic fibrosis, invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, exacerbation of asthma or ABPA related to ongoing pulmonary infection (supplementary material).

Inclusion and attack treatment

All included patients received an attack treatment including corticosteroids and itraconazole: oral prednisolone at $0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ for 2 weeks, followed by a gradual decrease over 6 weeks, based on clinical evolution and until discontinuation; and itraconazole (200 mg twice daily) for 4 months with dose-adjustment based on plasma monitoring (range $1.5\text{--}4 \mu\text{g}\cdot\text{mL}^{-1}$). In case of intolerance, itraconazole was substituted with voriconazole or posaconazole, according to the decision of the investigator.

Randomisation and masking

After the 4-month period of attack treatment, clinically controlled patients were randomised in a 1:1 ratio to either 6 months of nebulised L-amphotericin-B or nebulised placebo. The randomisation sequence was computer-generated, using a centralised web-based management system in permuted blocks of four (unknown to investigators), with stratification according to the centre. Only the investigator was informed on the patient's allocated maintenance treatment. The placebo kits were packaged (exterior presentation) and distributed in the same way as the nebulised L-amphotericin-B kits with the aim of keeping patients blinded to the treatment allocated by randomisation. The adjudication committee was unaware of the study groups and reviewed all severe clinical exacerbations (primary outcome) and severe clinical exacerbation related to ABPA or to asthma (secondary outcomes).

Maintenance treatment

In the nebulised L-amphotericin-B group, patients received 25 mg of nebulised L-amphotericin-B (AmBisome; Gilead Sciences, Boulogne-Billancourt, France) reconstituted in a 6 mL solution of water for injection once a week for 6 months, using a Pari TurboBoy nebuliser (Pari-GmbH; Munich, Germany). In the placebo group, patients received a nonactive treatment consisting of nebulised isotonic saline once a week for 6 months using the same procedure.

Prior to drug administration, pre-medication with nebulised salbutamol was carried out. If the first dose was well tolerated, patients were instructed by a trained staff nurse and therapy was continued at patient's home (supplementary material).

Outcomes

The primary outcome was occurrence of a first episode of adjudicated severe clinical exacerbation (related or not to ABPA) within 24 months following randomisation. Severe clinical exacerbation was defined by dyspnoea worsening beyond 7 days associated with an increasing dose of inhaled treatments (bronchodilators or corticosteroids), or the initiation of systemic corticosteroids, or hospitalisation (supplementary material) [17].

Secondary efficacy outcomes included occurrence of a first episode of adjudicated severe clinical exacerbation (related or not to ABPA) within 6 months following randomisation and of an ABPA-related or asthma-related severe clinical exacerbation within 6 and 24 months following randomisation, interval between randomisation and first severe clinical exacerbation and number of all adjudicated severe clinical exacerbations per patient during 24 months. An ABPA-related exacerbation was defined by a severe clinical exacerbation with 50% increase in total IgE from the baseline value with or without appearance of radiological infiltrates. An asthma-related clinical exacerbation was defined as being a severe clinical exacerbation without radiological changes consistent with ABPA exacerbation and absence of increase in baseline total IgE levels by >50%. Other pre-specified outcomes included number of visits or hospitalisations for respiratory symptoms as per the Asthma Control Questionnaire (ACQ)-5 [18], rate of deterioration of clinical symptoms (a composite criterion of symptom score, ACQ-5 score, Medical Research Council dyspnoea scale [19] and Global Initiative for Asthma score [20]), cumulative dose of corticosteroids, biological parameters (total IgE, *A. fumigatus*-specific IgE, *Aspergillus* precipitins, eosinophil count) at 6 and 24 months following randomisation (supplementary material). The secondary safety outcome was tolerance and side-effects of treatment during the study period.

Statistical analysis

We estimated that randomisation of 124 patients would provide the study with 80% power to show an absolute difference of 25% in the percentage of patients with first severe clinical exacerbation during the 24-month follow-up between the placebo group (absolute rate estimated at 65%) [21] and the nebulised L-amphotericin-B group at a two-sided α -level of 0.05. The number of eligible patients selected to receive the attack treatment was set at 174, allowing a dropout rate before randomisation up to 25% and a loss to follow-up of 10% during the 24 months following randomisation.

The primary outcome analysis was performed on an intention-to-treat basis. A Chi-squared test was used to compare rates of severe clinical exacerbations between the two study arms.

Numbers of severe clinical exacerbations per patient, visits or hospitalisations for respiratory symptom worsening were compared between the two groups using Poisson regression models with treatment included as an independent variable in the model. Among patients with at least one episode of severe clinical exacerbation, percentages of patients having two or more episodes were compared between the two groups of treatment using a Chi-squared test.

Kaplan–Meier curves were plotted to assess time from randomisation to a first severe clinical exacerbation and were compared using a log-rank test. Hazard ratios (HR) were calculated using Cox modelling. Median interval between randomisation and a first severe clinical exacerbation was calculated and compared between the two groups using a Wilcoxon test. Lung function parameters, ACQ-5 scores and biological parameters were compared between the two groups at 6 months and 24 months, using t-test or Wilcoxon test. Percentage changes of total IgE from randomisation to 6 months, and from 6 months to 24 months were calculated, and log-transformed changes between the two groups after adjustment on the log of the baseline level were compared using an ANCOVA.

For both primary and secondary outcomes, a planned sensitivity analysis was performed to adjust on potential unbalanced variables and on centre (considered as random effect) using logistic regression, multivariate Poisson regression or linear mixed-effect models.

A p-value <0.05 was considered statistically significant. Data analysis was performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

From March 2015 through July 2017, 174 patients were included and received the attack treatment. At 4 months, 35 did not satisfy criteria for randomisation (figure 1, supplementary figure S1). The remaining 139 patients were all asthmatic and after randomisation 65 patients were assigned to nebulised L-amphotericin-B and 74 to placebo treatment. The characteristics of the patients at inclusion and randomisation are shown in supplementary table S1 and table 1, respectively. Median time since the diagnosis of asthma was 28 years (interquartile range (IQR) 10–46 years); 106 (76.3%) out of 139 patients had a moderate airway obstruction (*i.e.* forced expiratory volume in 1 s \geq 60%). Among the 139 randomised patients, computed tomography scan showed bronchiectasis in 120 (86.0%), mucoid impactions in 38 (27.2%), high-attenuation mucoid impactions in 12 (8.6%) and infiltrates consistent with ABPA without bronchiectasis in six (4.2%).

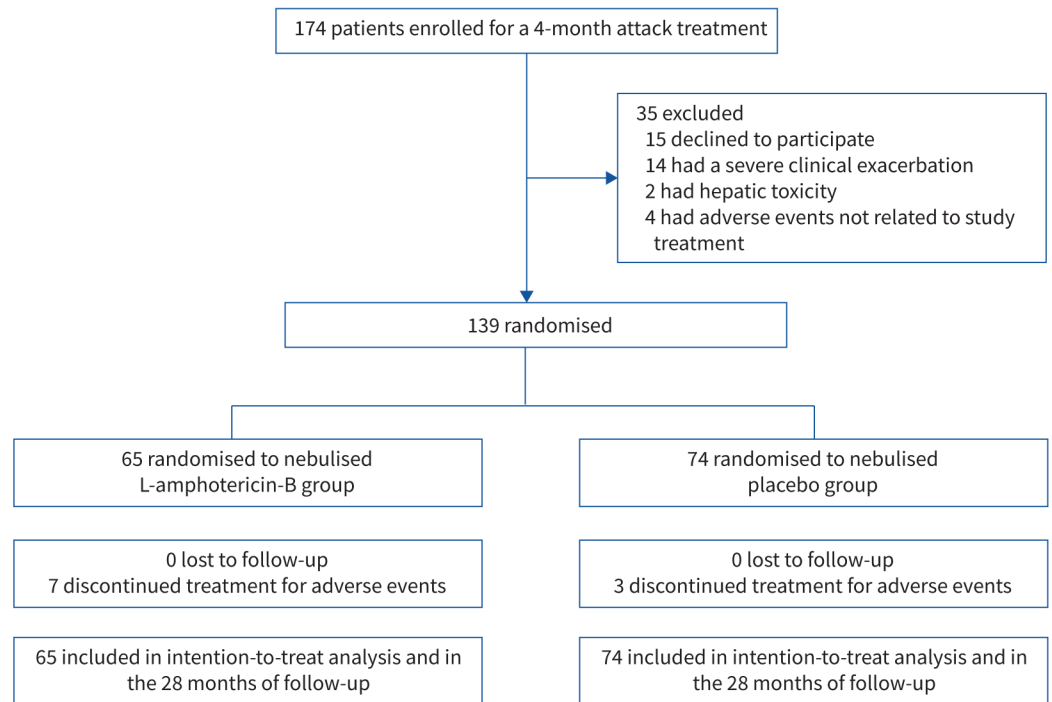


FIGURE 1 Enrolment, randomisation and follow-up of the study participants. The liposomal (L)-amphotericin-B group received therapy with 25 mg of nebulised L-amphotericin-B nebulised once a week for 6 months. Patients who were assigned to receive placebo received a nonactive treatment consisting of 2 mL nebulised isotonic saline once a week for 6 months using the same system of nebulisation.

Median (IQR) study treatment duration and post-treatment periods were 161 days (160–164 days) and 511 days (501–545 days), respectively, in the nebulised L-amphotericin-B group, and 162 days (160–168 days) and 507 days (500–531 days), respectively, in the placebo group. No loss to follow-up occurred during the 24-month study period.

Primary outcome

During the 24-month study period following randomisation, 33 (50.8%) out of 65 patients assigned to the nebulised L-amphotericin-B treatment and 38 (51.3%) out of 74 patients to placebo experienced a first severe clinical exacerbation (absolute difference -0.6% , 95% CI -16.8% – $+15.6\%$; OR 0.98, 95% CI 0.50–1.90; $p=0.95$) (table 2).

Secondary outcomes

During the 6-month study period following randomisation, nine (13.8%) out of 65 patients assigned to the nebulised L-amphotericin-B treatment group and 20 (27.0%) out of 74 patients assigned to placebo experienced a first severe clinical exacerbation (absolute difference -13.2% , 95% CI -26.0% – $+0.46\%$; OR 0.43, 95% CI 0.18–1.04; $p=0.06$) (table 2). Survival probability without severe clinical exacerbation did not differ between the two groups at 6 months (HR 0.48, 95% CI 0.22–1.05; $p=0.06$), at 12 months (HR 0.62, 95% CI 0.35–1.08; $p=0.09$) or at 24 months (HR 0.84, 95% CI 0.53–1.34; $p=0.47$) (table 2, figure 2, supplementary figure S2). Among patients who had a first severe clinical exacerbation, median (IQR) interval between randomisation and the first severe clinical exacerbation was delayed in the nebulised L-amphotericin-B group by 337 days (168–476 days) as compared to 177 days (64–288 days) in the placebo group ($p=0.004$).

In all randomised patients, the total number of severe clinical exacerbations (including first and recurrent episodes) within 24 months following randomisation was 45 in the nebulised L-amphotericin-B group and 64 in the placebo group (OR 0.80, 95% CI 0.55–1.17; $p=0.25$).

There was no significant difference in the proportion of patients experiencing a first clinical exacerbation related to ABPA or to asthma (table 2, supplementary figure S2). The rates of worsening of clinical

TABLE 1 Demographic and clinical characteristics of patients at randomisation after 4-month attack treatment, according to treatment group

	Nebulised L-amphotericin-B	Nebulised placebo
Patients	65	74
Age (years)	58±11	61±11
Male	30 (46.1)	37 (50.0)
Body mass index (kg·m⁻²)	23±3	24±4
Past or active smoker	24 (36.9)	31 (41.9)
Time since asthma diagnosis (years)	28±21	30±22
History of at least one ABPA exacerbation before attack treatment	37 (56.9)	41 (55.4)
Asthma control according to ACQ-5 score[#]		
Uncontrolled (>1.5)	23 (35.9)	32 (44.4)
Partly controlled (0.75–1.5)	18 (28.1)	12 (16.7)
Controlled (<0.75)	23 (35.9)	28 (38.9)
Asthma control according to GINA score[¶]		
Uncontrolled	17 (26.1)	17 (23.0)
Partly controlled	20 (30.8)	30 (40.5)
Controlled	28 (43.1)	27 (36.5)
Lung function		
FEV ₁ (L)	2.2±0.8	2.1±0.9
FVC (L)	3.4±1.0	3.3±1.0
FEV ₁ :FVC ratio (%)	65±14	63±13
Severity of airway obstruction		
Mild (FEV ₁ 60–80%)	52 (80.0)	54 (73.0)
Moderate (FEV ₁ 40–59%)	9 (13.8)	17 (23.0)
Severe (FEV ₁ <40%)	4 (6.2)	3 (4.0)
Biological parameters		
Total IgE levels (IU·mL ⁻¹)	366 (170–918)	618 (257–1874)
<i>Aspergillus fumigatus</i> -specific IgE levels (kUA·L ⁻¹)	7.8 (2.0–24.5)	12.5 (1.8–39.1)
<i>Aspergillus</i> precipitins	9/27 (33.3)	18/42 (42.9)
Positive <i>Aspergillus fumigatus</i> -specific IgG	27/44 (61.4)	25/53 (47.2)
Total eosinophil count (cells·μL ⁻¹)	200 (60–360)	131 (70–360)
Chest HRCT scan findings		
Normal HRCT scan	0	0
Bronchiectasis [†]	57 (88.0)	63 (85.0)
Bronchiectasis with muroid impactions	17 (26.1)	21 (28.4)
High-attenuation muroid impactions	5 (7.7)	7 (9.5)
Infiltrates consisting with ABPA without bronchiectasis	2 (3.1)	4 (5.4)
Asthma treatment		
Inhaled glucocorticoid	56 (86.1)	66 (89.2)
Dose of inhaled glucocorticoid (μg·day ⁻¹) [§]	598 (316)	530 (313)
Long-acting bronchodilator	55 (84.6)	56 (75.7)
Systemic glucocorticoids	13 (20.0)	19 (25.7)
Dose of systemic glucocorticoids (mg·day ⁻¹) ^f	10 (6)	15 (13)

Data are presented as n, mean±SD, n (%) or median (interquartile range). ABPA: allergic bronchopulmonary aspergillosis; ACQ-5: Asthma Control Questionnaire-5; GINA: Global Initiative for Asthma; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; Ig: immunoglobulin; HRCT: high-resolution computed tomography. [#]: scores after 4-month attack treatment. The ACQ-5 consists of five questions about asthma symptoms in the previous week, each of which is scored on a range from 0 (no impairment) to 6 (maximum impairment). Data were missing for one patient in the nebulised liposomal (L)-amphotericin-B group and for two patients in the nebulised placebo group. [¶]: six questions about asthma symptoms in the 7 previous days, defining three stages of asthma severity (controlled, partially controlled and uncontrolled). [†]: classified according to the ratio of the bronchial lumen and arterial diameters (mild: ratio <2; moderate: ratio 2–3; severe: ratio >3). [§]: cumulative dose expressed in beclomethasone dipropionate equivalents. ^f: cumulative dose expressed in prednisolone equivalents.

TABLE 2 Primary and secondary outcomes according to treatment group

	Nebulised L-amphotericin-B	Nebulised placebo	p-value	OR or rate ratio (95% CI)
Patients	65	74		
Primary outcome				
First severe clinical exacerbation at 24 months	33 (50.8)	38 (51.3)	0.95	0.98 (0.50–1.90)
Secondary outcomes				
First severe clinical exacerbation at 6 months (end of maintenance therapy)	9 (13.8)	20 (27.0)	0.06	0.43 (0.18–1.04)
First severe clinical exacerbation at 12 months	20 (30.8)	32 (43)	0.13	0.58 (0.29–1.17)
Interval between randomisation and exacerbation at 24 months (days)	337 (168–476)	177 (64–288)	0.004	
Number of severe clinical exacerbations at 24 months	45	64	0.25	0.80 (0.55–1.17)
Number of severe clinical exacerbations per patient at 24 months	0.7	0.9	0.28	
Number of severe clinical exacerbations/number of patients with at least one severe clinical exacerbation at 24 months			0.03	
One episode	24/33 (72.7)	18/38 (47.4)		
Two or more episodes	9/33 (27.3)	20/38 (52.6)		
First severe exacerbation related to ABPA				
At 6 months (end of maintenance therapy)	8 (12.3)	12 (16.2)	0.51	0.73 (0.28–1.90)
At 24 months	24 (36.9)	25 (33.8)	0.70	1.15 (0.57–2.30)
First severe exacerbation related to asthma				
At 6 months (end of maintenance therapy)	2 (3.1)	5 (6.8)	0.45	0.44 (0.08–2.34)
At 24 months	9 (13.8)	14 (18.9)	0.42	0.69 (0.28–1.72)
Number of consultations	320	397	0.25	0.92 (0.79–1.06)
Number of hospitalisations	42	47	0.93	1.02 (0.67–1.54)
Impairment of clinical symptoms[#]				
At 6 months (end of maintenance therapy)	54 (83.1)	62 (84)	0.91	
At 24 months	63 (96.9)	68 (91.9)	0.28	
Lung function				
At 6 months (end of maintenance therapy)				
FEV ₁ (L)	2.1±0.8	2.0±0.8	0.76	
FVC (L)	3.3±1.0	3.3±1.0	0.99	
At 24 months				
FEV ₁ (L)	2.1±0.8	2.1±0.8	0.45	
FVC (L)	3.4±1.0	3.2±0.9	0.39	
Biological parameters				
Total IgE levels (IU·mL⁻¹)[¶]				
At 6 months (end of maintenance therapy)	298 (184–1039)	679 (318–2339)	0.004	
At 24 months	579 (299–1181)	851 (253–1791)	0.44	
Change in total IgE (%)				
From randomisation to 6 months	-5.6 (-33.7–44.0)	21.9 (-16.7–87.6)	0.006	
From 6–24 months	50.0 (-11.6–125.3)	13.7 (-46.5–79.6)	0.31	
<i>Aspergillus fumigatus</i>-specific IgE levels (kUA·L⁻¹)⁺				
At 6 months (end of maintenance therapy)	5 (2–16)	13 (2–31)	0.06	
At 24 months	10 (3–20)	12 (2–38)	0.46	
Positive <i>Aspergillus</i> serology[§]				
At 6 months (end of maintenance therapy)	21/48 (43.7)	35/54 (64.8)	0.03	
At 24 months	34/54 (63.0)	30/54 (55.5)	0.43	
<i>Aspergillus</i> precipitins				
At 6 months (end of maintenance therapy)	9/34 (26.5)	20/35 (57.1)	0.01	
At 24 months	17/41 (41.5)	15/34 (44.1)	0.81	
Positive <i>Aspergillus fumigatus</i>-specific IgG				
At 6 months (end of maintenance therapy)	21/47 (44.7)	34/53 (64.1)	0.05	
At 24 months	33/54 (61.1)	29/54 (53.7)	0.44	
Total eosinophil count (cells·μL⁻¹)^f				
At 6 months (end of maintenance therapy)	400 (180–700)	440 (200–800)	0.67	
At 24 months	340 (200–580)	260 (100–560)	0.15	
Asthma treatment cumulative dose at 6 months				
Inhaled glucocorticoids (μg·day ⁻¹)	500 (288–640)	454 (278–563)	0.73	
Systemic glucocorticoids (mg)	0 (0–340)	0 (0–765)	0.16	

Continued

TABLE 2 Continued

	Nebulised L-amphotericin-B	Nebulised placebo	p-value	OR or rate ratio (95% CI)
Asthma treatment cumulative dose at 24 months				
Inhaled glucocorticoids ($\mu\text{g}\cdot\text{day}^{-1}$) ^{##}	500 (320–772)	487 (316–630)	0.44	
Systemic glucocorticoids (mg) ^{¶¶}	420 (0–2180)	858 (70–3374)	0.22	
Immediate tolerance of nebulised maintenance therapy				
Dyspnoea	15 (23.1)	7 (9.5)	0.02	
Cough	20 (30.7)	11 (14.9)	0.02	
Nausea	9 (13.8)	13 (17.6)	0.57	
Vomiting	2 (3.1)	4 (5.4)	0.69	
Headache	12 (18.5)	18 (24.3)	0.42	
Reasons for maintenance therapy discontinuation				
Decision of patient (not related to an adverse event)	4 (6.1)	1 (1.3)		0.19
Hypersensitivity syndrome	2 (3.1)	0 (0.0)		
Persistent cough	0 (0.0)	1 (1.3)		
Severe clinical exacerbation	1 (1.5)	1 (1.3)		

Data are presented as n, n (%), median (interquartile range) or mean \pm sd, unless otherwise stated. Results adjusted on total immunoglobulin (IgE) levels (expressed as log IgE) at randomisation and centre as random effect were as follows. 1) For first severe clinical exacerbation: adjusted OR at 6 months 0.43 (0.17–1.03), p=0.07; adjusted OR at 24 months 1.05 (0.53–2.08), p=0.89. 2) For first severe exacerbation related to allergic bronchopulmonary aspergillosis (ABPA): adjusted OR at 6 months 0.70 (0.24–1.94), p=0.50; adjusted OR at 24 months 1.18 (0.58–2.41), p=0.65. 3) For first severe exacerbation related to asthma: adjusted OR at 6 months 0.42 (0.06–2.12), p=0.32; adjusted OR at 24 months 0.64 (0.24–1.66), p=0.37. 4) For number of severe clinical exacerbations: adjusted rate ratio 0.80 (0.54–1.18), p=0.27. 5) For number of consultations: adjusted rate ratio 0.93 (0.80–1.08), p=0.37. 6) For number of hospitalisations: adjusted rate ratio 1.24 (0.66–1.57), p=0.93. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: composite criterion of symptoms score, i.e. cough, sputum, wheezing, chest pain according to a rating of 0–3, Asthma Control Questionnaire-5 score, Medical Research Council dyspnoea scale and Global Initiative for Asthma score; [†]: at 6 months therapy data were available in 62 and 68 patients, and at 24 months in 58 and 61 patients in the nebulised liposomal (L)-amphotericin-B and nebulised placebo groups, respectively; [‡]: at 6 months therapy data were available in 56 and 69 patients, and at 24 months in 52 and 54 patients in the nebulised L-amphotericin-B and nebulised placebo groups, respectively; [§]: patient showing *Aspergillus precipitins* ≥ 2 and/or positive *A. fumigatus*-specific IgG; [¶]: at 6 months therapy data were available in 61 and 71 patients, and at 24 months in 61 and 67 patients in the nebulised L-amphotericin-B and nebulised placebo groups, respectively; ^{##}: cumulative dose expressed in beclomethasone dipropionate equivalent; ^{¶¶}: cumulative dose expressed in prednisolone equivalent.

symptoms, mean cumulative dose of corticosteroids and lung function parameters did not differ between the two groups either at 6 or at 24 months following randomisation (table 2, table 3 and supplementary figure S3).

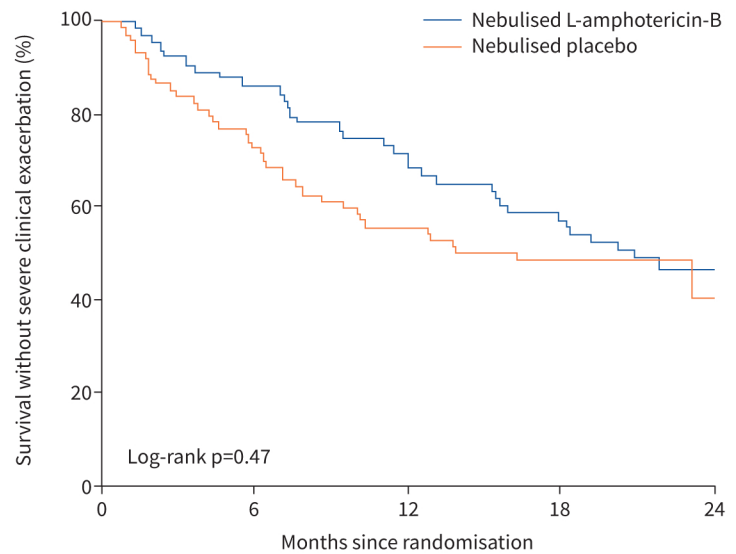
The plasma levels and the percentages of change of total IgE were significantly lower at 6 months in the nebulised L-amphotericin-B group as compared to the placebo group, even after adjustment for IgE levels at the end of attack treatment and on centre (adjusted p=0.046), but levels at 24 months and percentages of change from 6 to 24 months were not different (table 2, figure 3). Additionally, the levels of *Aspergillus precipitins* were significantly lower at 6 months in the nebulised L-amphotericin-B group as compared to the placebo group, but were not different at 24 months (table 2, figure 3). Levels of *A. fumigatus*-specific IgE and total eosinophil count did not differ between the two groups at either 6 or 24 months (table 2, supplementary figure S4).

In an exploratory analysis, among the 71 patients experiencing severe clinical exacerbations, nine (27.3%) out of 33 in the nebulised L-amphotericin-B group and 20 (52.6%) out of 38 in the placebo group had two or more exacerbation episodes (absolute difference –25.4%, 95% CI –44.6– –2.5; p=0.03).

Safety outcomes

During the 4-month attack treatment period, 40 (23.0%) out of 174 patients received 100 mg itraconazole (in place of 200 mg) twice daily after monitoring and adaptation to residual concentrations.

For two patients, itraconazole was switched to voriconazole due to hepatotoxicity. A complete list of adverse events before randomisation is provided in supplementary table S2. Immediate tolerance of nebulised L-amphotericin-B treatment was followed by an increased number of episodes of dyspnoea and cough as compared to placebo treatment leading to withdrawal from the study treatment for one patient (table 2). During the 6 months of maintenance therapy, no serious adverse event was observed, while 21 mild and moderate adverse events occurred in 13 patients, including 12 mild and two moderate events



At risk (n)	0	6	12	18	24
Nebulised L-amphotericin-B	65	54	43	36	30
Nebulised placebo	74	52	39	34	33

FIGURE 2 Kaplan–Meier plot of the cumulative probability of survival without severe clinical exacerbation from randomisation to 24-month follow-up. L-amphotericin-B: liposomal amphotericin-B.

during the nebulised L-amphotericin-B treatment. Maintenance therapy was discontinued in 10 patients: seven in the L-amphotericin-B group (two hypersensitivity syndromes) and three in the placebo group (supplementary tables S3 and S4).

TABLE 3 Deterioration of clinical symptoms at 6 and 24 months after randomisation according to treatment group

	Nebulised L-amphotericin-B	Nebulised placebo	p-value
Patients	65	74	
Score evaluated by patient			
At 6 months	30 (46)	24 (32)	0.96
At 24 months	47 (72)	43 (58)	0.08
MRC			
At 6 months	24 (37)	27 (36)	0.96
At 24 months	47 (72)	44 (59)	0.11
GINA			
At 6 months	20 (31)	27 (36)	0.48
At 24 months	37 (57)	42 (57)	0.98
ACQ-5			
At 6 months	45 (69)	50 (68)	0.83
At 24 months	59 (91)	65 (88)	0.58
Overall impairment of clinical symptoms[#]			
At 6 months	54 (83)	62 (84)	0.91
At 24 months	63 (97)	68 (92)	0.28

Data are presented as n or n (%), unless otherwise stated. MRC: Medical Research Council; GINA: Global Initiative for Asthma; ACQ: Asthma Control Questionnaire; L-amphotericin-B: liposomal amphotericin-B. [#]: defined by at least one of the following criteria: increase of $\geq 50\%$ in the score evaluated by patients (score evaluating each of the following symptoms: cough, sputum, wheezing and chest pain, according to a rating of 0–3); and/or a deterioration of dyspnoea as assessed by the MRC score; and/or a deterioration of asthma control, as assessed by the investigator, according to control levels defined by GINA guidelines; and/or a deterioration of asthma control as assessed by the patient according to the ACQ-5 questionnaire.

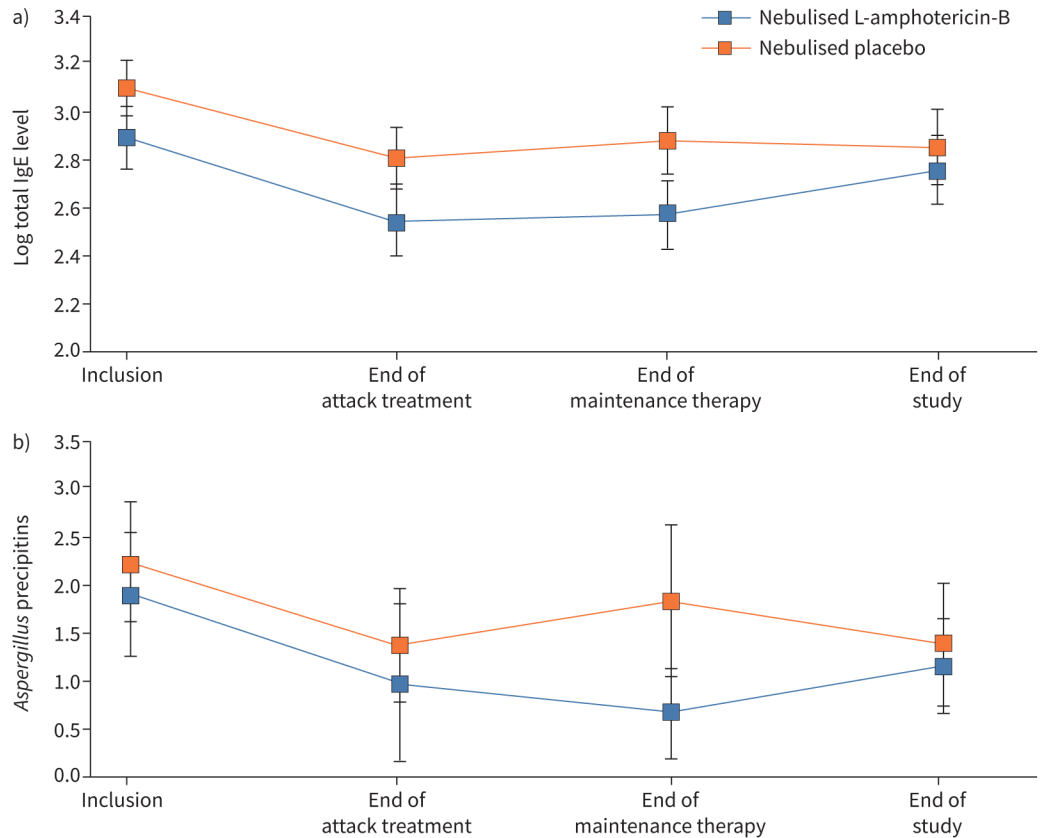


FIGURE 3 Changes in immunological findings, total immunoglobulin (IgE) level and *Aspergillus* precipitins in the two groups from inclusion to 28 months. Randomisation took place at 4 months. Data are presented as mean and 95% confidence intervals. **a)** Total IgE levels at the end of maintenance therapy were significantly lower in the nebulised liposomal (L)-amphotericin-B group than in the placebo group, even after adjustment on IgE levels at the end of attack treatment and on centre (not-adjusted $p=0.004$, adjusted $p=0.046$); **b)** numbers of *Aspergillus* precipitins at the end of maintenance therapy were significantly lower in the nebulised L-amphotericin-B group than in the placebo group, even after adjustment on IgE levels at the end of attack treatment and on centre (not-adjusted $p=0.01$, adjusted $p=0.034$).

Discussion

In this multicentre, randomised, clinical trial including patients with controlled ABPA after an initial 4-month attack treatment, an additional 6-month nebulised L-amphotericin-B treatment as compared to placebo did not improve the primary outcome on the rate of first severe clinical exacerbation during 24 months of follow-up. There were some differences favouring nebulised L-amphotericin-B in some secondary outcomes, including a longer median interval between randomisation and first severe clinical exacerbation and fewer recurrences of severe exacerbations per patient during 24 months of follow-up, and decreased levels of total immunoglobulin-E and *Aspergillus* precipitins at the end of the 6-month study treatment. Moreover, the study treatment was largely devoid of major side-effects and no bronchospasm occurred.

When planning the study, we assumed an exacerbation rate of 65% in the placebo group, based on a few retrospective cohorts [21]. Our results showed a rate of exacerbation lower than expected in the placebo group, possibly related to a strong effect of placebo treatment, and a rate in the nebulised L-amphotericin-B group in the upper level (51%) compared to those found in previous reports (22–67%) [10, 22, 23].

The observation of a decrease in ABPA-related biological parameters and a nonsignificant 50% reduction of severe exacerbation at the end of maintenance therapy is consistent with the results of two monocentre randomised trials evaluating the benefits at 1 year of prolonged therapy with nebulised amphotericin-B deoxycholate and itraconazole [10, 24]. The first study showed improvement of clinical and immunological

response during an additional 4-month period of itraconazole therapy *versus* placebo after an initial attack treatment [24] and the second, an open randomised trial, showed a reduction of clinical exacerbations during amphotericin-B deoxycholate maintenance therapy [10]. In patients with recurrent exacerbations or treatment-dependent ABPA, long-term therapy with oral azoles, low-dose glucocorticoids or nebulised amphotericin B has been proposed [7]. However, the available studies are lacking in power and highlight a sizable number of adverse effects that are well known for prolonged glucocorticoids (osteopenia, diabetes, Cushing disease, infection risks, *etc.*) [22], potentially persistent and severe for azoles (neurotoxicity, hepatotoxicity, cardiotoxicity, *etc.*) [8] and in some cases immediate bronchospasm limiting use of nebulised deoxycholate amphotericin-B [11].

Although during the 24-month follow-up period the experimental strategy did not result in a reduction of the overall cumulative incidence of a first severe exacerbation in ABPA patients, it was associated with delayed occurrence of a first severe exacerbation and a reduction of the number of exacerbation episodes per patient in the “frequent exacerbator” phenotype (exploratory outcomes). These are clinical elements of major importance regarding patient comfort and ABPA stability. Moreover, a significant reduction of major biomarkers in ABPA monitoring such as total IgE and *Aspergillus* precipitins was observed at the end of maintenance treatment, which represents supplementary favourable results underlining the achievement of stability. Biological improvements were gradually lost, suggesting that as long as it is pursued, maintenance therapy might be beneficial [25]. These raise the question of the first step of a maintenance therapy, which could be to maintain patient stability. Therefore, future studies evaluating the impact of longer duration of maintenance therapy on clinical outcomes and also on patient centred outcomes are needed.

Our study has several strengths. To date, it represents the first multicentre, randomised, placebo-controlled trial comparing extended therapy with nebulised L-amphotericin-B to nebulised placebo, during a long follow-up of 24 months. Second, liposomal formulation of amphotericin-B treatment ensured better tolerance than amphotericin-B deoxycholate [11]. It bears mentioning that the treatment is easy to apply in a home setting, its feasibility having previously been demonstrated in low-resource countries [10]. No cases were observed to be lost to follow-up during the 24-month study period. Lastly, primary and secondary outcomes included adjudicated exacerbations, as well as quality-of-life questionnaires, with subjective scoring.

The L-amphotericin-B regimen in our study can be considered as a limitation and consequently the cause of the negative result on the primary outcome. Once weekly dosing for 6 months may not be sufficient to eradicate the fungi and may subsequently result in persistent local inflammation and disease progression [7]. However, this regimen was based in a previous study including lung transplant patients and reporting that one weekly administration of 25 mg nebulized L-amphotericin-B achieved sufficiently high concentrations in bronchioloalveolar liquid to inhibit *Aspergillus* growth (minimal inhibitory concentration $>2\mu\text{g}\cdot\text{mL}^{-1}$) for a 2-week period [13].

Although this study did not meet its pre-specified primary outcome, our data provide some differences favouring nebulised L-amphotericin-B in secondary outcomes including a prolonged interval prior to exacerbation and fewer recurrences of severe exacerbations per patient during 24-month follow-up, and decreased levels of total IgE and *Aspergillus* precipitins at the end of 6 months of maintenance therapy. The clinical relevance of these findings raises the issue of benefit of a maintenance therapy as long as it is pursued and creates clinical equipoise for further research.

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