

ORIGINAL ARTICLE

Efficacy and safety of nebulised amphotericin B (NAB) in severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA)Livingstone Chishimba, MBChB, MRCP^{1,2,3}, Philip Langridge², Georgina Powell², Robert M. Niven, FRCP^{1,3}, and David W. Denning, FRCP^{1,2}¹Manchester Academic Health Science Centre, University Hospital South Manchester NHS Foundation Trust, The University of Manchester, Manchester, UK, ²The National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK, and ³North West Lung Centre, University Hospital of South Manchester, Manchester, UK**Abstract**

Background and rationale: Antifungal therapy for severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) remains poorly studied. We assessed the efficacy and safety of NAB as second and third line therapy in SAFS and ABPA. **Methods:** 21 adult asthmatics with SAFS ($n = 11$) and ABPA ($n = 10$) who had either failed itraconazole ($n = 8$), voriconazole proceeded by itraconazole ($n = 5$) or developed adverse events (AEs) to either agent ($n = 7$) were treated with 10mg of NAB (Fungizone) twice daily. We audited clinical and immunological response, using the Asthma Quality of Life Questionnaire (AQLQ-J) scores, asthma control, FEV1, healthcare utilisation and IgE. Patients were followed up for 12 months. **Results:** Twenty-one patients were treated (SAFS, $n = 11$) and (ABPA, $n = 10$), M: F = 8:12, median age 65 years (range, 24–78). The median duration of therapy was 30 days (0–1825). Clinical benefit was observed in three (14.3 %) in which overall mean AQLQ-J score improved by +2.9, mean FEV1 improved by 0.5 L and there was improvement in overall asthma control. Seven (33%) failed initial dose (bronchospasm). Eleven (52.4%) discontinued within 12 months of therapy due to delayed bronchospasm ($n = 3$, within 4 weeks), equipment problems ($n = 2$, within 4 weeks) and lack of clinical benefit ($n = 4$, within 16 weeks). **Conclusion:** Our data suggest that the overall efficacy of NAB in this group of patients is poor and associated with bronchospasm. However, the excellent response in 3 patients, suggest it may be considered when other alternatives have been exhausted. Overcoming the initial bronchospasm may improve tolerability.

Keywords

Asthma, asthma pharmacology, aspergillus lung disease, allergic lung disease

History

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Introduction

Severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA) are progressive and complex lung diseases whose treatment is not yet fully established. Not only are many patients with asthma desperately disabled by their disease, but, in the UK alone, asthma accounts for more than 1000 deaths per year [1,2]. The healthcare costs of these patients are enormous and any treatment option merits evaluation [3]. Epidemiological data estimates ABPA to occur in about 0.7–3.5% adult asthmatics [4] and 7.8% cystic fibrosis (CF) [5]. In the asthma population, severe asthma occurs in 5–10%, of which about 33% (25–50%) are estimated to have fungal sensitisation and

therefore qualify for the diagnostic label SAFS, unless they have ABPA with severe asthma [6].

Traditionally, treatment for allergic fungal disease has involved the use of systemic oral corticosteroids (OCS) to suppress inflammation and immunological activity [7]. Randomised controlled trials (RCTs) show that treatment with oral itraconazole offers therapeutic benefit to approximately 60% of ABPA patients [8]. Similarly, a marked beneficial effect on quality of life (QOL) and other end points have been demonstrated among patients with SAFS treated with itraconazole [9]. Recent data suggest that treatment with voriconazole or posaconazole improves asthma severity, control and QOL in both SAFS and ABPA and leads to resolution of pulmonary consolidation and cavitation in ABPA patients [10], although a blinded RCT with voriconazole and SAFS did not show more benefit than placebo [11].

Despite improving asthma and ABPA control, the chronic use of OCS has a number of adverse effects (AEs) including predisposition to diabetes, osteopenia, thinning of the skin.

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In COPD, corticosteroids may predispose to serious bacterial pneumonia [12]. Itraconazole is associated with several drug interactions and AEs, including suppression of adrenal glucocorticoids synthesis especially when co-administered with inhaled corticosteroids (ICS) [13]. Voriconazole is associated with intolerable AEs in about 26% patients, notably hepatic toxicity, photosensitivity and skin cancer, peripheral neuropathy, impaired thought process and frequent relapses [10]. Posaconazole therapy is better tolerated, but has some AEs and substantial cost limitations for long term therapy. Thus, there is need to evaluate other potential therapeutic options.

Over the last decade, NAB has been proposed and used in heart and lung transplant and neutropenic patients for prevention and treatment of invasive fungal infections (IFI) [14]. More recently, some published case reports indicate that liposomal NAB (L-NAB) may have a role in the treatment of CF ABPA and in corticosteroid dependant ABPA [15,16]. A major benefit was demonstrated in 3 CF ABPA patients with improvement in hypoxemia, FEV1, reduction in serum IgE and precipitins to *A. fumigatus* [17].

Despite these promising results, data in asthmatic patients are scanty, safety remains uncertain and most data relate to single case reports with short follow up durations. In some cases treatment has been used in combination with nebulised corticosteroid ($n = 3$) [17] or oral prednisone ($n = 2$) [18] and it is unclear which of the two therapeutic agents contributed to the reported efficacy [17]. The optimal duration of therapy is unclear and there is lack of clarity regarding the safety of prolonged use of nebulised therapy. The vast majority of data relate to transplant [19], hematological [20] and CF patients [15,17,21]. Little is known regarding the appropriateness of NAB in asthmatic ABPA patients or SAFS. In this study, we assessed the efficacy and safety of NAB as second and third line therapy in SAFS and ABPA asthmatics patients attending the National Aspergillosis Centre (NAC) and the regional severe asthma service.

Methods and materials

Study design and setting

Twenty-one adult asthmatics with SAFS ($n = 11$) and ABPA ($n = 10$) who were attending fungal allergic asthma outpatient clinics at the NAC and North West Lung Centre Severe Asthma Service (NWLCSAS), based at the University Hospital of South Manchester, UK, were treated with non-liposomal nebulised amphotericin B (NL-NAB) (January 2011–May 2013). Patients were only considered for this treatment if they had experienced adverse events, treatment resistance or had failed to respond to sequential trials of all available oral azoles. We audited clinical and immunological response.

Study endpoints

Our primary measure was change in Juniper Asthma Quality of Life Questionnaire (AQLQ-J) scores. We also examined asthma control parameters, change in lung function (FEV1), reduction in oral corticosteroid (OCS) dosages, change in IgE (total and specific) and healthcare utilisation.

Inclusion criteria

Men or women with asthma, age (18–70 years old), an established diagnosis of asthma (BTS asthma guidelines 2009) and either SAFS or ABPA based on standardised diagnostic criteria [22–24] were audited. Patients had either failed itraconazole and were refused funding for voriconazole ($n = 8$), failed voriconazole and itraconazole ($n = 5$) or developed adverse events (AEs) to either/both agents ($n = 8$). All patients needed to be symptomatic or to have any one or markers of significant clinical or radiological deterioration at the start of treatment.

Exclusion criteria

Subjects were excluded if they did not fulfil the diagnostic criteria for SAFS or ABPA could not follow instructions and/or were unable to do the treatment. We excluded patients with concomitant diseases or conditions that are known to affect serum IgE concentrations such as strongyloidiasis, eosinophilic pneumonia, hyper-IgE syndrome, and ongoing immunotherapy. Patients in whom more than 15% reduction in FEV1 following first NAB challenge was observed, were withdrawn immediately from the NAB therapy.

Definitions

Severe asthma was defined according to the BTS criteria (treatment steps 4 or 5) [25]. We used published criteria for the diagnosis of *SAFS* which included (i) severe asthma (ii) total IgE < 1000 kU/L and (iii) positive skin test or raised specific IgE to any fungus [24].

ABPA was diagnosed if they met the following criteria ii, iv and at least 2 others: (i) asthma (of any severity), (ii) highest total serum IgE ≥ 1000 kU/L, (iii) immediate cutaneous reaction to *A. fumigatus* of > 3 mm compared to control or (iv) elevated *A. fumigatus*-specific serum IgE levels, (v) precipitating antibodies to *A. fumigatus* in the serum, (vi) a history of pulmonary infiltrates (transient or fixed), (vii) central bronchiectasis (CB), (viii) a history of expectoration of brown plugs or flecks and (ix) isolation of *A. fumigatus* from sputum [23,26].

Drug administration procedure

Baseline spirometry was done in clinic immediately prior to drug administration followed by pre-medication with 2.5 mg nebulised salbutamol. 10mg amphotericin B (Fungizone) in 4 mL water for injection was administered via a Pari Sprint nebuliser fitted with exhaust filter under direct physiotherapist supervision. Spirometry was performed immediately post dose. Rescue bronchodilators (nebulised salbutamol) with or without prednisolone were administered if bronchospasm (demonstrated by breathlessness, wheeze) or if more than 15% reduction in FEV1 following NAB challenge was observed. If the initial dose was tolerated, 10mg of NAB (Fungizone) was self-administered twice daily at home. Patients were given education regarding drug dilution, adverse events including potential for delayed bronchospasm, care and sterilisation of equipment at time of challenge in clinic. To complete the challenge procedure successfully, patients had to demonstrate competence in performing the dilution process, equipment assembly and drug administration

at home. All patients had telephone access to the specialist nurses to discuss problems if/when encountered. Each of our patients received telephone calls from our specialist nurse within 72 h following initiation of therapy.

Follow up, data collection and assessments.

Patients were followed up and assessed at 1, 2, 6 and 12 months during which they were prospectively reviewed for clinical characteristics, immunological markers, GP or emergency room visits, lung function (FEV1) and medication use (including OCS use). The clinical data collected included percentage (%) of symptom-free days, number of exacerbations, hospitalisations per month and AEs.

Patients were given the AQLQ-J [27] for self-scoring and asthma control was assessed based on the GINA criteria. Retrospective scoring was also included for some patients whose scores were not available at the time of enrolment.

Prednisolone was used as the reference steroid when comparisons of OCS were required. Similarly, beclomethasone dipropionate (BDP) equivalent dose was used as reference for inhaled corticosteroid (ICS).

Statistical analysis

All analyses were performed with the software SPSS 20.0 (IBM, Armonk, NY) for Windows and excel statistics. Descriptive statistics was used to summarise the data. We included analysis on data collected prospectively on 15 (71.4%) and retrospectively on 6 (28%) patients. Subjects whose data was unavailable were excluded from analysis. Because of the small sample size that completed the study, no significance tests were conducted.

Results

Patient characteristics

There were 21 patients analysed (SAFS, $n = 11$) and (ABPA, $n = 10$), M: F = 12:9, median age 65.5 years (range, 24–78).

The mean BMI was 28.6 (SD = 4.9). The median duration of therapy was 30 days (0–1825). Eight (38 %) of the patients took therapy for more than 4 weeks (4–20 weeks, $n = 5$; > 20 weeks, $n = 3$). The mean baseline FEV1 was 1.86 L (± 0.53) for all patients. SAFS patients had slightly higher spirometry (FEV1, FEV1% predicted, FEV1/FVC %) values than ABPA patients (Table 1).

Treatment outcomes

Clinical benefit was observed in three (14.3%) patients and adverse events occurred in 12 (57.1%) (Figure 1). The most common AE was immediate bronchospasm occurring in 7 (33.3%) patients and accounting for 58.3% of all adverse events (AEs) (Figure 2). None of these were serious adverse events (SAEs). A further 11 (55%) patients discontinued therapy within 60 days of therapy due to delayed bronchospasm ($n = 3$, within 4 weeks), equipment problems ($n = 2$) and due to lack of clinical benefit ($n = 4$) (Figures 1 and 2). The time to discontinuation of therapy and the proportion of

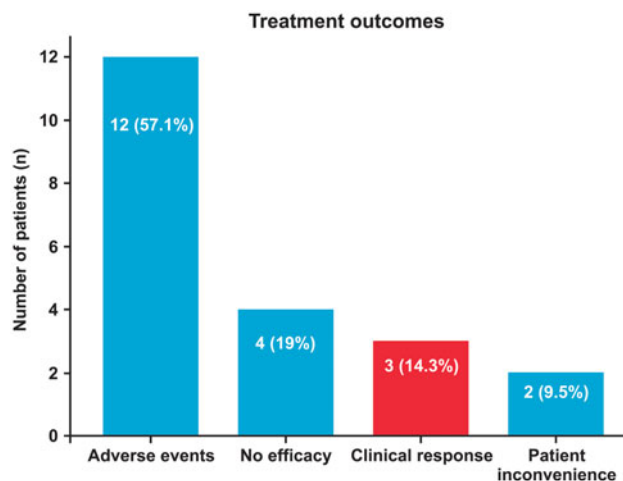


Figure 1. Treatment outcomes in SAFS and ABPA patients treated with Nebulised Amphotericin. SAFS = severe asthma with fungal sensitisation, ABPA = Allergic bronchopulmonary aspergillosis.

Table 1. Demographic characteristics for ABPA and SAFS patients treated with nebulised non-liposomal amphotericin.

Characteristic	All patients ($n = 21$)	ABPA ($n = 10$)	SAFS ($n = 11$)
Age (years), median (range)	65 (25–78)	67 (40–78)	63 (24–73)
Gender:			
Female (%)	9 (42.9)	5 (50)	4 (36.4)
Male (%)	12 (57.1)	5 (50)	7 (63.6)
Wt (kg), median(range))	74.7 (52.6–104), $n = 20$	74.2 (64–91.7), $n = 10$	81.4 (16.1), $n = 10$
Ht (cm), mean (SD)	165 (7.8), $n = 20$	166.8 (6.7), $n = 10$	162.8 (8.5), $n = 10$
BMI (kg/m ²), mean (SD)	28.6 (4.9)	26.2 (2.63), $n = 10$	30.4 (6), $n = 10$
FEV1(L), mean (SD)	1.86 (0.53), $n = 17$	1.57 (0.54), $n = 9$	2.02 (0.46), $n = 8$
FEV1% pred, mean (SD)	62.1 (18.7), $n = 17$	55.9 (23.6), $n = 9$	69 (12.2), $n = 8$
FVC (L), median(range)	2.68 (1.61–6.1), $n = 17$	2.57 (1.61–6.05), $n = 9$	2.74 (1.69–3.44), $n = 8$
FEV1/FVC %, median (range)	56 (33–84), $n = 17$	55.5 (33–80), $n = 9$	60.6 (34–84)
tIgE (kU/L), median (range)	215 (32–6700), 16	1200 (100–6700), $n = 7$	150 (32–3500), $n = 9$
AfIgE (kUa/L)	10.7 (0.5–100)	34.24 (0.6–100)	3.0 (0.5–41.7), $n = 6$
Co-existing lung diseases:			
Asthma (%)	21 (100)	10 (100)	11 (100)
Therapy duration (days), median (range)	30 (0–1825), $n = 21$	120 (0–1825), $n = 10$	0 (0–540), $n = 11$
Bronchiectasis (%)	18 (86), 21	8 (80)	10 (90.9)
Atopy (%)	11 (52.3)	5 (50)	7 (63.6)

ABPA = Allergic bronchopulmonary aspergillosis; SAFS = Severe asthma with fungal sensitisation; tIgE = total IgE, Af = aspergillus fumigatus; BMI = basal metabolic rate; Ht = height; SD = standard deviation; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; % pred = Percentage of the predicted value; L = litres; kUa/L = kilounits of allergen per litre; kU/L = kilounits per litre; %L/s = percent litre per second.

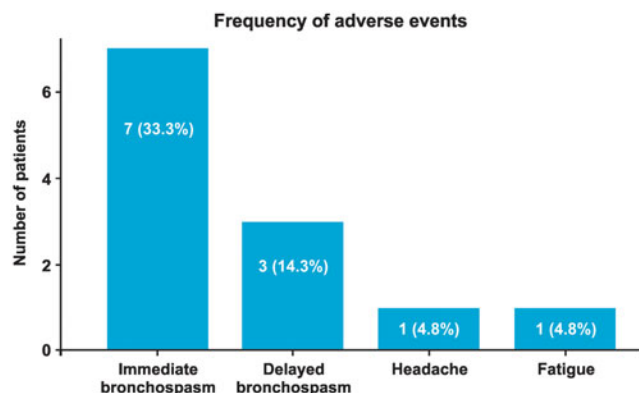


Figure 2. Frequency of adverse events in SAFS and ABPA patients treated with NAB. SAFS = severe asthma with fungal sensitisation, ABPA = allergic bronchopulmonary aspergillosis, NAB = nebulised amphotericin B.

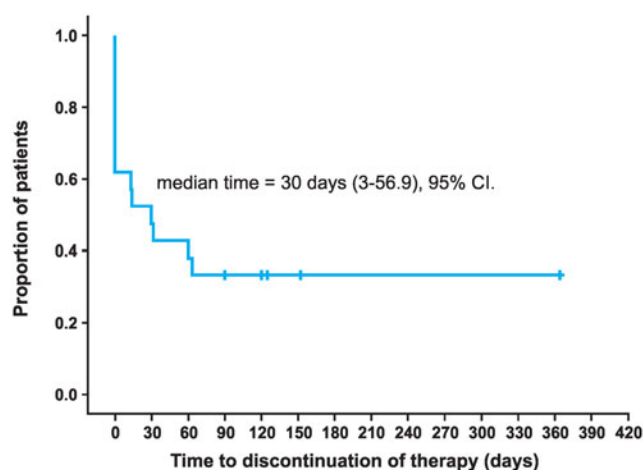


Figure 3. Kaplan–Meier curve showing time to discontinuation of therapy in SAFS and ABPA patients treated with NAB. AEs = adverse events, SAFS = severe asthma with fungal sensitisation, ABPA = allergic bronchopulmonary aspergillosis, NAB = nebulised amphotericin B.

patients on treatment in the study at each time point is illustrated in Figure 3. There was no correlation between baseline lung function (FEV1) and the occurrence of adverse events.

However, the responses were excellent in 3 (14%) patients who took therapy for 12 months or more (ABPA, $n=2$, SAFS = 1). The median duration of therapy for these 3 patients was 540 days (365–1825). Their overall mean AQLQ-J scores improved by +2.9 score (range, 2–6) at the end of 12 months therapy (Figure 4A) and this improvement corresponded with improvement in asthma control. Similarly, there was a significant improvement in median FEV1 by +0.5 L (Figure 4B). Two of these patients managed to return to work and one resumed her sporting activities. There was a reduction in daily median OCS dosages from 18.5 to 2.5 mg. We did not observe any reduction in ICS dosages. There were no significant changes observed in immunological outcomes.

Discussion

Current data regarding the efficacy and safety of NAB in ABPA are based on a few case reports, largely CF patients and

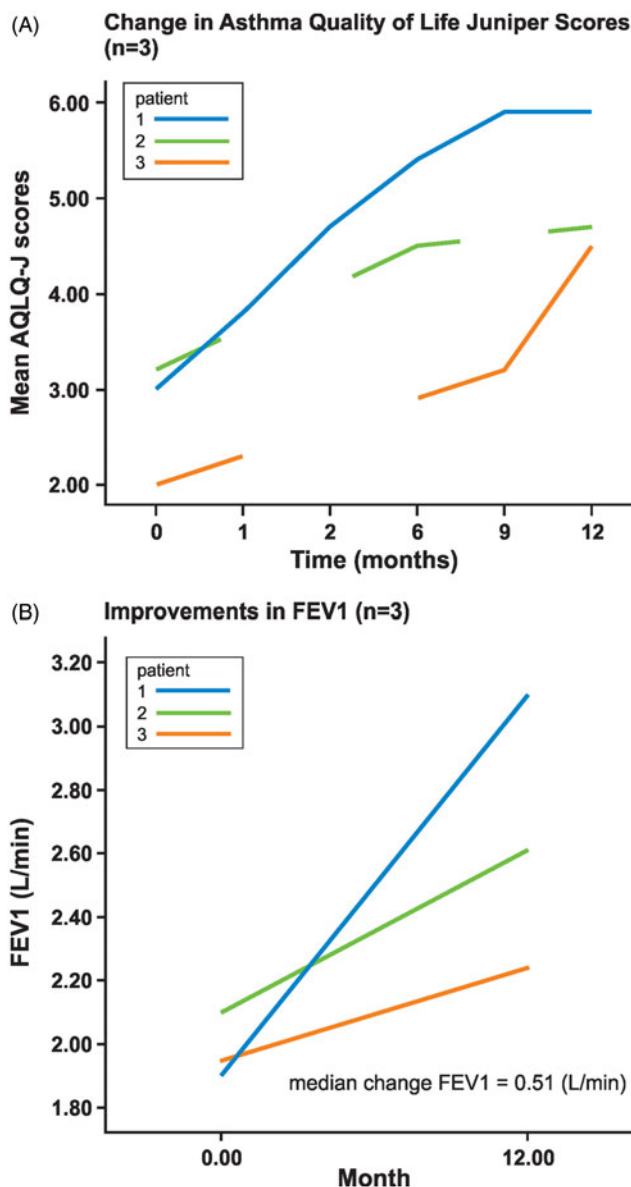


Figure 4. Trend in AQLQ-J scores and FEV1 in 3 patients with SAFS (patient 2) and ABPA (patients 1 and 3) who tolerated NAB beyond 12 months of therapy. SAFS = severe asthma with fungal sensitisation, ABPA = allergic bronchopulmonary aspergillosis, FEV1 = forced expiratory volume in the first second, AQLQ-J score = asthma quality of life juniper score.

no study has ever evaluated SAFS patients. Those few case reports suggest physiological and clinical efficacy along with the possibility of reducing OCS doses, although they did not consider non-liposomal formulations.

In this study, we assessed the efficacy and safety of non-liposomal nebulised amphotericin B (NL-NAB) in SAFS ($n=11$) and ABPA ($n=10$) patients. We observed major clinical benefits in 3 patients (ABPA, $n=2$; SAFS, $n=1$) (Figure 4A and B). We demonstrated major improvements in AQLQ-J scores by +2.9 and improvements in asthma control incorporating of daytime/nocturnal symptoms, reliever use and exacerbations within 12 months therapy. There are no previous studies that have assessed the efficacy of NAB in asthmatic ABPA or SAFS patients. However, our results support previous published case reports using liposomal

nebulised amphotericin (L-NAB) in CF ABPA and in corticosteroid dependant ABPA patients [15, 21].

Previous case reports have reported major improvements with the use of NAB in the CF population. The use of NAB therapy in these cases involved different NAB regimens that varied in doses and durations of therapy. In a case report involving a 14-year-old female with end-stage CF lung disease associated with frequent hospital admissions due to progressing symptoms, very poor lung function and severe bronchiectasis (listed for lung transplantation 6 months earlier), treatment with NAB using 10 mg twice daily via a Pari LC PlusTM nebuliser resulted in improvements in cough, dyspnoea, hypoxia, 6 minute walk, reduction in OCS dosages and improvements in pulmonary function (FVC, FEV1) with no adverse events [21]. However, this patient received concomitant therapy with itraconazole during the first 3 months and the synergistic effect of both treatments may have played a part in the observed clinical and physiological improvements. In our study we have demonstrated major improvements in these 3 patients with NAB alone without concomitant azole antifungal therapy.

We did not observe any clinical benefit in those patients who took therapy for less than 6 months. Our data also supports previous observations observed in CF ABPA children reported in 2008 by Laoudi et al. [17]. These authors reported major clinical and physiological responses observed from the 6th month in three CF ABPA children (aged 7, 12 and 13 years) treated with NAB using 5 mg twice a day that resulted in improvements in hypoxemia, FEV1, reduction of blood eosinophilia, total and specific serum IgE antibodies to *A. fumigatus* [17]. On the other hand, these reports did not specifically assess QOL. In our study, we have showed for the first time that the use of NAB can result in a substantial improvement of measures of QOL and physiological parameters in selected patients who pass the initial dose challenge.

In France, Godet et al. [16] described a case of a 67-year-old female with ABPA, previously unresponsive to itraconazole therapy which subsequently improved dramatically with a significant decrease in eosinophil count, precipitins, total and specific IgE levels complete resolution of consolidation (within 4 weeks) over time following 6 months therapy with liposomal NAB (l-NAB) [16]. These workers did not report any significant side-effects. In an article by Leon et al 1999, therapy with NAB showed good results for two ABPA patients but always in association with OCS [18]. Our study differs from prior literature in that co-administration of NAB with OCS, nebulised corticosteroids or azole antifungal was common [17,21]. It is therefore unclear which of the duo or trio of agents was responsible for the observed clinical benefit. In contrast, we did not use any concomitant OCS, nebulised corticosteroids or azole antifungals. Our data provide support for the hypothesis that fungal airways disease can be treated without systemic corticosteroids, in some patients.

Other outcomes

This study also demonstrated improvements in other parameters. Of the 3 responders, 2 who had been sick off from work returned to work after 6 and 9 weeks, respectively. Better diabetic control in one patient was also observed.

The improvement in diabetic control observed in this patient may be as a result of complete cessation of OCS as a result of better control of her airways disease. No significant changes were observed in immunological and radiological outcomes.

Adverse events

We observed a significantly high frequency of adverse events (AEs) with NL-NAB occurring in 57% patients (Figure 1). Immediate bronchospasm was the most frequent AE observed (33.3%). Other AEs included delayed bronchospasm occurring within 30 days of starting therapy (14.3%), headache (4.8%) and fatigue (4.8%) (Figure 2). We observed that bronchospasm was almost always associated with coughing.

There are no previous studies that have evaluated adverse events associated with the use of NAB in fungal sensitised asthma patients, but common adverse effects in previous studies in other diseases have been documented. These AEs approach 30–40% with NL-NAB when used in neutropenic or post-stem cell or autologous transplant patients [28,29].

The commonest documented AEs with NAB use are coughing and an after taste [28,30]. Other reported adverse events include; nausea, vomiting, dysphagia, bad taste, epistaxis and renal insufficiency [28]. An RCT involving 65 patients receiving prophylactic NAB at a dose of 10 mg twice daily versus placebo demonstrated that coughing (54%), bad taste (51%), and nausea (37%) caused early cessation of treatment in 23% (15/65) cases [17].

The frequency and nature of AEs observed in our study differ from historical literature due to a high frequency of bronchospasm. The bronchospasm has not been widely reported with the use of NAB except for few incidences reported in lung transplant patients. It is possible that the observed large frequency of bronchospasm in our patients may be due to the airway hyperresponsiveness which characterise most asthmatics. In some previous studies, all patients with severe asthma were excluded and may partly explain why those studies had less frequent bronchospasm compared to our patients [31]. Another possibility for the differences might be the presence of denervated lungs in transplant patients.

Effect of nebuliser types and dosages

Some of the main challenges involving the use of NAB lies in determining the correct type of nebuliser. It is not clear whether the observed AEs in our study are due in part to differences in nebuliser type, pressure or dosages as compared to those used in previous studies. We used the Pari Sprint nebuliser (PARI UK PARI Medical Ltd., Surrey, UK) for our study.

In contrast, different nebulisers and dosages have been used in many previous reports such as 12.5 mg twice weekly using an adaptive aerosol delivery system in neutropenic patients, the Pari LC plus nebuliser using 10 mg twice per day and the Misty nebuliser using 30 mg daily [31]. The breath-actuated nebuliser (AeroEclipse[®]) has been shown to deliver 24mg of liposomal amphotericin B solution (AmBisome[®]) successfully without disrupting the liposomes and minimise drug loss with less nephrotoxicity [32].

The pharmacokinetics of NL-NAB may also account for the observed difference in adverse events compared to

previous studies. Previous studies have utilised amphotericin B lipid complex (ABLC) and very few utilised NL-NAB. In many respects, the study of NL-NAB or ABLC in lung transplant recipients is at a crossroads and there are pharmacokinetic differences between the 2 formulations. In animal models, amphotericin B (fungizone) tends to foam in the nebulisation chamber [33]. This foam may be inhaled during nebulisation and may contribute towards cough and bronchospasm. Liposomes, on other hand, do not exhibit this characteristic and are well tolerated by the lung. This may partly explain the tolerability exhibited in previous studies using liposomal amphotericin B.

In human subjects, ABLC aerosols are better tolerated than is NL-NAB. In a prospective, randomised, double-blinded trial ($n = 100$) comparing safety of aerosolised NL-NAB with ABLC in lung-transplant recipients, subjects receiving NL-NAB were more likely to have experienced an AE. However, the nebuliser doses used in this study were different between the two treatment groups (25 mg and 50 mg daily, respectively) and it is unclear whether the observed differences in their study were due to the dose differences. Hence, there remains a need to determine the most appropriate equipment and optimal dosages.

Limitations

This study has many limitations. Some of the data (28%) patients included are based on retrospective data for the patients who started treatment before the study started. Data on these patients therefore is likely to be less accurate due to subjective recording and reporting by clinicians. However, most of these patients did not pass the initial challenge (except for one) and therefore did not affect the follow up data. The number of measures and frequency varied from patient to patient and this might have affected data interpretation. Some had fewer data points compared to others.

Treatment options

These patients were considered for this trial of treatment if options for azole antifungals had been exhausted at the time of the study, due to limitations in funding of alternative oral azoles, after failed trials of itraconazole $\pm$ voriconazole. SAFS patients particularly were unlikely to be funded for voriconazole and even less likely for posaconazole in our unit.

Other treatment options currently would include anti-IgE therapy, though a specific trial in ABPA/SAFS patients has not been published. At the time of this study many patients were unsuitable for this treatment option as they did not fulfill the UK criteria for funding for Omalizumab.

Ultimately treatments that influence eosinophilic airway inflammation such as anti IL5 and anti IL13 may be suitable for such patients and ultimately inhaled anti fungal drugs with less toxicity than ambizone may be more appropriate options, but at present these patients represent an unmet need and all treatment options should be considered

Conclusions

Our data suggests that the overall efficacy of NAB in this group of patients may be poor and is associated with high frequency of adverse events. However, the responses were

excellent in 3 (14%) patients. It is not clear which patients are likely to respond. Further studies need to be conducted to establish the optimal dose range (dose, frequency), nebuliser type, pressures and identification of patients who may respond. Antifungal treatment by inhalation could provide a new, simple therapeutic approach in patients unsuitable for azole antifungals or in whom there has been no clinical benefit with first line therapies, azole resistance or where it has been difficult to maintain adequate therapeutic drug levels with azole antifungal. Another advantage is that local administration of NAB to the airways also decreases the risk of drug interactions that is commonly observed with azole antifungals. It allows higher lung tissue deposition and concentrations and only limited absorption into blood, as previously illustrated by negligible serum concentrations post dose. This is especially true for liposomal and lipid forms.

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Declaration of interest

Dr Livingstone Chishimba has received travel and conference sponsorship from Astra Zeneca, GSK, Novartis, Astellas and Chiesi pharmaceuticals. He has received speaker fees from Chiesi. None of these activities have any relationship with design, conduct of study, analysis or publication of this study.

Prof David Denning holds founder shares in F2G Ltd, a University of Manchester spin-out company, and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, the European Union and the Fungal Infection Trust. He acts as a consultant to Trinity group, T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology as well as other companies over the last 5 years including Merck and Astellas. In the last 3 years, he has been paid for talks on behalf of Astellas, Gilead and Pfizer.

Dr Robert Niven Has received travel and conference sponsorship from Astra Zeneca, GSK and Novartis pharmaceuticals. None of these activities have any relationship with design, conduct of study, analysis or publication of this study.

Mrs Georgina Powell and Mr Philip Langridge have no interests to declare.

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