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Brief Report

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Impact of high baseline *Aspergillus*-specific IgG levels on weight and quality-of-life outcomes of patients with chronic pulmonary aspergillosis

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Abstract

This study aimed to evaluate the impact of quantitative baseline *Aspergillus*-specific immunoglobulin G (IgG) serum levels on weight changes of patients with chronic pulmonary aspergillosis (CPA) under antifungal treatment. We retrospectively reviewed data of patients diagnosed with CPA between April 2015 and March 2018 at the National Aspergillosis Centre (Manchester, UK). All patients were on continued antifungal treatment for 12 months. Data on *Aspergillus*-specific IgG levels, St George's quality of life (SGQoL) variables and weight at baseline, 6 months and 12 months were extracted. We defined a high serum *Aspergillus*-specific IgG as $\geq$ 200 mg/l (Group A) and low level $<$ 200 mg/l (Group B). Forty-nine patients (37 male; 12 female), median age 65 years (range: 29–86) were studied. Overall, 33% ($n = 16$) of the patients were in Group A. The baseline characteristics between the two groups were similar. The median Charlson comorbidity index was 4 (range: 0–5) and 3 (range: 0–9) for Group A and Group B, respectively ($P = .543$). There was a sustained decline in median *Aspergillus* IgG levels from baseline, through 6 month to 12 months of continues therapy from 170 (range: 20–1110) to 121 (range: 20–1126), and finally 107 (15–937) mg/l, respectively ($P < .001$). Group A patients gained more weight at 6 months (9/15 [60%] vs. 7/33 [21%], $P = .012$) and at 12 months of treatment (9/15 [60%] vs. 7/33 [22%]), and more patients in Group B lost weight ((13/33 [41%] vs. 1/15 [7%]), $P = .015$). However, there was no difference in QoL outcomes across groups at 6 ($P = .3$) and 12 ($P = .7$) months. A very high *Aspergillus* IgG may confer a higher likelihood of weight gain as a key, objective marker of clinical response, if patients can tolerate 12 months of antifungal therapy.

Key words: *Aspergillus* IgG, CPA, weight, and quality of life.

Introduction

Chronic pulmonary aspergillosis (CPA) is a respiratory syndrome characterized by radiological features of a nodule, progressive cavitation with or without a fungal ball, pericavitary fibrosis, or pleural thickening; associated with pulmonary and respiratory symptoms in an immunocompetent individual with a preexistent structural lung disease.[1]

Globally, CPA is estimated to affect over 3 million people annually,[2] causes a significant negative impact on quality of life (QoL)[3] with 5- and 10-year mortality rates as a high as 38% and 53%, respectively, even when treated with antifungal therapy.[4] Diagnosis of CPA requires a combination of clinical and radiological characteristics along with microbiologic or immunologic evidence of *Aspergillus* infection.[1,5,6]

Aspergillus-specific immunoglobulin G (IgG) is almost always positive in patients with CPA and thus plays a central role in the immunological confirmation of CPA.[7] In addition, serial regular testing of serum *Aspergillus*-specific IgG levels have been shown to have a utility in monitoring of treatment and possibly in the diagnosis of CPA relapse.[8] A more recent study has shown that *Aspergillus* IgG levels inconsistently increase or decrease following antifungal therapy.[9] However, the correlation between serum *Aspergillus*-specific IgG levels, weight, and QoL outcome measures is not well documented. We hypothesize that a high baseline *Aspergillus*-specific IgG levels may be associated with an efficient anti-*Aspergillus* immune response, which may consequently translate into better treatment outcomes.

In the present study, we sought to evaluate the impact of quantitative baseline *Aspergillus*-specific IgG serum levels on weight changes and the QoL outcomes of patients with CPA in a national center of clinical excellence for the management of CPA.

Methods

We retrospectively reviewed clinical notes of consecutive patients registered for care at the National Aspergillosis Centre (Manchester, UK), with a diagnosis of CPA between April 2015 and March 2018. All patients met the diagnostic criteria for CPA as per the European Society for Clinical Microbiology and Infectious Diseases (ESCMID)/European Confederation of Medical Mycology (ECMM), and the European Respiratory Society (ERS) Guidelines.[5]

Patients who were on continued therapy with the same antifungal agent since commencement of therapy for at least 12 months constituted the study population. For each patient, in addition to demographic characteristics and the primary antifungal agent used, we extracted data on *Aspergillus*-specific IgG levels, St George's QoL (SGQoL) variables, and weight at baseline, 6 months and 12 months. *Aspergillus*-specific IgG was estimated using the ImmunoCAP (Phadia, Inc., Uppsala, Sweden) enzyme-linked immunosorbent assay kit and was interpreted with a single diagnostic cut-off value of 40 mg/l. Results >200 mg/l were diluted 1/10 to achieve a final result (and were provided for research use only as this dilution procedure is not CE marked). The predilution level was entered as 10 on the ImmunoCap 250 instrument so that the instrument data management system (IDM) knows to multiply the final on-board result by this dilution factor. The sample then was diluted 1/10 manually off-line in a fresh LP4 tube (50 µl serum + 450 µl specific IgG diluent).

We defined a high serum *Aspergillus*-specific IgG as ≥ 200 mg/L [Group A] and low level < 200 mg/L [Group B]. For the purpose of this study, a weight gain or loss of more than 2 Kg was considered significant and a value in between as stable. SGQoL measures were interpreted as previously described.[10] In brief, a ≥ 4 unit change in any of the four domains was considered a minimal clinically significant difference, that is, ≥4 unit increment (deterioration), ≥4 unit reduction (improvement), and stable QoL for values in between.

Data were entered in Microsoft Excel and exported to GraphPad 8.3 and IBM SPSS Statistics Subscription for data analysis. We compared sociodemographic, primary antifungal regimen, primary underlying conditions, QoL outcomes and weight changes between across the two groups. A χ^2 and Fischer exact test were used to compare categorical data. Normality of numerical data was assessed using the Kolmogorov-Smirnov Z test. We used independent sample t-test, Mann Whitney U, and Friedman test as appropriate. $P \leq .05$ was considered statistically significant.

Being a retrospective audit of anonymized routine clinical data, informed consent and institutional ethics review was not required. Patients' identifiable data were anonymized prior to analysis.

Results

Baseline characteristics

Forty-nine patients (37 male; 12 female), median age 65 years (range: 29–86) were on continued therapy with the same antifungal agent (either itraconazole ($n = 35$) or voriconazole ($n = 14$)) for at least 12 months. Ten (20%) patients were on the same dose, while 39 had their doses either reduced ($n = 31$, 63%) or increased ($n = 8$, 16%) based on therapeutic drug monitoring results. The baseline characteristics of both groups were statistically similar, with *Aspergillus*-specific IgG being the only notable difference (Table 1).

Aspergillus-specific IgG serology

Overall, 33% ($n = 16$) of the patients had IgG levels ≥ 200 mg/l at baseline (Group A). Of these, 69% (11/16) and 31% (5/16) had levels ≥ 200 mg/l at 6 months and 12 months, respectively. There was a sustained decline in median *Aspergillus* IgG levels from baseline, through 6 to 12 months of continues therapy from 170 (range: 20–1,110) to 121 (range: 20–1126), and finally 107 (15–937) mg/l, respectively ($P < .001$ by Friedman test). Median serum *Aspergillus*-specific IgG levels at baseline, 6 and 12 months for those on itraconazole versus voriconazole were (172 vs. 169, $P = .370$), (113 vs. 145, $P = .129$), and (103 vs. 139, $P = .167$), respectively.

Baseline *Aspergillus* IgG levels and weight

At 6 months, Group A patients had a median weigh gain of 6 Kg (range: 1–9) compared to 2 Kg (range: 0.1–9) among patients in Group B (difference between medians: 3.9; $P = .09$). Overall, the majority of patients in Group A gained weight (9/15 [60%] vs. 7/33 [21%]), a similar proportion in both groups had stable weight (5/15 [33%] vs. 12/33 [36%]. However, more patients

Table 1. Baseline characteristics for Group A and Group B patients.

Characteristics	Total, $n = 49$ Frequency (%)	Group A, $n = 16$ Frequency (%)	Group B, $n = 33$ Frequency (%)	*P*-value
Demographics				
Age: median (range)/years	65 (29–86)	66 (29–75)	65 (36–86)	.765
Sex: M	37 (75.5)	13 (81.3)	24 (72.7)	.726
Baseline IgG, median (range) mg/l	172.0 (20.0–1110.0)	438.5 (201.0–1110.0)	121.0 (20.0–194.0)	**<.0001**
Primary antifungal agent				
Itraconazole	35 (71.4)	10 (62.5)	25 (75.8)	.501
Voriconazole	14 (28.6)	6 (37.5)	8 (24.2)	
Quality of life outcomes				
Total SGRQ score: median, range	55.6 (0–100)	68.3 (0–100)	50 (0–100)	.159
Self assessment of QoL				
Very good	1 (2.0)	1 (6.3)	0 (0.0)	.192
Good	9 (18.4)	3 (18.8)	6 (18.2)	
Fair	19 (38.8)	5 (31.3)	14 (42.4)	
Poor	16 (32.7)	4 (25.0)	12 (36.4)	
Very poor	4 (8.2)	3 (18.8)	1 (3.0)	
Weight: median, range/Kg	66.1 (44.2–114.8)	61.4 (45.6–114.8)	70.8 (44.2–97.6)	.247
MRC Dyspnoea scale: median, range	3 (1–5)	3.75 (1–5)	2.5 (1–5)	.399
Primary underlying condition				
Chronic obstructive pulmonary diseases	11 (22.4)	3 (18.8)	8 (24.2)	
Tuberculosis	8 (16.3)	3 (18.6)	5 (15.2)	
Nontuberculous mycobacteriosis	7 (14.3)	2 (12.5)	5 (15.2)	
Allergic bronchopulmonary aspergillosis	3 (6.1)	1 (6.3)	2 (6.1)	
Sarcoidosis	3 (6.1)	1 (6.3)	2 (8.1)	
Pneumothorax	2 (4.1)	2 (12.5)	0 (0.0)	.533
Lobectomy	2 (4.1)	1 (6.3)	1 (3.0)	
Ankylosing spondylitis	1 (2.0)	1 (6.3)	0 (0.0)	
Asbestosis	1 (2.0)	0 (0.0)	1 (3.0)	
Asthma	1 (2.0)	1 (6.3)	0 (0.0)	
Lung cancer (treated)	1 (2.0)	0 (0.0)	1 (3.0)	
Bronchiectasis	1 (2.0)	0 (0.0)	1 (3.0)	
Community acquired pneumonia	1 (2.0)	0 (0.0)	1 (3.0)	
None	6 (12.2)	1 (6.3)	5 (15.2)	
Comorbidity				
Charlson comorbidity index: median, range	3 (0–9)	4 (0–5)	3 (0–9)	.543

Abbreviations. MRC: Medical Research Council; QoL: Quality of life; SGRQ: St George's Respiratory Questionnaire.

in Group B lost weight ((1/15 [7%] vs. 14/33[42%]), $P = .012$) (Fig. 1).

At 12 months, a higher proportions of patients in Group A gained weight (9/15 [60%] vs. 7/33 [22%]) and more patients in Group B lost weight ((13/33 [41%] vs. 1/15 [7%]), $P = .015$) (Fig. 1). For those who gained or lost weight, weight gain (3 Kg [range: 1–9] vs. 3 Kg [0.2–12], $P = .4$) and weight loss (2 Kg [range: 2–16] vs. 3 Kg [0.4–18], $P = .9$) were similar across groups.

Aspergillus IgG levels and quality of life

At 6 months, more patients in Group A reported improvement in QoL, but this was not statistically different. Improvement (9/16 [56%] vs. 12/33 [36%]), stability (6/16 [38%] vs. 14/33 [42%]), and deterioration (1/16 [6%] vs. 7/33 [21%]) in QoL were observed among Group A versus Group B patients, respectively ($P = .3$) (Fig. 2). At 12 months, differences were less marked. Improvement (8/16 [50%] vs. 13/33 [39%]), stability (3/16 [19%] vs. 9/33 [27%]), and deterioration (5/16 [31%] vs. 11/33 [33%]) in QoL were comparable across the two groups ($P = .7$) (Fig. 2).

Discussion

Long-term antifungal treatment for at least 6 months is the recommended medical management of choice for the majority of patients with symptomatic CPA.[5] In this study, we have

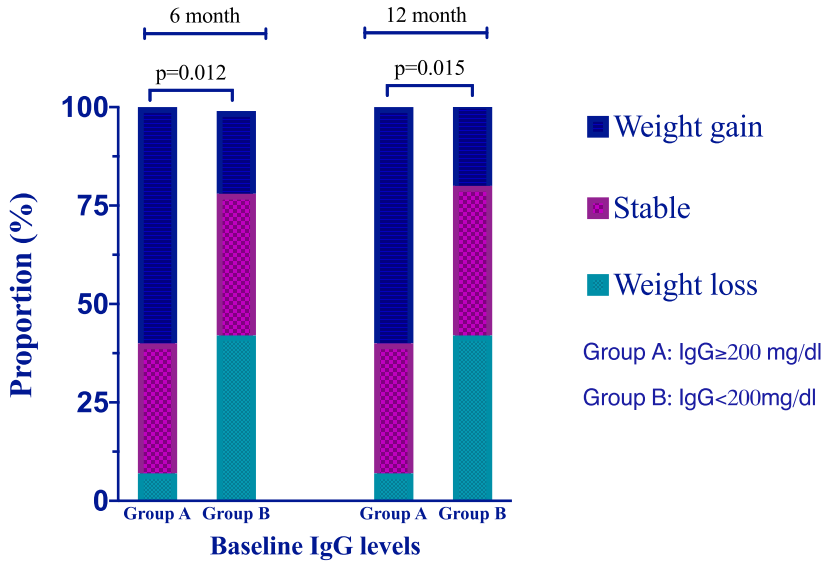

Figure 1. Proportions of patients with weight gain, stable weight, and weight loss at 6 and 12 months of treatment.

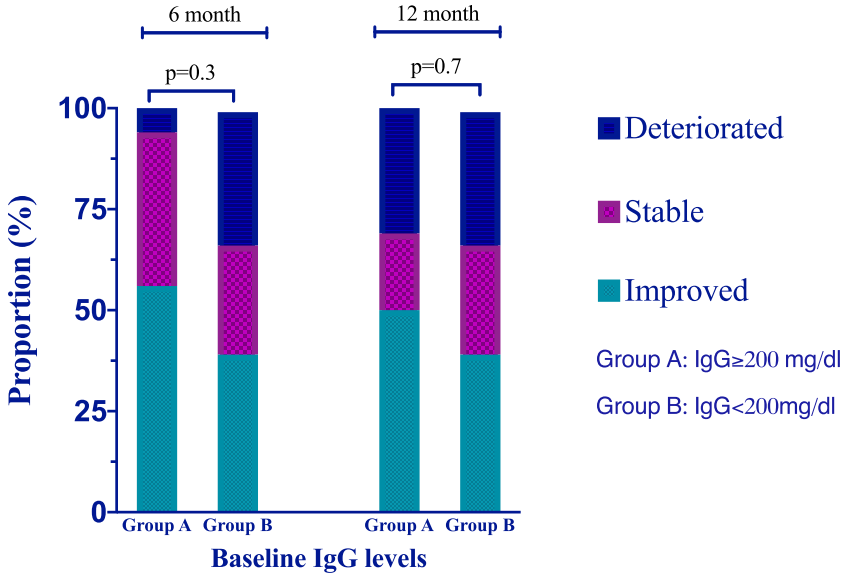

Figure 2. Proportions of patients with improved, stable, or deteriorated quality of life at 6 and 12 months.

shown that continuous antifungal treatment is associated with a significant decline in serum *Aspergillus* IgG levels in patients with CPA especially in the first 6 months of treatment. This finding is consistent with our previous report[8] and with other previously published data from other centers.[9,11] In addition, we show that a disproportionate number of patients with low baseline *Aspergillus*-specific IgG levels had significant weight loss on antifungal therapy. Moreover, we did not find any association between baseline *Aspergillus* IgG levels and QoL outcomes. Although not statistically significant, Group A patients had better QoL outcomes at 6 months compared to Group B patients.

It is counterintuitive that those with the highest *Aspergillus* IgG levels have the greatest improvements on antifungal therapy. Our supposition is that the same patients with very high IgG responses to *Aspergillus* are also patients with the least compromised (but subtle) immune defects. The defects we have documented include poor vaccine responses and low CD4 cells and low CD19 cells (B cells).[12,13] Therefore, the height of the *Aspergillus* IgG could be a proxy indicator of how intact antigen processing and B cell response pathway is in patients, separately from any other defects in CPA.

The main limitation of this study lies in its retrospective, single-center design. We had incomplete data on heights of the patients (to record body mass index) and did not database radiological phenotypes of CPA. In addition, we had a small sample size; thus, our results should be interpreted with caution before generalization to the growing number of patients with CPA. However, our study provides a basis for further research in the

utility of serum *Aspergillus*-specific IgG levels in the monitoring and prognostication of patients with CPA.

For laboratories measuring *Aspergillus* IgG, it is clearly important to produce an accurate titration of high titers, to be able to follow therapy and also it seems to predict therapeutic response. The manufacturer of the ImmunoCap system has not formerly endorsed a dilution step as a component of regulatory approval. Our laboratory now issues 2 reports for those with very high *Aspergillus* IgG – initially >200 mg/l and then a second report which is a titer.

In conclusion, a very high *Aspergillus* IgG confers a likelihood of weight gain as a key, objective marker of clinical response, if patients can tolerate 12 months of antifungal therapy. Additional study and observation is required to assess the longevity of this 12-month initial response.

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Declaration of interest

D.W.D. and family hold founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company. He acts or has recently acted as a consultant to Scynexis, Pulmatrix, Zambon, iCo Therapeutics, Roivant, Biosergen and Fujifilm. In the last 3 years, he has been paid for talks on behalf of Dynamiker, Hikma, Gilead, Merck, Mylan and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and the British Society for Medical Mycology Standards of Care committee. F.B. and T.G. report no conflicts.

Ethical approval

As this study was a retrospective service evaluation, patient consent was waived. All the principles of confidential transfer and handling of patients' identifiable information were observed.

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