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CT Imaging Assessment of Response to Treatment in Allergic Bronchopulmonary Aspergillosis in Adults With Bronchial Asthma

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Keywords:

ABPA; CT scan; allergic bronchopulmonary aspergillosis; radiologic response; treatment outcomes.

ABBREVIATIONS:

ABPA = allergic bronchopulmonary aspergillosis;; ABPA-CPF = allergic bronchopulmonary aspergillosis-chronic pleuropulmonary fibrosis.

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Abstract

Background:

One of the major challenges in managing allergic bronchopulmonary aspergillosis remains consistent and reproducible assessment of response to treatment.

Research question:

What are the most relevant changes in CT scan parameters over time for assessing response to treatment?

Study design and methods:

In this ancillary study of a randomized clinical trial (NEBULAMB), patients with asthma with available CT scan and without exacerbation during a 4-month allergic bronchopulmonary aspergillosis exacerbation treatment period (corticosteroids and itraconazole) were included. Changed CT scan parameters were assessed by systematic analyses of CT scan findings at initiation and end of treatment. CT scans were assessed by two radiologists blinded to the clinical data. Radiologic parameters were determined by selecting those showing significant changes over time. Improvement of at least one, without worsening of the others, defined the radiologic response. Agreement between radiologic changes and clinical and immunologic responses was likewise investigated.

Results:

Among the 139 originally randomized patients, 132 were included. We identified five CT scan parameters showing significant changes at end of treatment: mucoid impaction extent, mucoid impaction density, centrilobular micronodules, consolidation/ground-glass opacities, and bronchial wall thickening ($P < .05$). These changes were only weakly associated with one another, except for mucoid impaction extent and density. No agreement was observed between clinical, immunologic, and radiologic responses, assessed as an overall response, or considering each of the parameters (Cohen κ , -0.01 to 0.24).

Interpretation:

Changes in extent and density of mucoid impaction, centrilobular micronodules, consolidation/ground-glass opacities, and thickening of the bronchial walls were found to be the most relevant CT scan parameters to assess radiologic response to treatment. A clinical, immunologic, and radiologic multidimensional approach should be adopted to assess outcomes, probably with a composite definition of response to treatment.

Trial registration:

ClinicalTrials.gov; No.: [NCT02273661](https://clinicaltrials.gov/ct2/show/study/NCT02273661); URL: www.clinicaltrials.gov.

Clinicaltrials:

(gov).

Allergic bronchopulmonary aspergillosis (ABPA) is a complex bronchopulmonary disease resulting from immunologic reactions mediated against *Aspergillus fumigatus*, occurring in about 2.5% to 32% of patients with asthma and 6% to 10% of those with cystic fibrosis.^{1, 2} Untreated and repeated exacerbations of ABPA increase the risk of irreversible sequelae,³ including development of bronchiectasis, permanent obstructive ventilation defect, and fibrotic lung lesions.¹ The diagnosis of ABPA is based on a combination of clinical, immunologic, and thoracic imaging findings. Thin-section CT scan of the thorax is the imaging modality of choice for the diagnosis and management of ABPA. Among the different radiologic findings associated with ABPA, central bronchiectasis with or without high-attenuation mucus is the most commonly observed.^{1, 2.}

Because most patients require prolonged therapy, one of the challenges in ABPA management remains the assessment of response to treatment, in a consistent and reproducible manner that would consider the different phenotypes of the disease. The lack of standardization of clinical, immunologic, and thoracic imaging findings makes it difficult to compare response rates between clinical studies.⁴⁻⁷ So far, response to treatment has been based on “either clinical or radiological improvement with at least 25% decline in immunoglobulin-E (IgE) levels of baseline.”^{1, 2.} Thereby, its definition is conditioned by subjective clinical evaluation, immunologic criteria (ie, total serum IgE), of which the threshold can be equivocal and be influenced by corticosteroids, and imprecise radiologic criteria.¹ Modification of radiologic parameters is a key feature in the definition of response to treatment, relapse, and remission. Although CT scan findings have been profusely described at diagnosis, the precise changes occurring during ABPA exacerbations and under treatment have not been rigorously detailed. In addition, agreement between radiologic, clinical, and immunologic response is unknown.

The primary aim of this study was to assess CT scan changes occurring after standardized treatment of ABPA exacerbation to determine the most relevant CT scan parameters associated with a radiologic response to treatment. The secondary aim was to investigate agreement between these radiologic changes and clinical and immunologic response.

Study Design and Methods

Study Design

This study is an ancillary study of the NebuLamB trial, which was a randomized, single-blind, placebo-controlled clinical trial. In the NebuLamB trial, patients with ABPA were included from March 2015 to July 2017 in 30 French hospitals. The design was previously reported.⁷ ABPA was defined as follows: (1) atopy or history of asthma and elevated serum total IgE level (> 417 International Units/mL); (2) elevated *A. fumigatus*-specific IgE level (> 0.35 kUA/L) or immediate cutaneous hypersensitivity to *Aspergillus* species antigen, associated with the following criteria: documented precipitating antibodies or positive *A. fumigatus*-specific IgG; (3) total blood eosinophil count > 500 cells/mL; and (4) documented radiologic infiltrates consistent with ABPA.⁷ Briefly, patients were first treated by a 4-month ABPA exacerbation treatment including corticosteroids and itraconazole and secondarily randomized to receive either 6 months of nebulized liposomal amphotericin B or nebulized placebo as maintenance therapy. The original trial was registered at clinicaltrials.gov (No. NCT02273661). The study protocol was approved by the ethics committee at Centre Hospitalier Universitaire de Poitiers, France (No. 2014-000872-24). Written informed consent was obtained from all patients.

This study reports the analysis of radiologic data collected during the 4-month ABPA exacerbation treatment and does not overlap with the results presented elsewhere.⁷

Patients

Patients were included in this ancillary analysis if they met the following criteria: absence of severe exacerbation during a 4-month ABPA exacerbation treatment period (glucocorticoids and itraconazole) and available CT scan at initiation (M0) and end of the 4-month ABPA exacerbation treatment (M4).⁷

The ABPA exacerbation treatment included corticosteroids and itraconazole as follows: oral prednisolone at 0.5 mg/kg/d 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, 1.5-4 mg/mL).⁷ In case of intolerance, itraconazole was replaced with voriconazole or posaconazole, according to the decision of the investigator.⁷ No biological medications were administered during the study.

Patients with cystic fibrosis, invasive pulmonary aspergillosis, chronic pulmonary aspergillosis, exacerbation of asthma, or ABPA related to ongoing pulmonary infection were excluded ([supplementary material](#)).

CT Scan Parameters and Measurement

CT scan images (without IV contrast agent) at M0 and M4 were independently reviewed by two chest radiologists (A.-L. B. and F. L.) blinded to the clinical data. In case of discrepancies, the two radiologists examined the issue together to reach a consensus. The initial M0 and M4 CT examinations were analyzed based on axial acquisitions, the readers being free to use multiplanar, maximum intensity projection, and minimum intensity projection algorithms. Definitions were those of the Fleischner Society glossary of terms.⁸ Radiologic abnormalities were categorized for the presence and extent of bronchiectasis, severity of bronchial dilatation, severity of bronchial wall thickening, and mucus plugging, using the CT grading system described by Reiff et al,⁹ a modified version of that described by Bhalla et al.¹⁰

The following features were examined in each lung (16 radiologic parameters included in the analysis): bronchiectasis, mucoid impaction, bronchial wall thickening, centrilobular micronodules with or without tree-in-bud features, non-calcified nodules, ground glass opacities and consolidations, mosaicism, allergic bronchopulmonary aspergillosis-chronic pleuropulmonary fibrosis (ABPA-CPF) features, focal parenchymal atelectasis, aspergilloma, pleural effusion, and pneumothorax (details of measurements are shown in [e-Table 1](#)).^{4-6,11}

Bronchiectasis analysis included craniocaudal location (per lobe, considering three lobes on the right and two on the left), central/ peripheral location (central, distal, and central þ distal), number of segments involved per lung (one to three, four to seven, and eight to 10), and severity (mild, bronchial diameter < 2 times the neighboring arterial lumen; moderate, bronchial diameter 2-3 times as large as the neighboring arterial lumen; severe, bronchial diameter > 3 times as large as the neighboring arterial lumen).

Mucoid impaction analysis included craniocaudal location per lobe, number of segments involved per lung (one to three, four to seven, and eight to 10), and spontaneous attenuation.^{12,13}

Bronchial wall thickening was categorized in three classes (normal, mild bronchial thickening within 20% to 50% of the external diameter of the bronchus, and marked bronchial thickening > 50% of the external diameter of the bronchus).

In each lobe, the following variables were categorized in four classes depending on their extension (absence, < 25% of the lobe volume, 25%-50%, 50%-75%, and > 75%): centrilobular micronodules with or without tree-in-bud features, non-calcified nodules, ground-glass opacities and consolidations, and mosaicism.

ABPA-CPF features including evidence of fibrosis and parenchymal scars, cavitating lesions were defined as present/absent and categorized depending on their extension (one to three segments, four to seven segments, and eight to 10 segments). Pleural fibrosis was defined as present or absent and categorized based on its extension and thickness (< 2 mm, 2-5 mm, 5-10 mm, and > 10 mm thickening).

Focal parenchymal atelectasis/collapse was noted (absence, subsegmental or segmental, lobar, and plurilobar). Aspergilloma, pleural effusion, and pneumothorax were noted when present. Labeled examples of CT scan parameters scoring are shown in [Figure 1](#).

Response to ABPA Exacerbation Treatment

Radiologic Response:

For each CT scan parameter, the change between semiquantitative value at M0 and M4 (after 4-month ABPA exacerbation treatment) was calculated separately for the left and right lungs as the difference between M4 and M0. CT parameter change was then categorized in four groups combining both sides as follows: 1 (worsening if either side worsened), 2 (improvement if no side worsened and at least one side improved), 3 (stability if all remained the same), and 4 (maintained normality).

CT parameters demonstrating significant changes between M0 and M4 were then identified. Improvement of at least one of these parameters without worsening of the others defined the overall radiologic response.

Clinical Response:

Clinical response was defined by improvement between M0 and M4 of at least one of the four following criteria without worsening of the others: (1) decreased symptom score (score grading from 0 to 3 of the following symptoms: cough, sputum, wheezing, and chest pain) of at least 50%; (2) improvement of dyspnea as assessed by the Medical Research Council¹⁴ of at least 1 point; (3) improvement of asthma control as assessed by the investigator, according to control levels defined by GINA guidelines¹⁵; and/or (4) improvement of asthma control as assessed by the patient according to the ACQ5 questionnaire.¹⁶

Immunologic Response:

Immunologic response was defined by a decrease at least 25% of serum total IgE levels between M0 and M4.¹

Statistical Analysis

CT scan parameters at M0 and M4 and qualitative changes between M0 to M4 (worsening, improvement, stability, and maintained normality) were described as number (%) for each category. To identify statistically significant change CT scan parameters during the ABPA exacerbation treatment, a one-sample Wilcoxon signed rank test was performed against 0 on parameter differences between M0 and M4; $P < .05$ indicated a statistically significant variation in the parameter tested; and the parameter was then included in the definition of the overall radiologic response. To evaluate the homogeneity of the response for the different CT scan parameters, we calculated the nonparametric Spearman correlation coefficient between each of the parameter changes considered 2 _ 2 and presented the results in a correlogram. In addition, we carried out an exploratory hierarchical clustering on principal component analysis to classify the patients according to their CT scan parameter changes between M0 and M4.

A Venn diagram was used to describe agreement between clinical response, immunologic response, and overall radiologic response. Agreement between each radiologic parameter change and the observed clinical response and the immunologic response was quantified by Cohen kappa coefficient. McNemar test was used to test the symmetry of discordant observations. $P < .05$ was statistically significant. Data analysis was performed with R statistical package version 4.0.4 (The R Foundation for Statistical Computing).

Results

Patient Characteristics

From March 2015 to July 2017, 174 patients were included in the NebuLamB trial to receive an initial ABPA exacerbation treatment (M0). At 4 months (M4), 35 were excluded, 14 of them because of severe clinical exacerbation according to the investigators ([e-Fig 1](#)). Among the remaining 139 patients, 132 had CT scan data available at both M0 and M4 and were included in the current analysis. All of them were patients with asthma, whose clinical and demographic characteristics are detailed in [e-Table 2](#).

CT Scan Characteristics at M0

At initiation of ABPA exacerbation treatment (M0) in 132 patients, CT scans showed bronchiectasis in 122 (92%), bronchial wall thickening in 117 (89%), centrilobular micronodules in 108 (82%), mucoid impaction in 81 (61%), including high-attenuation impactions in 47 (36%), consolidation and/or ground-glass opacities in 72 (55%), and mosaicism in 63 (48%). Subsegmental or segmental collapse was present in 30 patients (23%), and lobar collapse was present in four patients (3%). Pleural fibrosis was present in four patients (3%), evidence of ABPA-CPF was present in three patients (2%), and intrabronchial aspergilloma was present in one patient (1%) ([Table 1](#)). Two patients required a double reading because of inconsistencies in the initial radiologic report regarding bronchiectasis.

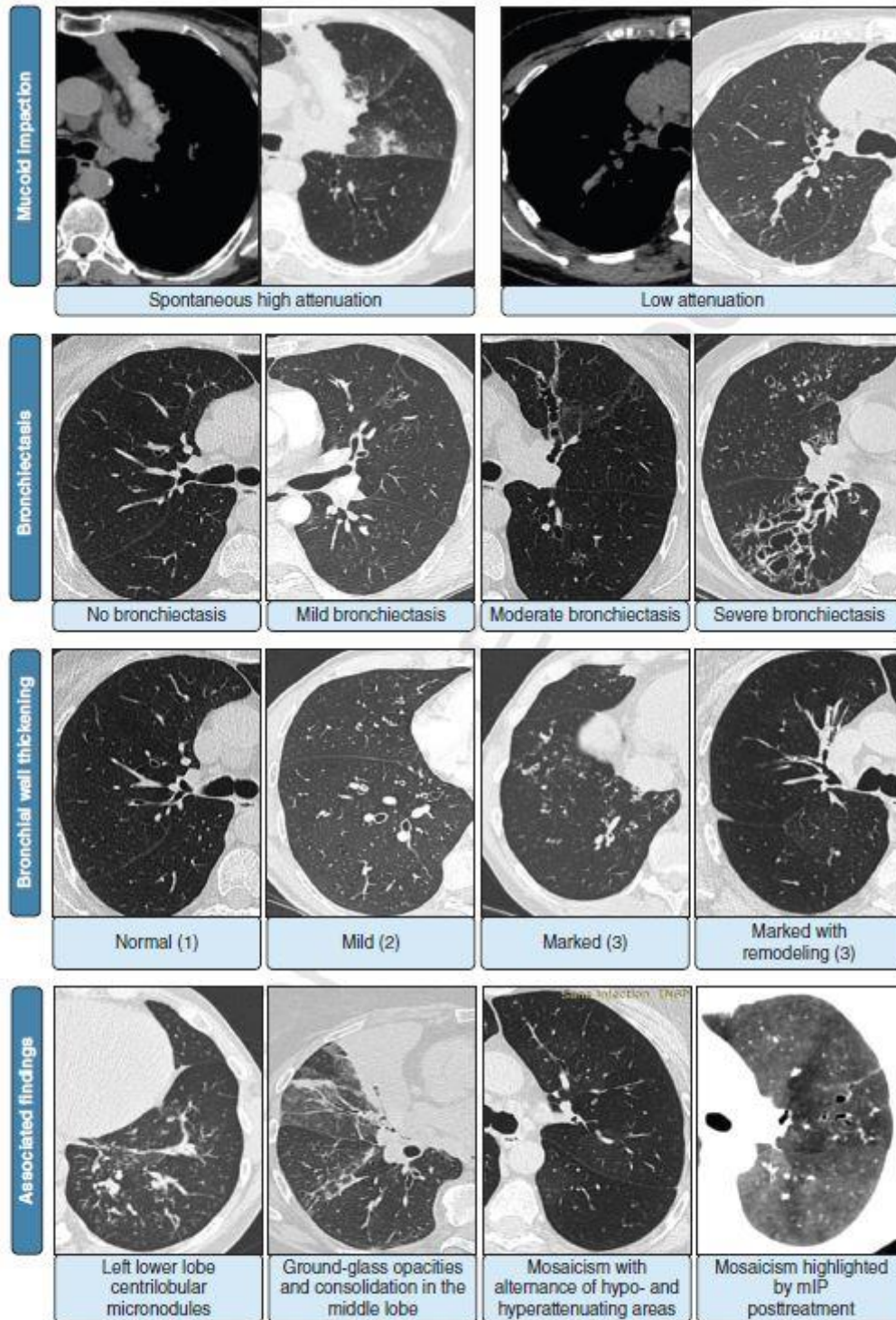


Figure 1 – Labeled examples of CT scan parameter scoring.

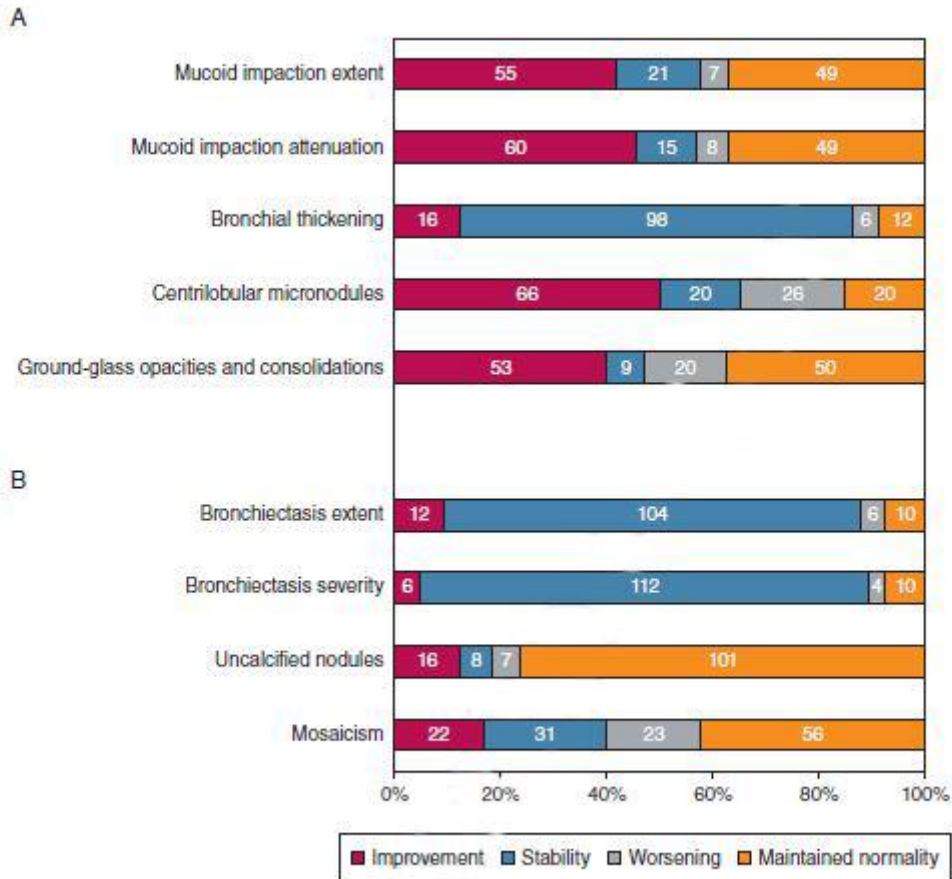


Figure 2 – A, Significant changes and nonsignificant changes (B) of CT scan parameters after 4-mo allergic bronchopulmonary aspergillosis exacerbation treatment. The x-axis represents percentage of patients. The number of patients in each level of change is indicated in the graph bars.

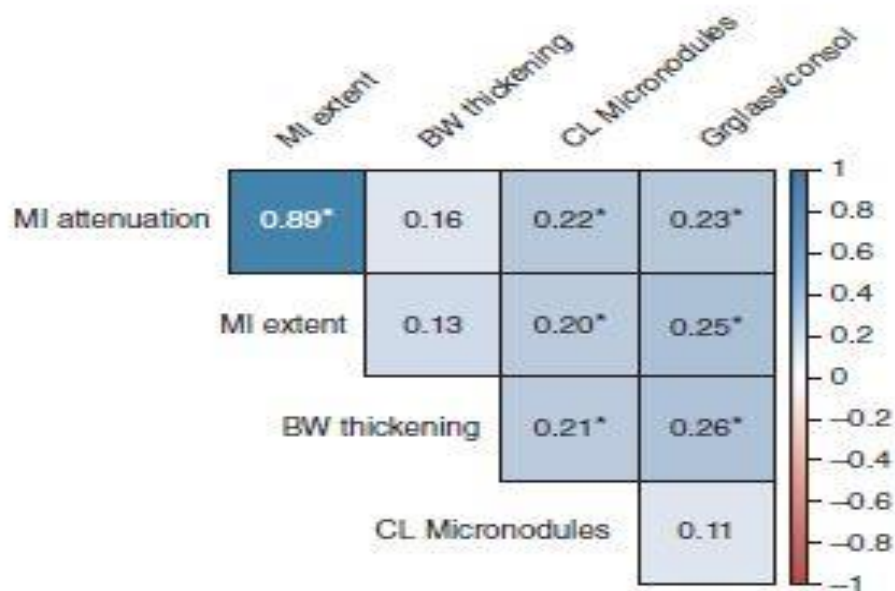


Figure 3 – Corrologram showing Spearman correlations between CT scan parameter changes * $P < .05$. BW = bronchial wall; CL = centrilobular; Grglass/consol = ground-glass opacities and consolidations; MI = mucoid impaction.

Changes of CT Scan Parameters Between M0 and M4

Changes of CT scan parameters after 4-month ABPA exacerbation treatment (M4) are shown in [Table 1](#). Among the 16 CT scan parameters analyzed, five parameters were identified as showing significant radiologic improvement between M0 and M4 in 70 of 132 patients (53%): mucoid impaction extent, mucoid impaction density, centrilobular micronodules, consolidation/ground-glass opacities, and bronchial wall thickening. These five CT scan parameters were used to define the overall radiologic response.

Categorization of the CT scan changes in four classes (improvement, stability, worsening, and maintained normality) between M0 and M4 is shown in [Figure 2](#): 55 of 132 patients (42%) showed improvement in the extent of mucoid impaction, and 60 (45%) showed a decrease of their attenuation. The extent of centrilobular micronodules decreased in 66 patients (50%), and the extent of the consolidation/ground-glass opacities decreased in 53 patients (40%). Sixteen patients (12%) showed improvement in bronchial wall thickening. The other CT parameter changes are detailed in [Figure 2](#).

The correlations between changes in the five CT scan parameters, which define the overall radiologic response, are shown in [Figure 3](#). A strong correlation was found between mucoid impaction density and mucoid impaction extent changes ($r = 0.89$, $P < .001$), indicating that a change in density is closely associated with a change in extent. All the other correlations were nonsignificant or weak significant (Spearman coefficient correlation range, 0.20-0.26).

Hierarchical clustering analysis using the first eight axes of principal component analysis performed on CT scan parameter changes retained 88% of the information. This analysis confirms the heterogeneity of the radiologic response by the identified four clusters of patients ([e-Fig 2](#); [e-Tables 3, 4](#)).

Agreement Between Radiologic, Clinical, and Immunologic Responses After 4-Month ABPA Exacerbation Treatment (M4)

A scoring evaluation of clinical response at M4 was available for 117 of 132 patients (89%), and clinical improvement was observed for 72 of them (62%) by using this scoring evaluation.

Immunologic data were available for 125 patients (95%) at M4, and immunologic response was observed for 98 of them (78%).

No concordance between changes in any of the five previously identified radiologic parameters and the clinical or immunologic response was found ($k = -0.01$ to 0.24) ([Tables 2, 3](#)). Considering the overall radiologic response, no concordance was found with either clinical ($k = -0.19$) or immunologic responses ($k = 0.03$) ([Tables 2, 3](#)). Among patients with discrepancies between clinical and radiologic responses, improvement was more frequently observed with clinical response than with each radiologic parameter ($P < .05$ by McNemar test) ([Table 2](#)). Similarly, the discrepancies between immunologic and radiologic responses showed that improvement was more frequently observed with immunologic response than with each radiologic parameter, and with overall radiologic parameters ($P < .05$ by McNemar test) ([Table 3](#)).

TABLE 2] Radiologic and Clinical Response Agreement

	Clinical Response		κ Coefficient (95% CI)	McNemar P Value ^a
	Improvement (n = 72)	Stability or Deterioration (n = 45)		
Mucoid impaction extent			0.07 (-0.09 to 0.24)	.0003
Improvement	30 (26)	15 (13)		
Stability or deterioration	42 (36)	30 (26)		
Mucoid impaction attenuation			0.07 (-0.09 to 0.24)	.0033
Improvement	33 (28)	17 (15)		
Stability or deterioration	39 (33)	28 (24)		
Bronchial wall thickening			-0.02 (-0.12 to 0.08)	< .0001
Improvement	8 (7)	6 (5)		
Stability or deterioration	64 (55)	39 (33)		
Centrilobular micronodules			0.24 (0.07 to 0.41)	.0253
Improvement	42 (36)	15 (13)		
Stability or deterioration	30 (26)	30 (26)		
Ground-glass opacities and consolidations			0.06 (-0.11 to 0.22)	.0006
Improvement	30 (26)	16 (14)		
Stability or deterioration	42 (36)	29 (25)		
Overall radiologic response			-0.19 (-0.37 to -0.02)	.0943
Improvement	42 (36)	17 (15)		
Stability or deterioration	30 (26)	28 (24)		

Values are No. (%) or as otherwise indicated.

^aMcNemar test used to test the symmetry of discordant observations. *P* < .05 indicates significant imbalance in the discordant pairs.

TABLE 3] Radiologic and Immunologic Response Agreement

	Immunologic Response		κ Coefficient (95% CI)	McNemar P Value ^a
	Improvement (n = 98)	Stability or Deterioration (n = 27)		
Mucoid impaction extent			-0.02 (-0.15 to 0.12)	< .0001
Improvement	41 (33)	12 (10)		
Stability or deterioration	57 (46)	15 (12)		
Mucoid impaction attenuation			-0.08 (-0.22 to 0.06)	< .0001
Improvement	42 (34)	15 (12)		
Stability or deterioration	56 (45)	12 (10)		
Bronchial wall thickening			0.01 (-0.06 to 0.07)	< .0001
Improvement	12 (10)	3 (2)		
Stability or deterioration	86 (69)	24 (19)		
Centrilobular micronodules			-0.01 (-0.15 to 0.14)	< .0001
Improvement	50 (40)	14 (11)		
Stability or deterioration	48 (38)	13 (10)		
Ground-glass opacities and consolidations			-0.06 (-0.19 to 0.07)	< .0001
Improvement	38 (30)	13 (10)		
Stability or deterioration	60 (48)	14 (11)		
Overall radiologic response			0.03 (-0.12 to 0.18)	.0001
Improvement	55 (44)	14 (11)		
Stability or deterioration	43 (34)	13 (10)		

Values are No. (%) or as otherwise indicated.

^aMcNemar test used to test the symmetry of discordant observations. *P* < .05 indicates significant imbalance in the discordant pairs.

The agreement between clinical and immunologic responses was also quite poor ($\kappa \frac{1}{4} 0.03$) (e-Table 5), and the improvement was significantly more frequent with immunologic than with clinical response (30% and 13%, respectively; *P* = .0056 by McNemar test). Among 110

patients with available data for the three categories of response, five patients did not show any response. As shown in Figure 4, of the remaining 105 patients, five patients (5%) showed isolated radiologic response, and 34 patients (32%) showed a combined radiologic, clinical, and immunologic response.

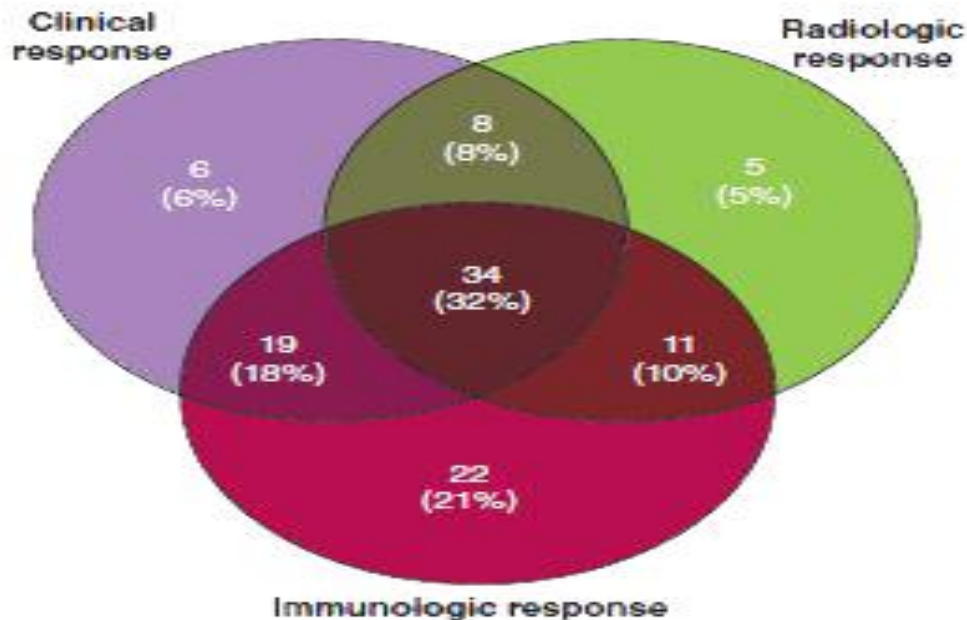


Figure 4 – Venn diagram showing agreement between overall radiologic response, clinical response, and immunologic response between CT scan at initiation and end of the 4-mo exacerbation treatment in the 105 patients with available data for the three types of response who were responders for at least one type of response (five patients did not show any type of response and are not represented in the diagram).

Discussion

To our knowledge, this study is the first to assess CT scan changes in 132 patients with ABPA having received 4 months of standardized ABPA exacerbation treatment. Among the 16 CT scan parameters conventionally analyzed, this analysis identified five CT scan parameters showing significant improvement after a 4-month standardized ABPA exacerbation treatment: mucoid impaction extent, mucoid impaction density, centrilobular micronodules, consolidation/ground-glass opacities, and bronchial wall thickening.

This study simplifies the CT scan analysis by identifying only five relevant parameters changing over time under ABPA exacerbation treatment. Among these five CT parameters, only the extension and the attenuation of mucoid impaction were strongly correlated. Although the characteristics of mucoid impaction are important factors in ABPA detection and prognosis,¹⁷ they had never previously been linked. Whereas central bronchiectasis and distal bronchiectasis have often been described in the literature as associated in about one-

third of the patients,¹ in our study, up to 25% of the patients presented with isolated distal bronchiectasis.

This study showed that the presence of high-attenuation mucus impaction is compatible with radiologic improvement, even if high-attenuation mucus has previously been found to be an independent predictor factor of frequent relapse.^{12,18} In fact, we identified a large cluster of patients whose response was mainly linked to improvement in density/extent of mucoid impaction, thereby highlighting the distinctive features of this population as previously reported.³ Moreover, these patients sometimes showed complete resolution of mucoid impaction, with bronchial diameter returning to normal, raising the question of the so-called irreversibility of bronchiectasis.

Regarding changes in the other CT scan parameters (apart from mucoid impaction), the absence of strong correlations among them suggests that changes in CT scan features over time and under treatment are not related to each other and that each parameter should be considered separately, whereas mucoid impaction, its density, centrilobular nodules, consolidation, and bronchial wall thickening represent different imaging manifestations of mucus plugging in large or small airways. The identification of four clusters also reinforces the concept of heterogeneous radiologic response.

The clinical and radiologic responses are sometimes discordant because some patients present with radiologic deterioration without experiencing clinical worsening.¹ This deserves a radiologic approach in addition to a clinical approach to assess response to treatment, as proposed in the International Society for Human and Animal Mycology recommendations.¹ In fact, the criteria proposed to evaluate clinical response (eg, improvement in daily life activities, health status) are subjective and suffer from lack of specificity for ABPA. Moreover, worsening of symptoms can be secondary to viral, bacterial, or mycobacterial infection, or exacerbation of underlying asthma.¹ Regarding immunologic investigations, the threshold of total serum IgE for diagnosing ABPA, and the percentage of total IgE decline for evaluating response to treatment, remains controversial.¹ Accordingly, these weaknesses justify consideration of not only both clinical and immunologic criteria, but also of objective radiologic parameters for assessing response to treatment. In this study, there was no concordance between the radiologic response and the clinical or immunologic response.

These findings highlight the importance of a multidimensional evaluation of response to treatment.¹

Our study has several limitations. The response was evaluated after 4 months of itraconazole associated with corticosteroids during the first 2 months, and not after only 2 months of corticosteroids. However, a 4-month ABPA exacerbation treatment was better suited to a mixed population of patients with newly diagnosed ABPA and recurrent exacerbations. Moreover, radiologic changes were assessed after a 4-month exacerbation treatment to specify the current definition of stage 2 (ie, response) of the clinical staging of ABPA.¹ Radiologic changes after maintenance therapy could represent another approach to disease progression, as proposed in patients with severe persistent asthma.¹⁹

The variable scheme of corticosteroid dose reduction may have had an impact on total IgE levels at 4 months, but this scheme corresponds to real-life management adapted to a mixed population of patients suffering from newly diagnosed ABPA and recurrent exacerbations in

the context of severe corticoid-dependent asthma, in which the goal is to limit duration of corticosteroids.

Because the study population included only patients with asthma, our results may not be extrapolated to other underlying conditions (eg, COPD, cystic fibrosis).

Finally, to date, the radiologic scheme has no clear therapeutic implications. The added value of CT scan in assessing response to treatment still needs to be clarified by further studies, and in the absence of clinical worsening of the patient, a chest radiograph could be used during follow-up. These results should be regarded as exploratory.

The strengths of our study lie in a prospective and consensual blinded CT scan evaluation of a homogeneous population of patients with ABPA, who received a standardized ABPA exacerbation treatment, with therapeutic drug monitoring and absence of severe exacerbation during a 4-month ABPA exacerbation treatment period.

Interpretation

This study showed that changes in extent and density of mucoid impaction, centrilobular micronodules, consolidation/ground-glass opacities, and thickening of the bronchial walls were the most relevant CT scan parameters to assess the radiologic response after a 4-month ABPA exacerbation treatment. A strong correlation between CT scan parameter changes was observed only for mucoid impaction density and mucoid impaction extent.

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Author contributions:

C. G. is the investigator of the study; contributed to study design; obtained funding; is a member of the steering committee; and contributed to data acquisition and collection, data analysis and interpretation, and drafting the manuscript. F. C., J. C., J.-P. F., A. B., A.-L. B., H. M., and F. L. contributed to study design, data acquisition and collection, data analysis and interpretation, drafting the manuscript, and critical revisions of the manuscript for important intellectual content. S. M.-A., F. G., E. B., C. T., B. P., S. H., C. A., A. B., C. C., S. D., G. M., M. M.-E., F. R., G. G., F.-X. B., F. G., T. F., and P. P. contributed to data acquisition and

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