J Infect Chemother 20 (2014) 375–379

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original article

Recurrence of chronic pulmonary aspergillosis after discontinuation of maintenance treatment by antifungal triazoles

Kazuya Koyama [a,*], Nobuharu Ohshima [b], Junko Suzuki [a], Masahiro Kawashima [a], Keita Takeda [a], Takahiro Ando [a], Ryota Sato [a], Hideaki Nagai [a], Hirotoshi Matsui [a], Ken Ohta [a,b]

[a] Center for Pulmonary Diseases, National Hospital Organization Tokyo National Hospital, Japan
[b] Asthma and Allergy Center, National Hospital Organization Tokyo National Hospital, Japan

ARTICLE INFO

Article history:
Received 26 December 2013
Received in revised form
15 February 2014
Accepted 20 February 2014

Keywords:
Chronic pulmonary aspergillosis
Maintenance treatment
Treatment duration
Recurrence
Anti-Aspergillus antibody
Triazole

ABSTRACT

Objective: To assess the prevalence and risk factors of recurrence of chronic pulmonary aspergillosis (CPA) after discontinuation of antifungal triazoles.
Method: We reviewed the medical records of CPA patients who achieved resolution of clinical and radiographic manifestations and stopped taking antifungal triazoles between June 2006 and June 2012 at Tokyo National Hospital. We evaluated whether there was CPA recurrence within 1 year after treatment cessation and investigated risk factors for relapse. The association of anti-Aspergillus antibody conversion with CPA recurrence was also reviewed.
Results: A total of 39 patients were included in this study and there was CPA recurrence in 14 patients. Compared with the Non-recurrence group, the Recurrence group exhibited 1) younger age ($p = 0.017$), 2) more than one lung lobe affected by CPA more frequently ($p = 0.008$), 3) longer duration needed to remit manifestations of chest radiograph ($p = 0.031$), 4) longer antifungal treatment duration ($p = 0.042$). The present study did not reveal an association between negative conversion of serum anti-Aspergillus antibody and recurrence risk. Multivariate logistic regression analysis revealed that patients with CPA with affected area of more than one lung lobe had increased risk (odds ratio, 10.20; 95% confidence interval, 1.49–69.77; $p = 0.018$).
Conclusion: CPA recurrence can be seen in about one-third of cases after discontinuing azole treatment. We should make decisions about treatment duration and follow up depending on the severity of each case, particularly on the expansion of CPA-affected area.

1. Introduction

Chronic pulmonary aspergillosis (CPA) is a slow progressive disease caused by destruction of the lung by *Aspergillus* spp. CPA occurs in patients with underlying lung disease or mild immunosuppression and needs relatively long treatment duration. Although treatment in the acute phase consists of administration of various antifungal drugs such as liposomal amphotericin B and voriconazole, maintenance treatment consists of a prescription of oral itraconazole or voriconazole in the majority of cases [1,2]. There have been some recommendations about the duration of maintenance treatment. Guidelines published by the Infectious Diseases Society of America say that antifungal treatment may be required for the 'long-term, perhaps lifelong' [3]. The American Thoracic Society statement recommends that treatment should continue until resolution or stabilization of all clinical and radiographic manifestations [1]. Treatment durations in previous studies evaluating the effectiveness of triazoles were within 1 year [8,11–13]. However, there have been few studies reporting the appropriate duration of treatment, prevalence of relapse and risk factors for recurrence.

In an attempt to reveal the prevalence of CPA recurrence after treatment discontinuation and risk factors for CPA recurrence, we performed a retrospective study of CPA patients at Tokyo National

* Corresponding author. Center for Pulmonary Diseases, National Hospital Organization Tokyo National Hospital, 3-1-1 Kiyose-shi, Tokyo 204-8585, Japan. Tel.: +81 42 491 2111; fax: +81 42 494 2168.
E-mail address: d.er.leier@hotmail.co.jp (K. Koyama).

http://dx.doi.org/10.1016/j.jiac.2014.02.003
1341-321X/

Hospital. We also evaluated whether conversion of serum anti-Aspergillus antibody was associated with CPA relapse because there have been several reports referring to the relationship between the titer of the antibody and stage of disease [4,5].

2. Patients and methods

2.1. Design

This was a retrospective cohort study evaluating CPA patients who were treated at Tokyo National Hospital. The hospital was found as sanatorium for tuberculosis patients and now plays a role as a core hospital for community health care. In patients with CPA, we reviewed whether there had been CPA recurrence within 1 year after treatment cessation and investigated risk factors for relapse. A patient was considered to have recurrence of CPA when new infiltration or wall thickening of lung cavity appeared at the site diagnosed as aspergillosis previously. We excluded cases in which other lung diseases including infection with other pathogens were considered. We divided the CPA patients into the Recurrence group and Non-recurrence group and determined risk factors for recurrence by comparing the clinical and radiologic manifestations mentioned below.

2.2. Patients

We investigated the medical records of CPA patients who achieved resolution of clinical and radiographic manifestations and discontinued antifungal triazoles between June 2006 and June 2012 at Tokyo National Hospital. Patients with CPA were defined as patients with the presence of: 1) underlying lung disease, 2) one or more of the following evidences suggesting *Aspergillus* infection: positive serum anti-Aspergillus antibodies, positive cultures of *Aspergillus* spp. from respiratory specimens including sputum and bronchial wash, or histological evidences of *Aspergillus* spp. in lung biopsy specimens, 3) slowly progressive chest CT abnormalities suggesting spp. infection such as lung infiltrations, thickening of cavity wall and fungus ball. Since meeting the "criteria 2)" was a prerequisite for the inclusion of this study, we selected patients using database of serum anti-Aspergillus antibody, pathological examinations and microbiological tests between January 2001 and June 2012, and reviewed treatment course examining whether treatment completed. Although triazole discontinuation might have been decided with various additional reasons by the physicians, we included, in this study, only those patients who met the recommendation for the discontinuation, i.e. clinical and radiological resolution. Patients were excluded if they discontinued medication for reasons other than CPA improvement or underwent resection of *Aspergillus* infection sites.

We checked chest images and clinical information including patients' sex, age, clinical symptoms, comorbidities, smoking history, pre-existing pulmonary disease, medication history and treatment duration. Treatment duration included not only the period of triazole administration, but also the duration of induction therapy by other antifungal drugs including intravenous triazole, micafangin and amphotericin B. Chest CT scans obtained before the initiation of treatment were reviewed; we evaluated the presence of fungal ball and whether the pathological change by aspergillosis extended over more than one lung lobe. We also evaluated the period needed to achieve remission of radiological findings of CPA. A patient was considered to have radiological remission if the infiltration or thickening of lung cavity improved and became stable on chest radiographs.

Table 1
Characteristics of the CPA patients.

	All ($n = 39$)	Recurrence ($n = 14$)	Non-recurrence ($n = 25$)	P value[a]
Median age (years old)(range)	59 (35–84)	55 (35–76)	61 (40–84)	0.017*
Never smoker (%)	8 (21%)	5 (36%)	3 (12%)	0.109
Male (%)	31 (79%)	9 (64%)	22 (88%)	0.109
BMI (kg/m^2) (range)	18.8 (14.1–26.2)	18.5 (14.9–21.1)	19.4 (14.1–26.6)	0.209
Preexisting lung disease				
Tuberculosis sequelae (%)	21 (54%)	9 (64%)	12 (48%)	0.504
Emphysema (%)	18 (46%)	7 (50%)	11 (44%)	NS
Bulla (%)	3 (8%)	0 (0%)	3 (12%)	0.540
NTM disease (%)	2 (5%)	1 (7%)	1 (4%)	NS
Postoperation (%)	2 (5%)	1 (7%)	1 (4%)	NS
Underlying extrapulmonary disease				
Diabetes mellitus	6 (15%)	1 (7%)	5 (20%)	0.391
Coronary heart disease	2 (5%)	0 (0%)	2 (8%)	0.528
HIV infection	1 (3%)	1 (7%)	0 (0%)	0.359
Positive sputum culture (%)	10 (26%)	2 (14%)	8 (32%)	0.279
Positive bronchial washing culture (%)	1 (3%)	0 (0%)	1 (4%)	NS
Hypha proven by TBLB (%)	2 (5%)	1 (7%)	1 (4%)	NS
Positive serum Aspergillus antibody	34 (87%)	12 (86%)	22 (88%)	NS
CT findings				
Aspergilloma	4 (10%)	2 (14%)	2 (8%)	NS
Expansion of CPA affected area >1 lung lobe	19 (49%)	11 (79%)	8 (32%)	0.008**

BMI: body mass index, NTM: nontuberculous mycobacteria, TBLB: transbronchial lung biopsy, CPA: chronic pulmonary aspergillosis.
*$p < 0.05$, **$p < 0.01$.
[a] The significance of differences between the Recurrence and Non-recurrence groups.

2.3. Anti-Aspergillus antibody

We compared the serum anti-Aspergillus antibody level at the times of treatment initiation and treatment completion. Whether negative conversion of anti-Aspergillus antibody by treatments affected CPA recurrence was evaluated. The serum antibody level was measured by the Ouchterlony method [6,7]. After patients' serum and *Aspergillus fumigatus* antigen were placed in adjacent wells cut in a diffusion gel, visible precipitation, indicating the presence of anti-Aspergillus antibody, was checked. The antibody was considered positive when the serum reacted either *A. fumigatus culture* filtrate antigen or *A. fumigatus* somatic antigen, 2 mg/ml and 20 mg/ml for each.

2.4. Statistical analysis

Data are shown as number of patients with percentage. Age, treatment duration and time needed for resolution of chest radiograph are shown as median and range.

Fisher's exact or Chi-squared test and Mann Whitney U test were used to compare patients' characteristics between the Recurrence and Non-recurrence groups. The risks for recurrence of CPA were evaluated by logistic analysis. $P < 0.05$ was considered as statistically significant.

2.5. Ethics

This study was reviewed and approved by the ethics committee of the National Hospital Organization, Tokyo National Hospital, and was conducted according to principles expressed in the Declaration of Helsinki.