Treatment of Chronic Pulmonary Aspergillosis by Voriconazole in Nonimmunocompromised Patients*

Juliette Camuset, MD; Hilario Nunes, MD; Marie-Christine Dombret, MD; Anne Bergeron, MD; Priscilla Henno, MD; Bruno Philippe, MD; Gaelle Dauriat, MD; Gilles Mangiapan, MD; Antoine Rabbat, MD; and Jacques Cadranel, MD

Background: **There is no recognized medical treatment for chronic pulmonary aspergillosis (CPA) apart from surgery in patients with simple aspergilloma. To evaluate the efficacy of voriconazole in this setting, we conducted a retrospective multicenter study over a 3-year period.**
Methods: **For inclusion in the study, patients had to have received voriconazole for treatment of confirmed or probable CPA with a follow-up of at least 6 months. Clinical, radiologic, and mycologic data were collected at baseline, every 2 to 3 months, and at the end of treatment or at the date point.**
Results: **Twenty-four patients were included in the study, among which 9 patients presented with chronic cavitary pulmonary aspergillosis and 15 presented with chronic necrotizing pulmonary aspergillosis (CNPA). Voriconazole was given as a first-line treatment to 13 patients. The median duration of treatment and follow-up were 6.5 and 10 months, respectively. Three patients had to stop treatment with voriconazole because of toxicity. Symptoms and imagery findings were improved in 16 of 24 patients and 17 of 24 patients, respectively, at the end of follow-up. Mycology, which was positive at baseline in 21 of 23 patients, was negative in 18 of 19 patients at the end of follow-up; serologic test results were also negative in 6 of 19 evaluable patients, all of whom had CNPA. Improved radioclinical findings and mycologic eradication were observed at the end of follow-up in 11 of 19 patients (58%). Patients in whom the disease was controlled had a significantly longer median duration of treatment than patients in whom it was uncontrolled (9 vs 6 months, respectively; p = 0.04).**
Conclusion: **Voriconazole provides effective treatment of CPA with an acceptable level of toxicity.**
(CHEST 2007; 131:1435–1441)

Key words: aspergillosis; lung disease; triazole

Abbreviations: CCPA = chronic cavitary pulmonary aspergillosis; CNPA = chronic necrotizing pulmonary aspergillosis; CPA = chronic pulmonary aspergillosis; IPA = invasive pulmonary aspergillosis; SA = simple aspergilloma

The definition of chronic pulmonary aspergillosis (CPA) in nonseverely immunocompromised patients remains vague, and a wide range of clinical, radiologic, and anatomopathologic entities have been described with a variety of names (*ie*, simple aspergilloma [SA],[1] semi/chronic invasive aspergillosis,[2] chronic necrotizing pulmonary aspergillosis [CNPA],[3] complex aspergilloma,[1]

*From the Department of Pneumology and Respiratory Intensive Care (Drs. Camuset and Cadranel), Assistance Publique-Hopitaux de Paris, Tenon Hospital, Paris, France; the Department of Pneumology (Dr. Nunes), Assistance Publique-Hopitaux de Paris, Avicenne Hospital, Bobigny, France; the Department of Pneumology (Dr. Dombret), Assistance Publique-Hopitaux de Paris, Bichat Hospital, Paris, France; the Department of Pneumology (Dr. Bergeron), Assistance Publique-Hopitaux de Paris, Saint-Louis Hospital, Paris, France; the Department of Pneumology (Dr. Henno), Assistance Publique-Hopitaux de Paris, George Pompidou European Hospital, Paris, France; the Department of Pneumology (Dr. Philippe), Foch Hospital, Suresnes, France; the Department of Pneumology (Dr. Dauriat), Beaujon Hospital, Clichy, France; the Department of Pneumology (Dr. Mangiapan), Inter-Commune Hospital Centre, Creteil, France; and the Department of Pneumology (Dr. Rabbat), Assistance Publique-Hopitaux de Paris, Hôtel-Dieu Hospital, Paris, France.
The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Manuscript received October 9, 2006; revision accepted January 14, 2007.

Correspondence to: Jacques Cadranel, MD, Department of Pneumology and Respiratory Intensive Care, AP-HP, Tenon Hospital, 4 rue de la Chine, 75970 Paris, France; e-mail: jacques.cadranel@tnn.aphp.fr
DOI: 10.1378/chest.06-2441

chronic cavitary and fibrosing pulmonary and pleural aspergillosis,[4] and pseudomembranous tracheobronchitis caused by aspergillus[5]). However, these disease entities all share common characteristics, suggesting that they belong to the same group of CPA disorders, as follows: (1) a specific cause (*eg*, alcohol, tobacco abuse, or diabetes) that is responsible for the deterioration in local or systemic defenses against infection[6]; (2) an underlying bronchopulmonary disease (*eg*, active tuberculosis or tuberculosis sequelae, bronchial dilatation, sarcoidosis, or COPD) that is responsible or not for the presence of a residual pleural or bronchopulmonary cavity[6–17]; (3) generally, the prolonged use of low-dose oral or inhaled corticosteroids[6]; and (4) the absence of or presence of very little vascular invasion, a granulomatous reaction, and a low tendency for metastasis.[4] These characteristics, however, are not sufficient for CPA to be considered to be acute invasive pulmonary aspergillosis (IPA) as defined in the literature,[18] although this definition does not fit very well for categories other than oncohematologic patients.

There are no codified treatment guidelines for CPA. Bronchial artery embolization may stop hemoptysis in certain cases.[19] Surgery is generally impossible because of impaired respiratory function or the severity of the comorbidity, and when it is possible that morbidity and mortality are very high.[7,9–15,20] Numerous clinical cases and short retrospective series[21–27] have reported the effect over time of the various antifungal agents that are available. Oral triazoles (*ie*, itraconazole and voriconazole, and in particular voriconazole) appear to provide suitable treatment for CPA; however, there are no data concerning posaconazole. Unlike itraconazole, voriconazole has an *in vitro* fungicidal activity against Aspergillus. Moreover, its efficacy was demonstrated in immunocompromised patients with IPA,[28] and its prolonged oral administration seems to be possible with an acceptable tolerability.[27] Finally, two recently published studies[27,29] showed that useful results were obtained in 11 patients with chronic cavitary pulmonary aspergillosis (CCPA) and 15 patients with CPA who were receiving voriconazole as first-line therapy or after a lack of response to one or several antifungal treatments. In order to complement these preliminary results, we conducted a retrospective cohort study including all confirmed or probable cases of CPA in patients who had been admitted to pneumology departments in teaching hospitals in the Ile de France region from November 2001 to May 2004 and had been treated with voriconazole.

Materials and Methods

All pneumology departments (n = 12) in teaching hospitals in Paris were contacted in order to identify patients who had been treated with voriconazole therapy between November 2001 and May 2004 and whose conditions were consistent with a diagnosis of CPA. Patients were easy to identify, as the dispensing of voriconazole in France requires a nominative hospital prescription. Declared cases of CPA were reviewed by one of us (Dr. Camuset) to check the diagnostic criteria. Data were collected on a standardized and anonymous data collection form. For this retrospective, observational, noninterventional analysis of medical records, French law does not require the specific approval of an internal review board or the consent of patients.

Inclusion Criteria and Case Definition

For inclusion in the study, patients had to have received voriconazole for the treatment of CPA, except for SA (*ie*, CNPA[4] or CCPA[5]) with a follow-up duration of at least 6 months until November 2004. A diagnosis of CPA was considered to be certain if it was associated with the following: (1) compatible chest imagery findings; (2) positive results of serologic tests for Aspergillus using a detection method with a method of confirmation by immunoelectrophoresis showing at least two precipitation arcs; and (3) positive mycology results on a bronchopulmonary sample (*ie*, cytobacteriologic examination of sputum bronchial aspiration or BAL fluid or a culture of a surgical specimen), which was defined as positive direct microscopy and positive mycological culture results, or positive culture finding alone but with at least two colonies grown after two inoculations. In the absence of a positive mycologic examination finding, the diagnosis of CPA was defined as being probable. The CPA was classified as CNPA or CCPA after a second reading of the chest CT scan by Drs. Camuset and Cadranel.

Exclusion Criteria

The following patients were excluded from the study: (1) patients with possible CPA presenting with negative Aspergillus antibody detection; (2) patients with SA,[2] acute IPA,[18] pseudomembranous tracheobronchitis aspergillosis,[5] or allergic bronchopulmonary aspergillosis[30]; (3) patients with progressive tumoral or infectious lung disease at the time of the diagnosis of CPA; and (4) patients with cystic fibrosis or overt primary or secondary immune deficiency.

Data Collection

The following data were collected at the time of the institution of voriconazole: age; gender; comorbidity and underlying pulmonary disease; history of treatment with antifungal agents and systemic or inhaled corticosteroids; the presence of one or several symptoms from among fever (temperature $\geq 38°C$), cough, expectoration, hemoptysis, dyspnea and chest pain; the number of Aspergillus precipitation arcs determined by immunoelectrophoresis; the results for mycologic samples with positive direct microscopy and/or positive mycologic culture findings and the type of Aspergillus infection that was identified; and the results of chest radiographs and CT scans. These data were also collected during subsequent evaluations that were carried out after 2 to 3 months and 5 to 6 months of treatment and during the final evaluation of patients in November 2004, as well as during the occurrence of side effects that were considered to be related to voriconazole therapy causing a discontinuation of treatment.

Outcome Variables

Clinical improvement was defined by the disappearance during follow-up visits of more than half the symptoms noted at the initial evaluation. Radiologic improvement was defined as the partial or complete disappearance of findings initially considered to be related to CPA; however, abnormalities related to the lung disease that contributed to the development of the CPA could persist. Finally, control of the disease was defined at the final evaluation by a combination of clinical and radiologic improvement, and negative findings from the testing of mycologic samples; serologic tests results could remain positive. The other outcomes were classed as stabilization or worsening.

Statistical Analysis

All the data were expressed as the mean (SD) or median (range). Categoric variables were expressed as percentages and were compared with the Fisher exact test. A p value of < 0.05 was considered to be statistically significant.

Results

Forty patients who received voriconazole from November 2001 to May 2004 were identified, among which there were 24 cases of certain or probable CPA. The 16 other case records were not included for the following reasons: possible CPA (n = 2); other forms of aspergillosis (n = 3); and incomplete records or follow-up for < 6 months (n = 11).

Characteristics of CPA

Fifteen patients (62.5%) presented with CNPA, and 9 patients (37.5%) presented with CCPA (Fig 1). Aspergillus antibody detection was positive in all cases (median, 4.3 arcs; range, 2 to 8 arcs). The detection for Aspergillus antigen was performed in 15 of 24 patients. Results were negative in 13 patients (87%) and positive in 2 patients (CPPA, 1 patient; CNPA, 1 patient). Initial mycologic samples were available in 23 of the 24 patients. Results were positive in 21 of the 23 patients (97%) from whom they were collected. The culture findings were positive in 15 patients (65%), positive by direct microscopy and culture in 6 patients (26%), and negative in 2 patients. *Aspergillus fumigatus* was identified in 20 of 21 cases, and *Aspergillus flavus* was identified in the remaining case. Hence, a diagnosis of CPA was considered to be certain in

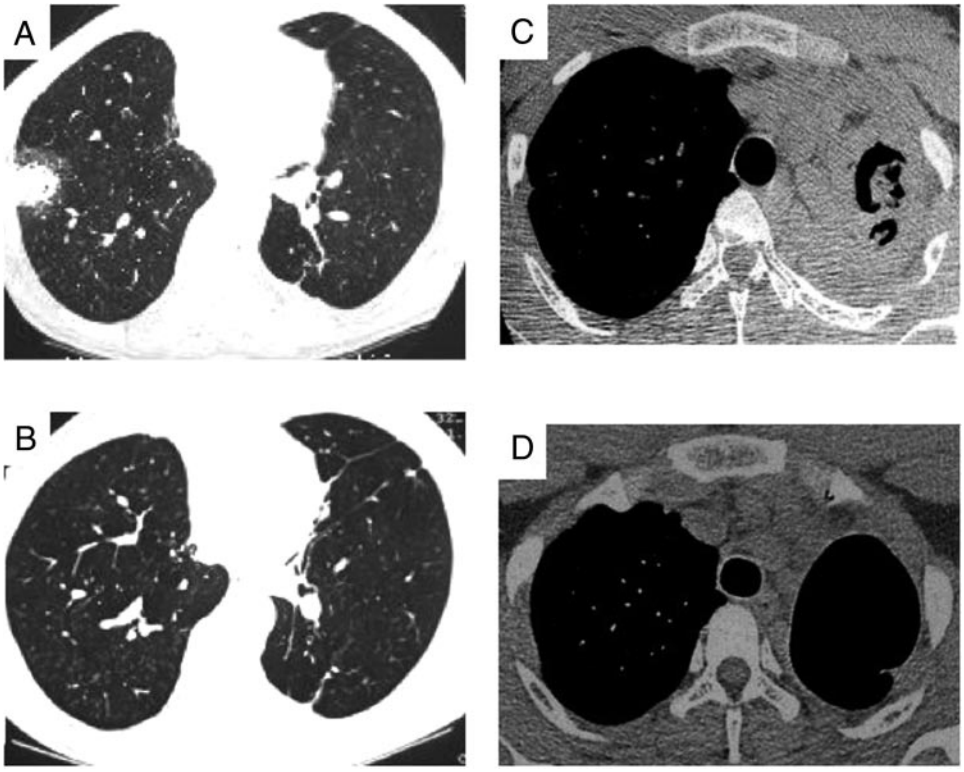

Figure 1. Lung CT scan of two patients with CPA before and after a dramatic radiologic response to voriconazole. *Top left*, *A*: Typical CT scan aspect (parenchymal window) of a CNPA occuring in a patient with severe obstructive bronchopulmonary disease who had received oral corticosteroids; *bottom left*, *B*: after voriconazole treatment. *Top right*, *C*: Typical CT scan aspect (mediastinal window) of a cavitary pulmonary aspergillosis occuring in a young patient with previous tuberculosis; *bottom right*, *D*: after voriconazole treatment

21 patients (87.5%) in whom mycologic culture findings were positive for Aspergillus, and probable in the 3 patients (12.5%) in whom clinical and lung CT scan presentations were compatible with CPA, and who had at least 2 arcs of precipitation in Aspergillus antibody detection but negative culture findings for Aspergillus.

Patient Characteristics

Patients ranged in age from 24 to 75 years (median age, 58.5 years), and 15 of them (62.5%) were men. At study inclusion, all patients presented with at least one of the following respiratory symptoms: dyspnea (n = 21; 87%); cough (n = 19; 79%); expectoration (n = 19; 79%); chest pain (n = 8; 33%); hemoptysis (n = 9; 37%); and fever (temperature $\geq$ 38°C) [n = 7; 29%].

All of the patients presented with at least one underlying lung disease (Table 1). Furthermore, almost all patients had an obstructive pattern detected in their pulmonary function test results, with a reduction in their FEV_1/vital capacity ratio (median, 49% predicted; range, 28 to 84% predicted; n = 23). Eight patients (33%) presented with concomitant extrapulmonary comorbidity, as follows: chronic alcoholism (n = 3); diabetes (n = 2); rheumatoid arthritis (n = 1); malnutrition (n = 1); and hepatitis C and splenectomy (n = 1). Twelve patients (50%) had received therapy with systemic or inhaled corticosteroids.

Treatment by Voriconazole and Follow-up

Voriconazole therapy was indicated in 13 patients (54%) as first-line treatment for CPA and in 11 cases (46%) after lack of response to a first treatment (itraconazole, n = 7; amphotericin B, n = 4). In all cases, oral administration of voriconazole was prescribed at doses respecting the laboratory recommendations according to body weight. The median duration of treatment was 6.5 months (range, 4 to 36 months). Treatment with voriconazole had to be stopped in three patients (12.5%) because of the following serious adverse effects: hepatitis (month 4), one patient; neuropathy (month 4), one patient; and severe toxidermia due to photosensitization (month 9), one patient. Other adverse effects were reported but did not lead to the discontinuation of treatment, as follows: visual disorders at the start of treatment, 7 patients (29%); nausea, epigastralgia, or diarrhea, 5 patients (21%); cholestasis with elevated γ-glutamyl transpeptidase of $<$ 10 N, 4 patients (17%); and cytolysis of $<$ 6 N, 3 patients (7%).

Table 1—*Underlying Lung Disease*

Lung Disease	No. (%)
Sequelae of tuberculosis	10 (42)
COPD	10 (42)
Type IV sarcoidosis	4 (17)
History of infection with *Mycobacterium xenopi*	3 (12)
History of pneumothorax	3 (12)
Asthma without criteria of allergic aspergillosis	3 (12)
History of bronchial cancer or chest lymphoma	3 (12)
History of chest radiotherapy	2 (8)
History of operated aspergilloma	2 (8)

All 24 patients were followed up and regularly evaluated until death for clinical, radiologic, and mycologic parameters. Ten of the 22 patients (45%) evaluated at between 2 and 3 months presented with clinical improvement, and 6 of 20 patients (30%) presented with both radiologic and clinical improvement (Table 2). After 5 to 6 months of treatment, 6 of the 16 evaluated patients (37.5%) presented with radioclinical improvement (Table 2). During the final evaluation, which was conducted after a median follow-up time of 10 months (range, 6 to 36 months), all patients except two were alive. One patient with CNPA who did not respond to 12 months of treatment with voriconazole died from a stroke. The other death was caused by hemoptysis 2 months after the discontinuation of voriconazole, whereas the disease was considered to be controlled after 9 months of treatment for CCPA. During the final evaluation, 16 of 24 patients (67%) presented with clinical improvement and 17 patients (70%) presented with radiologic improvement (Table 2). In 11 patients, the radiologic improvement was complete (65%), and in 6 cases it was partial (35%). Mycologic eradication was observed in 18 of 19 evaluated patients (95%), and the results of Aspergillus antibody detection were negative in 6 of those patients (32%); 6 of 12 evaluated patients who had CNPA (50%) and none of the 7 patients with CCPA had negative results of Aspergillus antibody detection (p = 0.04 [Fisher exact test]).

Finally, disease control, as defined in the "Materials and Methods" section, could only be evaluated in 19 of the 24 patients in whom a culture of respiratory secretion for Aspergillus was performed during the final evaluation. The disease was considered to be controlled in 11 of these 19 patients (58%), whereas it was stabilized in 3 patients (16%). There were 5 patients who did not respond to treatment (26%). Although not statistically significant, radiologic and clinical improvement and control of the disease were more frequently observed in patients with CNPA (10 of 15 patients [67%] and 8 of 13 patients [62%], respectively) than in those with CCPA (4 of 9 patients [44%] and 3 of 6 patients

Table 2—*Evaluation of Response to Voriconazole

Criteria of Response to Voriconazole	M2/M3, No. (%)	M5/M6, No. (%)	Final Evaluation, No. (%)
Clinical improvement	10/22 (45)	11/20 (55)	16/24 (67)
Radiologic improvement	9/20 (45)	11/17 (65)	17/24 (70)
Radioclinical improvement	6/20 (30)	6/16 (37.5)	14/24 (58)
Mycologic eradication	9/11 (82)	9/12 (75)	18/19 (95)
Negative antibody detection	2/16 (12.5)	4/16 (25)	6/19 (32)
Controlled disease	NA	NA	11/19 (58)

*M2/M3 = evaluation between 2 and 3 mo; M5/M6 = evaluation between 5 and 6 mo; NA = nonapplicable.

[50%], respectively) [Table 3]. The median duration of treatment was also significantly longer in patients whose disease was controlled than in the other patients (9 vs 6 months, respectively; $p = 0.04$ [Mann-Whitney test]). However, there was no relationship between disease control and gender, age, previous use or not of corticosteroids, or other anti-Aspergillus treatment, and a decrease in the number of arcs of Aspergillus antibody detection.

Complementary surgical treatment was conducted in four patients. In one patient, surgery was conducted for massive hemoptysis at 6 months, when CPA had not been controlled by voriconazole. In the three other cases, the control of CPA permitted curative surgery after 2, 2, and 6 months of treatment. In these three cases, the findings of microscopic pathologic examinations and mycologic cultures of surgical specimens remained negative for Aspergillus.

Discussion

In our study of 24 patients with CPA, including 21 confirmed cases, both radiologic and clinical improvements were observed in 58% of patients. This radioclinical improvement was accompanied by mycologic eradication in 95% of cases, and control of the disease was observed in 58% of cases. Our results also suggested that the efficacy of voriconazole was higher in CNPA patients than in CCPA patients and that the control of the disease was better in patients who had received a more prolonged course of treatment.

Table 3—*Comparison Between Patients With CNPA and CCPA During Final Evaluation

Criteria	CNPA Patients (n = 15)	CCPA Patients (n = 9)
Clinical improvement	10/15 (67)	6/9 (67)
Radiologic improvement	12/15 (80)	5/9 (56)
Radioclinical improvement	10/15 (67)	4/9 (44)
Negative antibody detection	6/12 (50)	0/7 (0)†
Mycologic eradication	12/13 (92)	6/6 (100)
Controlled disease	8/13 (62)	3/6 (50)

*Values are given as No. of patients with condition/total No. (%).
†$p = 0.04$ (Fisher exact test).

The diagnostic criteria of CPA were those recommended by Denning et al.[4] All of our patients were positive for Aspergillus antibody detection, and 87.5% of them also had culture findings that were positive for Aspergillus. All of our patients were symptomatic and presented with at least one underlying respiratory disease. Sequelae of tuberculosis and COPD alone represented > 80% of the causes as usually described.[6–17] Finally, 33% of our patients also had concomitant extrapulmonary comorbidity, and 50% of patients had received oral or inhaled corticosteroids, as has been underlined.[6,31]

The management of patients with CCPA, which was previously called *complex aspergilloma*, was for a long time based on surgery[7,9–15,20] with a much higher perioperative mortality rate (1 to 17%) and morbidity rate (18 to 60%) than in patients with SA.[32] No methodologically satisfactory study has been carried out on the systemic use of antifungal agents for the treatment of CCPA. Amphotericin B and amphotericin B lipid formulations do not seem to be effective in this indication.[26] Several retrospective studies have been conducted on itraconazole therapy in patients with SA and complex aspergillosis. Itraconazole induced a clinical improvement in 47 to 57% of patients,[24,25] but a radiologic improvement in only 20% of patients.[33] Expert recommendations[34] nevertheless suggest that it should be used in patients with complex aspergilloma either as perioperative treatment or in patients with inoperable disease. In our series, the nine patients with CCPA presented with clinical, radiologic, and clinicoradiologic improvement during the final evaluation in 67%, 56%, and 44% of cases, respectively (Table 3). These results are similar to those obtained in three other more recently published studies.[27,29,35] However, in these three series no information was given on the mycologic effect of voriconazole. Finally, in our series, control of the disease, as defined by clinical and radiologic improvement with myco-

logic eradication, was observed in 50% of cases after a median of 6.5 months of treatment (Table 3); on the contrary, none of the evaluable patients had negative findings for Aspergillus antibody detection (0 of 7 patients), although mycologic samples were negative for Aspergillus in every case (6 of 6 patients) [Table 3].

CNPA treatment guidelines were based on data from retrospective studies and isolated clinical cases, or on expert opinions. CNPA is considered to be a formal indication for antifungal treatment,[31] although it may be useful to combine it with surgical resection. A wide range of antifungal treatments has been used in patients with CNPA. Initially, amphotericin B was used by the IV route, but also by intralesional injection or even as nebulization, with results that are difficult to analyze. At the present time, there is no published case concerning caspofungin. It is only more recently that the use of itraconazole has transformed the prognosis of CNPA. In the series by Dupont,[25] 8 of 14 patients (57%) treated with itraconazole for a mean duration of 7 months were cured and 5 patients were stabilized, with a follow-up time of approximately 11 months. Likewise, in the series by Loeuille et al,[24] seven of the eight patients presenting with confirmed CNPA were cured after 4 months of itraconazole treatment, although the follow-up time was only 6 months. Clinical, radiologic, and clinicoradiologic improvements during the final evaluation were observed in 67%, 80%, and 67% of our cases, respectively (Table 3). Moreover, control of the disease, as defined by clinical and radiologic improvement with mycological eradication, was observed in 62% of patients after a median of 6 months of treatment. Finally, Aspergillus antibody detection became negative, and mycologic cultures became sterile in 50% of evaluable patients (6 of 12 evaluable patients) and 92% of evaluable patients (12 of 13 evaluable patients), respectively (Table 3).

Overall, our results suggest that voriconazole provides a good alternative for the treatment of CPA in nonimmunocompromised subjects with an acceptable safety profile. Clinicoradiologic improvement was observed in 70% of patients (17 of 24 patients) after a median follow-up time of 10 months. This radioclinical improvement was accompanied by mycologic eradication in 95% of cases, leading to control of the disease in 58% of cases. Moreover, it is interesting to note that the analysis of surgical specimens in three patients confirmed mycologic eradication, which might suggest the fungicidal activity of voriconazole against Aspergillus *in vivo* in humans. Our results also suggest that voriconazole is more effective in patients with CNPA than in those with CCPA and when treatment is more prolonged. The safety profile of voriconazole is very similar to that recently reported[27,29] in similar populations of patients who were given prolonged treatment. Three patients had to interrupt treatment because of toxicity (12.5%), and the three side effects that were reported most often were visual disorders (29%), GI disorders (21%), and hepatic disorders (17%). These interesting results led us to set up a national, prospective, multicenter, phase II study that began in September 2005. The first results should be available by the end of 2007.

References

1 Belcher JR, Plummer NS. Surgery in broncho-pulmonary aspergillosis. Br J Dis Chest 1960; 54:335–341
2 Gefter WB, Weingrad TR, Epstein DM, et al. Semi-invasive pulmonary aspergillosis. Radiology 1981; 140:313–321
3 Binder RE, Faling LJ, Pugatch RD, et al. Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine 1982; 61:109–124
4 Denning DW, Riniotis K, Dobrashian R, et al. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change and review. Clin Infect Dis 2003; 37(suppl):265–280
5 Hines DW, Haber MH, Yaremko L, et al. Pseudomembranous tracheobronchitis caused by aspergillus. Am Rev Respir Dis 1991; 143:1408–1411
6 Saraceno JL, Phelps DT, Ferro TJ, et al. Chronic necrotizing pulmonary aspergillosis: approach to management. Chest 1997; 112:541–548
7 Garvey J, Crastnopol P, Weisz D, et al. The surgical treatment of pulmonary aspergillomas. J Thorac Cardiovasc Surg 1977; 74:542–547
8 Faulkner SL, Vernon R, Brown PP, et al. Hemoptysis and pulmonary aspergilloma: operative versus non-operative treatment. Ann Thorac Surg 1978; 25:389–392
9 Massard G, Roeslin N, Wihlm JM, et al. Surgical treatment of pulmonary and bronchial aspergilloma. Ann Chir 1993; 47: 147–151
10 Chen JC, Chang YL, Luh SP, et al. Surgical treatment for pulmonary aspergilloma: a 28 year experience. Thorax 1997; 52:810–813
11 Kabiri H, Lahlou K, Achir A, et al. Pulmonary aspergilloma: results of surgical treatment: report of a series of 206 cases. Chirurgie 1999; 124:655–660
12 Kaestel M, Meyer W, Mittelmeier HO, et al. Pulmonary aspergilloma: clinical findings and surgical treatment. Thorac Cardiovasc Surg 1999; 47:340–345
13 Babatasi G, Massetti M, Chapelier A, et al. Surgical treatment of pulmonary aspergilloma: current outcome. J Thorac Cardiovasc Surg 2000; 119:906–912
14 Regnard JF, Icard P, Nicolosi M, et al. Aspergilloma: a series of 89 surgical cases. Ann Thorac Surg 2000; 69:898–903
15 Park CK, Jheon S. Results of surgical treatment for pulmonary aspergilloma. Eur J Cardiothorac Surg 2002; 21:918–923
16 Hafeez I, Muers MF, Murphy SA, et al. Non-tuberculous mycobacterial infection complicated by chronic necrotizing pulmonary aspergillosis. Thorax 2000; 55:717–719
17 Kato T, Usami I, Morita H, et al. Chronic necrotizing pulmonary aspergillosis in pneumoconiosis: clinical and radiological findings in 10 patients. Chest 2002; 121:118–127
18 Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients

with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002; 34:7–14
19 Glimp RA, Bayer AS. Pulmonary aspergilloma: diagnostic and therapeutic considerations. Arch Intern Med 1983; 143:303–308
20 Personne C, Toty L, Colchen A, et al. True and false problems in surgery of pulmonary aspergilloma: study of 220 cases. Rev Fr Mal Respir 1979; 7:43–44
21 Giron J, Poey C, Fajadet P, et al. CT-guided percutaneous treatment of inoperable pulmonary aspergillomas: a study of 40 cases. Eur Respir J 1998; 28:235–242
22 Giron JM, Poey CG, Fajadet PP, et al. Inoperable pulmonary aspergilloma: percutaneous CT-guided injection with glycerin and amphotericin B paste in 15 cases. Radiology 1993; 188:825–827
23 Yamada H, Kohno S, Koga H, et al. Topical treatment of pulmonary aspergilloma by antifungals. Chest 1993; 103: 1421–1425
24 Loeuille GA, Berthou C, Hilmarsdottir I, et al. Aspergillosis treated with itraconazole: analysis of 64 cases and review of literature. J Mycol Méd 1993; 3:1–13
25 Dupont B. Itraconazole therapy in aspergillosis: study in 49 patients. J Am Acad Dermatol 1990; 23:607–614
26 Hammerman KJ, Sarosi GA, Tosch FE. Amphotericine B in the treatment of saphrophytic forms of pulmonary aspergillosis. Am Rev Respir Dis 1974; 109:57–62
27 Jain LR, Denning DW. The efficacity and tolerability of voriconazole in the treatment of chronic cavitary pulmonary aspergillosis. J Infect 2006; 52:e133–e137
28 Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002; 347:408–415
29 Sambatakou H, Dupont B, Lode H, et al. Voriconazole treatment for subacute invasive and chronic pulmonary aspergillosis. Am J Med 2006; 119:527.e17–e24
30 Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977; 86:405–414
31 Denning DW. Chronic forms of pulmonary aspergillosis. Clin Microbiol Infect 2001; 7(suppl):25–31
32 Kim YT, Kang MC, Sung SW, et al. Good long-term outcomes after surgical treatment of simple and complex pulmonary aspergilloma. Ann Thorac Surg 2005; 79:294–298
33 Campbell JH, Winter JH, Richardson MD, et al. Treatment of pulmonary aspergilloma with itraconazole. Thorax 1991; 46:839–841
34 Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by aspergillus. Clin Infect Dis 2000; 30:696–709
35 Grysczyk H, De Roux A, Grassot A, et al. Antimycotic treatment of pulmonary aspergilloma in patients without neutropenia. Dtsch Med Wochenschr 2002; 127:492–496