Allergy 2002: 57: 723–728
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ALLERGY
ISSN 0105-4538

Short communication

Itraconazole treatment of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis

Background: Allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis (CF) patients is a potentially fatal inflammatory disease due to the dual-type immune response provoked by the fungal antigens. Despite serious side effects long-term treatment with corticosteroids is often required. Itraconazole has been reported to be a useful steroid-sparing agent.
Methods: In a retrospective follow-up of 21 CF patients from a total of 250 treated once or twice within a five-year study period (1994–98), 9 patients were treated with systemic glucocorticosteroids in combination with itraconazole and 12 patients were treated with itraconazole (200–600 mg/day) as monotherapy.
Results: During treatment the percentage of *Aspergillus fumigatus* (AF)-positive sputum cultures significantly reduced ($P<0.05$); precipitating antibodies to AF decreased significantly in all patients ($P<0.05$); forced expiratory volume ($FEV_{1)}$ increased to pre-exacerbation level; total IgE levels decreased in 42% of patients on monotherapy and in 56% on combination therapy. Specific IgE (radio-allergosorbant; RAST) level decreased in 6 of 21 patients. Eleven patients had transient increased levels of alanine transaminase (ALAT). One patient had isolated increase in alkaline phosphatase and another in aspartate transaminase (ASAT).
Conclusions: High dose itraconazole as monotherapy or in combination with systemic glucocorticosteroids seems effective in CF patients with ABPA. No hepatotoxicity was observed during long-term therapy.

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Key words: allergic bronchopulmonary aspergillosis (ABPA); *Aspergillus fumigatus*; cystic fibrosis; itraconazole; liver function; precipitating antibodies; treatment.

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Accepted for publication 5 March 2002

The nomenclature for allergy is according to the EAACI recommendations (1). Allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity reaction to *Aspergillus fumigatus (*AF*)* antigens is most commonly seen in patients with asthma or cystic fibrosis (CF) (2). Up to 57% of patients with CF become colonized in the lower respiratory tract with AF (3) but only a minority of 1–11% of the patients develop ABPA (3–5), which is characterized by a combined IgE and IgG hypersensitivity reaction (6). The diagnosis may be delayed because several clinical and paraclinical diagnostic criteria for ABPA overlap with common manifestations of the lung disease in CF. Early diagnosis and treatment is important, however, to prevent permanent lung damage (7). The conventional treatment of ABPA, systemic glucocorticosteroids, may be particular problematic in CF patients since the side effects such as osteoporosis and steroid-induced diabetes may be more pronounced (8, 9). Treatment with itraconazole, an orally active triazole antifungal agent, is reported to improve lung function and lower the peripheral eosinophil count and total IgE, and act as a steroid-sparing treatment (10–13). However, data on efficacy and safety are scarce. The aim of the present 5-year retrospective study of 21 CF patients treated with itraconazole was (a) to evaluate itraconazole treatment regarding duration and dosage by following lung function and specific parameters for ABPA during treatment; and (b) to evaluate whether itraconazole can be safely administered in relatively high doses with specific regard to liver function.

Abbreviations: AF: Aspergillus fumigatus; ABPA: allergic bronchopulmonary aspergillosis; ALAT: alanine transaminase; ASAT: aspartate transaminase; CF: cystic fibrosis; $FEV_{1:}$ forced expiratory volume in one second; FVC: forced vital capacity; PA: Pseudomonas aeruginosa.

Material and methods

Patients

A total of 21 patients (10 females/11 males) with CF (8.4%) were treated for one or several times for ABPA during the five-year period 1994–98 of a total of 250 patients followed in the center during this period. All patients diagnosed as having ABPA fulfilled a median 6 (range 4–8) of the commonly used diagnostic criteria (3). The median age was 13 years (8–30) at study start (Table 1). Fourteen patients (67%) were homozygous and 7 (33%) were heterozygous for the ΔF508 CFTR mutation. Six of 7 compound heterozygous patients carried another severe mutation (all class I) (Table 1). Fourteen

Table 1. Characteristics of the patients

			CFTR		Treatment		PA-status#		SPT‡				
										Positive			
CF patient	Gender F/M	Age* years	Homozygous†	Heterozygous†	Steroid/itra.	Itra.**	Chr.	Intermittent	Af.	Af.+others	Others	Negative	Not done
1	M	30		F508/W1282X		x	x						x
2	M	21	x		x		x		x				
3	F	27		F508/unknown		x		x			x		
4	M	21		F508/3659delC		x		x		x			
5	F	15		F508/394delTT	x		x			x			
6	M	13	x	F508/G542X	x		x			x			
7	F	14	x			x	x						x
8	M	13		F508/1571delG	x			x	x				
9	M	13	x			x		x					x
10	F	15	x			x	x						x
11	M	13	x		x		x			x			
12	F	13	x		x		x						x
13	F	13	x			x	x						x
14	F	12	x			x	x						x
15	M	17		F508/3905insT		x	x						x
16	M	11	x		x		x			x			
17	M	9	x		x			x		x			
18	F	7	x		x		x					x	
19	M	8	x			x	x						x
20	F	16		x		x		x				x	
21	F	8	x			x		x	x				
Totals	11M/10F	median 13	*n*=14	*n*=7	*n*=9	*n*=12	*n*=14	*n*=7	*n*=3	*n*=6	*n*=1	*n*=2	*n*=9

* Age at end of the study. ** Itraconzaole. # Pseudomonas aeruginosa. SPT: skin prick test.
† Patients who were heterozygous for CFTR had all severe mutations.

patients were chronically infected with *Pseudomonas aeruginosa* (PA) and 7 were intermittently colonized with PA (Table 1). Chronic PA infection was defined as presence of PA in the lower respiratory tract secretions for at least six consecutive months, or for a shorter period but combined with a titre of specific PA-precipitating antibodies of two or more (14, 15). Intermittent PA colonization was defined as presence of PA at least once and normal PA precipitin level (0–1). All patients with CF are seen every month in a prospective regular manner and each visit includes sputum microscopy and culture at a specific Sabouraud media for fungal growth. Eleven patients were on ABPA treatment at entry of the study period whereas 10 patients started treatment within the study period.

Treatment of ABPA

Nine of the 21 patients (43%) were treated with oral glucocorticosteroids (15–20 mg/day prednisolone as starting dose; 40 mg/day in one patient) in combination with itraconazole (initially 400 mg/day; 200 mg/day in one patient; in two patients the dose was increased to 600 mg/day) (7 with chronic PA and 2 with intermittent PA). Five of the nine patients treated with combination therapy were later treated with itraconazole alone during a subsequent recurrence of ABPA. Twelve patients (57%) were treated with itraconazole alone. The initial dose was 200 mg/day (5–7.5 mg/kg/day). In five of these patients the dose was subsequently increased to 400 mg/day and in three patients to 600 mg/day (7.5–10 mg/kg/day). The maximal dose of itraconazole in any patient was 10 mg/kg/day. Itraconazole was prescribed as capsules and recommended to take with a meal. The doses of itraconazole were increased due to clinical worsening or if AF-specific antibodies increased or were persistently high in spite of treatment. Seven patients were treated with itraconazole continuously during the five-year period (four for all 60 months and three with a pause of 2.5, 2.5 and 4.5 months, respectively). The rest were treated for a median of 33 months (6–54). Nine patients were treated twice.

Procedures

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured using a spirometer (Pneumotach, MasterScreen Pneumo, Erich Jaeger, Germany) and expressed as percentage of predicted values (16). The lung function was assessed at each of the regular monthly visits to the outpatient clinic. Total serum IgE was measured by a commercially available PRIST kit (Pharmacia, Uppsala, Sweden). Values were given in kIU/l. Eosinophil counts were given as 10^9/ml. Precipitating antibodies were measured by immunodiffusion using AF antigens prepared from mycelial mats (17). Results were given as titres.

AF-specific IgE was measured according to the instructions of the manufacturer by Pharmacia CAP FEIA system (Pharmacia, Uppsala, Sweden). Results were given in kU/l (measuring range 0.35–100 kU/l). Liver function including measurement of ALAT, ASAT, bilirubin and alkaline phosphatase is controlled at least once a year in all patients and more regularly in patients treated with itraconazole.

Statistics

Statistical analysis was performed using Mann–Whitney test. *P*-values of <0.05 were considered significant. The values given are medians (range).

Results

Sputum cultures

The percentage of AF positive sputum cultures of total sputum cultures was calculated for each patient. The seven patients who were treated for the entire five-year period had 49% positive cultures (median, range 8–94%). In 14 patients treatment was started within

Table 2. Change in lung function during the study period in 21 CF patients

CF patient number	FEV1 (94)	FEV1 (98)	FEV1 difference	FVC (94)	FVC (98)	FVC difference
CF patients treated with itraconazole alone						
1*	3.00	2.80	(–) 0.20	5.17	4.57	(–) 0.60
3	3.08	3.90	0.82	4.16	5.00	0.84
4*	1.54	1.44	(–) 0.10	1.96	2.57	(–) 0.61
7*	1.74	1.40	(–) 0.34	2.29	2.53	0.24
9	1.91	3.54	1.63	2.64	4.73	2.09
10	1.90	1.64	(–) 0.26	2.99	2.77	(–) 0.22
13	2.11	3.20	1.09	2.99	4.43	1.44
14	0.74	1.02	0.28	1.63	1.94	0.31
15	3.65	2.90	(–) 0.75	4.81	4.90	0.09
19	1.50	2.37	0.87	1.98	3.53	1.55
20*	2.62	3.12	0.50	3.37	4.20	0.83
21*	1.25	2.4.0	1.15	1.47	3.10	1.63
Median	1.91	2.6.0	0.39	2.87	3.87	0.57
P-value			0.36			0.15
CF patients treated with steroids and itraconazole						
2	2.33	2.57	0.24	3.35	3.97	0.62
5*	2.48	2.00	(–) 0.48	3.58	3.20	(–) 0.38
6*	1.92	3.66	1.74	1.92	4.57	2.66
8*	2.12	2.50	0.38	2.50	3.50	1.00
11	1.37	3.50	2.13	2.19	4.30	2.11
12	1.67	2.25	0.58	2.70	3.00	0.30
16	1.53	3.07	1.54	2.66	4.80	2.14
17*	1.43	2.57	1.14	1.67	3.50	1.83
18	0.39	0.66	0.27	1.03	1.30	0.27
Median	1.67	2.57	0.58	2.50	3.50	1.00
P-value			0.02			0.02
Median fot all patients	1.90	2.60	0.50	2.60	3.50	0.80
P-value			0.03			0.01

(94): first value in 1994 and (98): last value in 1998.
* Indicates patients treated twice.

the study period. The percentage of positive cultures in these patients decreased significantly from 91% positive cultures before treatment (median, range 60–100%) to 62% positive cultures after treatment start (median, range 0–100%) ($P<0.05$).

Lung function

FEV_1 (% of predicted) was registered three and one months before, at treatment start, and one, three and six months after start of treatment (representing 21 patients and 30 courses). FEV_1 increased in both groups within the first month after start of treatment. However, none of the changes were significant ($P>0.1$). Pre-exacerbation levels were reached within six months. During the study period, primo 1994 to ultimo 1998, there was a significant increase in median FEV_1 as well as FVC ($P=0.01$ and $P = 0.03$, respectively) (Table 2). Among the three groups only patients treated with steroids and itraconazole increased significantly.

Total IgE and eosinophil count

Total IgE levels decreased during treatment in 42% of patients on monotherapy and in 56% on combination therapy. Eosinophil counts did not change (data not shown). It should be noticed, however, that several patients only had a slight or no elevation in eosinophil counts prior to treatment.

Precipitating antibodies and IgE-AF (RAST)

Precipitating antibodies decreased significantly during treatment in all patients ($P<0.05$). Median titre of the entire group was 16 (4–32) before treatment and 2 (0–8) after treatment. Various examples of the changes in titre of precipitating antibodies during treatment indicate that (a) combination treatment with a sufficient dose of itraconazole can reduce the steroid dose early and efficiently; (b) a higher itraconazole dose may be as efficient as combination therapy with a lower itraconazole dose; (c) itraconazole should be continued at a relatively high dose until the precipitating antibody titre is low; and (d) a continuous low dose of itraconazole may be needed to avoid exacerbation. Six of 21 patients showed a decrease in specific IgE (RAST) (1–2 classes) (data not shown).

Liver function

In 10 patients all four liver parameters were within normal range during the entire period. Eleven patients had increased levels of ALAT (> normal level

Table 3. Studies of itraconazole treatment of allergic bronchopulmonary aspergillosis

First author	Year	*n*	Underlying diagnosis	Itraconazole dose	Duration	Effects					
						Lung function	AF culture	Total IgE	Eosinophils	AF IgG	Steroid dose
Stevens	2000	28	NI (not CF)	400 mg/d	16 weeks	↑	ND	↓	ND	ND	Reduced
		27	NI (not CF)	Placebo	DO						
Salez	1999	14	Asthma	200 mg/d	>12 months	↑	ND	↓	↓	↓	All reduced
Nepumuceno	1999	13	CF	20-30 mg/d	NI	ND	ND	ND	ND	ND	Reduction**
Germaud	1995	12	Asthma	200 mg/d	>6 months	ND	ND	↓	↓	↓	6 stopped
Denning	1991	6	3 asthma/3 CF	400 mg/d	Mean 3 months	↑	ND	↓	ND	ND	5 reduced
De Beule	1988	5	Asthma	50-400 mg/d	NI	↑	3 negative	ND	ND	ND	***
Lebeau	1993	3	CF	200 mg/d	NI	↑	ND	ND	ND	ND	1 stopped
Mannes	1993	2	CF/twins	400 mg/d	NI	ND	ND	↓	ND	↓	Reduction
Pachero	1993	1	Asthma	200 mg/d	4 months	↑	ND	↓	↓	↓	Reduced
Nikaido	1998	1	Asthma	150 mg/d	NI	↑	Negative	↓	↓	↓	No steroid given
Matsuzaki	1997	1	Asthma	NI	NI	#	ND	ND	ND	ND	No steroid given
Fujimori	1998	1	Asthma	NI	NI	ND	ND	↓	↓	ND	No steroid given

↑ increase; ↓ decrease; * = undetectable; * = and fewer ABPA episodes; *** = 4/5 on steroids, no change indose reported; ND = not done; NI = no information; # = clinical improvement.

but < two times the upper limit of normal in five patients and median 4.1 (2.8–6.5) times the upper limit in six patients). The elevations were transient and all except one (at 1.2 times upper level) returned to normal levels. One patient showed an isolated increase in alkaline phosphatase and another patient an isolated increase in ASAT. With these exceptions alkaline phosphatase, bilirubin and ASAT were within normal ranges during the whole period.

Discussion

ABPA in CF patients is often recognized in a late phase (7) and thus associated with a rapid progression of the lung disease (18). Treatment that suppresses inflammation caused by the immunologic response to AF (19) is conventionally systemic glucocorticosteroids, in spite of undesirable side effects (19, 20). Itraconazole, anecdotally reported to be effective (21), has been introduced in some CF centres. In our five-year retrospective study of ABPA treatment we found that itraconazole treatment may not eradicate but lower the degree of *Aspergillus* colonization and thereby the antigenic burden, as indicated by the significant decrease in the percentage of positive AF cultures. Improvement in lung function is difficult to evaluate due to the influence of other concurrent infections and PA status. We tried to overcome this by studying patients with different PA status and looking at long-term changes. Pre-treatment lung function levels were reached within 6 months. Furthermore, the long-term median lung function of all patients improved significantly, indicating that treatment with itraconazole suppressed low-grade inflammation mediated by the combined presence of AF in the lower respiratory tract and of specific antibodies. The improvement was greater than that expected due to the growing within the five-year period of some of the patients. Patients with the largest decline in FEV_1 were the ones most likely to receive both glucocorticosteroids and itraconazole. The same patients reached the highest FEV_1 after treatment, explained by an effect on ABPA as well as a nonspecific steroid-induced anti-inflammatory effect in the lungs (22). The patients on itraconazole alone had higher pre-treatment lung function and did not have significant changes over the five-year period. Furthermore, expected declines in lung function seem to have been avoided. AF-precipitating antibody titres decreased significantly, whereas a nonsignificant decrease in total IgE and AF-IgE (RAST) was observed. Details about fluctuations in AF-IgE antibodies were not available since these were not measured as regularly over the period as AF-IgG antibodies.

A limited number of reports, most uncontrolled and including only few patients, refer to itraconazole treatment of ABPA in asthma (10, 11, 23–28) and in CF (10, 11, 24–31). A single controlled study showed no improvement in 14 asthma patients treated with steroids during a two-year reference period as compared to clinical improvement, decrease in IgE, eosinophil count and AF-IgE, increase in lung function, and reduction of steroid dose observed during a subsequent itraconazole treatment period of at least 12 months (23). Recently, to our knowledge the first randomised double-blind, placebo-controlled study showed that patients with corticosteroid-dependent ABPA benefit from itraconazole therapy (32). Decrease in corticosteroid dose, total IgE, as well as increase in exercise tolerance and improvement in lung function was achieved in patients on itraconazole therapy as compared to placebo-treated patients. In a subsequent open-label phase in which patients were given 200 mg itraconazole daily as monotherapy, 31% of patients on itraconazole responded as compared to 40% of patients initially included in the placebo group. An actual treatment effect of 200 mg daily is suggested. Analyses of the subgroups in the study showed that patients without bronchiectasis had a greater overall

response rate than those with bronchiectasis. This may explain why our CF patients (most of them having bronchiectasis) benefit from a higher dose. Apart from two reports of negative AF culture after itraconazole treatment (in one and three patients, respectively) (24, 26) the present study is, to our knowledge, the first to demonstrate that itraconazole treatment significantly decreases the percentage of positive AF sputum cultures in ABPA patients. We believe this is an important finding, especially if the hypersensitivity reaction requires a certain burden of AF antigens. In accordance with our results most studies (Table 3) showed improvement in lung function (19, 20, 22, 23, 25, 26, 29). Total IgE decreased during treatment in most other studies including ours (10, 11, 25, 26, 28, 30). We found that AF-precipitating antibody titres decreased as did two of the largest studies (11, 23) and three smaller studies (25, 26, 30), whereas we could not confirm the decrease in eosinophil count seen in other studies (11, 23, 25, 26, 28). AF-IgE (RAST) showed a minor decrease in 6 of 21 patients in our study which is similar to the findings in two of the largest studies (11, 23). A steroid-sparing effect, reduction as well as withdrawal, was reported in most of the studies (10, 11, 25, 29–32). Concomitant administration of itraconazole and corticosteroids enables us to evaluate a possible steroid-sparing effect. Corticosteroids were, however, administered in relatively low doses as compared to recent recommendations (20) and to most other studies (10, 11, 23, 29, 31). Conversely, itraconazole was generally given in higher doses in our patients. The present results suggest that efficient treatment of ABPA in CF patients requires itraconazole doses of probably no less than 400 mg daily for several months (three to six), and a reduced dose of 200 mg daily may be sufficient as maintenance therapy which is supported by the findings in the recent randomised study in patients with and without bronchiectasis. Additional randomised controlled studies are needed for determination of the optimal strategy of ABPA treatment.

Itraconazole is exclusively metabolized in the liver and may be hepatotoxic (33). No serious hepatotoxic side effects were observed in our study despite treatment with itraconazole for more than five years in some patients. Only minor, self-limiting and transient elevations in ALAT were observed. One patient continued to have ALAT values above the normal upper limit, but continued on itraconazole as well as glucocorticosteroids because of the severity of the ABPA. A study of 189 patients treated with itraconazole for systemic mycoses in daily doses of 400 mg revealed only minor elevations of transaminases in 5% (34). Another study of 13 itraconazole-treated CF patients showed only mild, transient elevations in ALAT and ASAT (31). No patient had to discontinue therapy due to hepatotoxicity. Nor did itraconazole treatment of onychomycoses in daily doses of 400 mg for one to three weeks every month for three months (35, 36) show significant hepatotoxiticity.

Inhaled corticosteroids as an alternative to oral steroids have been suggested in combination with itraconazole. High doses of inhaled steroids have been shown to be effective in ABPA treatment in non-CF patients with asthma (37). We recently observed adrenal insufficiency in CF patients on high-dose itraconazole and high-dose budesonide therapy. Itraconazole inhibits CYP3A (part of the P450 enzyme system) which is involved in steroidogenesis in the adrenals as well as the metabolism of budesonide. The pathogenesis was most likely an increased systemic budesonide concentration, inhibiting adrenocorticotropic hormone (ACTH) secretion. No evidence was found for direct inhibition of steroidogenesis on high-dose itraconazole monotherapy. (38). Budesonide inhalations in high doses (1600 μg daily) are given to the majority of patients routinely as anti-inflammatory treatment in our center. Thus, regular control of the adrenal function if patients are on combined itraconazole and budesonide treatment is recommended. Until further details are known, we suggest that budesonide is not given to patients who are on itraconazole therapy.

In conclusion, high-dose itraconazole may be an efficient treatment of ABPA in CF patients. The degree of AF-colonization as well as the titre of AF-specific precipitating antibodies has been shown to reduce significantly, FEV_1 (% of predicted) has been shown to increase and not only to prevent a decline but significantly to improve long-term lung function. No hepatotoxicity was observed during long-term high-dose itraconazole therapy.

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