

Voriconazole therapy in children with cystic fibrosis

Tom Hilliard^{a,*}, Siân Edwards^b, Roger Buchdahl^a, Jacqueline Francis^a, Mark Rosenthal^a,
Ian Balfour-Lynn^a, Andrew Bush^a, Jane Davies^a

^a Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

^b Department of Pharmacy, Royal Brompton Hospital, London, UK

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Abstract

Background: There is increasing evidence for the efficacy of the antifungal voriconazole, particularly in immunosuppression. We describe our experience of using voriconazole in children with CF.

Methods: We performed a retrospective case note review of children with CF treated with voriconazole in a single centre over an 18 month period.

Results: A total of 21 children aged 5 to 16 years (median 11.3) received voriconazole for between 1 and 50 (22) weeks. Voriconazole was used as monotherapy in 2 children with recurrent allergic bronchopulmonary aspergillosis (ABPA); significant and sustained improvements in clinical and serological parameters for up to 13 months were observed, without recourse to oral steroids. Voriconazole was used in combination with an immunomodulatory agent in a further 11 children with ABPA, with significant improvement in pulmonary function and serology. 8 children without ABPA but who had recurrent *Aspergillus fumigatus* isolates and increased symptoms also received voriconazole; this group did not improve with treatment. Adverse effects occurred in 7 children (33%: photosensitivity reaction 3, nausea 2, rise in hepatic enzymes 1, hair loss 1).

Conclusions: Voriconazole may be a useful adjunctive therapy for ABPA in CF. Voriconazole monotherapy appears to be an alternative treatment strategy when oral corticosteroids may not be suitable.

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Keywords: Cystic fibrosis; Allergic bronchopulmonary aspergillosis; Antifungal agents; Voriconazole

1. Introduction

Aspergillus fumigatus is frequently isolated from respiratory secretions of patients with CF [1]. Although simple isolation is usually thought to be unimportant and not treated, allergic bronchopulmonary aspergillosis (ABPA) is a much more serious response to the fungus [2]. ABPA occurs in approximately 10% of CF patients [3], and involves IgG and IgE mediated hypersensitivity reactions [4]. The typical presentation is with wheezing, new pulmonary infiltrates, a rise in serum total IgE and specific IgE to *A. fumigatus*, with a fall in pulmonary function.

A consensus guideline on management of ABPA in CF has been published recently [4]. The mainstay of treatment is oral corticosteroid therapy, but this may need to be continued for several months and is associated with significant adverse effects [5]. It may also be worth attempting to reduce the burden of *A. fumigatus* in the respiratory tract [6]. Studies of itraconazole, initially in an uncontrolled setting in CF [7,8], and recently in randomised trials in adults with asthma and ABPA [9,10] have shown evidence of benefit, including the ability to reduce steroid dosage.

Voriconazole is a recently introduced triazole antifungal with superior oral bioavailability to itraconazole which has been approved for the treatment of invasive aspergillosis [11]. It is however expensive, has a high potential for drug interactions and has been associated with a number of adverse effects [11]. We began using voriconazole as an

* Corresponding author. Department of Respiratory Paediatrics, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol, BS2 8BJ, United Kingdom. Tel.: +44 117 342 8258; fax: +44 117 342 8494.

E-mail address: t.hilliard@imperial.ac.uk (T. Hilliard).

alternative antifungal to itraconazole in selected children with CF in 2002. The decision to start voriconazole was made by individual physicians with the following indications: (i) in ABPA as adjunctive therapy to immunomodulatory agents and a second-line antifungal therapy after itraconazole, (ii) in ABPA as monotherapy where oral corticosteroids were deemed unsuitable and (iii) for increased respiratory symptoms with multiple positive cultures for *A. fumigatus*, without serological evidence for ABPA. We describe our experience in these three groups of children, and in particular highlight the cases of two children with ABPA in whom voriconazole therapy alone appeared to be beneficial.

2. Methods

We performed a retrospective case note review of all children with CF who had received voriconazole between October 2002 and March 2004 in a tertiary paediatric CF centre with a clinic population of 350 children. Children were identified from pharmacy records and clinical and serological data were collected from case notes and computerised laboratory records by a single investigator (TH). All children had been reviewed on at least a 2 monthly basis at our centre. Microbiological data from the 12 months prior to starting voriconazole were recorded. For children receiving voriconazole at the time of this review, the most recent available data were included in the overall analysis. For children who had received 2 courses of voriconazole, parameters at the end of the second course were recorded. Statistical analysis was performed with Minitab13.1 (Minitab Inc, State College, PA, USA). Wilcoxon signed ranks test was used to compare paired data at the beginning and end of the treatment periods. A *p* value of less than 0.05 was considered statistically significant.

3. Results

21 children received voriconazole over the 18 month period to March 2004 (Table 1). 15 girls and 6 boys, median age 11.3 years (range 5 to 16), were treated for a median of 22 weeks (1 to 50). The overall median FEV₁ (% predicted) at the time of starting therapy was 56% (29 to 88). The dose of voriconazole was as recommended by the manufacturer's summary product characteristics. Children under 12 years of age received 6 mg/kg (maximum 200 mg) twice a day (BD) for 1 day and then 4 mg/kg (maximum 100 mg) BD. Those over 12 years and less than 40 kg received 200 mg BD for 1 day and then 100 mg BD; if over 12 years and more than 40 kg, they received 400 mg BD for 1 day and then 200 mg BD. 3 children are still on voriconazole at the time of writing and 3 received 2 courses of treatment. If used alongside a tapering course of oral corticosteroids, vorico-

nazole was generally given for at least month after stopping the steroids. No child received intravenous voriconazole. We did not determine the blood concentration of voriconazole in any patient.

3.1. Children with ABPA

13 children had evidence of ABPA according to current diagnostic criteria [4] (clinical deterioration, a rise in total serum IgE to greater than 500 IU/ml and presence of both IgE and IgG antibody to *A. fumigatus*), at the time of starting voriconazole. Two children were given voriconazole as a single agent against ABPA and they are described in detail below (Cases 1 and 2). Nine children were also treated with oral corticosteroids and a further 2 children had alternative immunomodulatory therapy (methotrexate in one and monthly infusions of intravenous immunoglobulin in the other). Oral corticosteroids were given at an initial dose of 2 mg/kg per day of prednisolone (maximum 40 mg) for up to 2 weeks, followed by 1 mg/kg for the same period, before changing to alternate day therapy. Weaning was guided by the clinical response over the following weeks.

11 children had previous episodes of ABPA, and 9 had isolated *A. fumigatus* on sputum or cough swab samples in the previous year. All 11 with previous ABPA had been treated with itraconazole during these episodes, and 3 were switched from itraconazole to voriconazole during therapy for this exacerbation. Both children without previous ABPA had been started on itraconazole prior to starting voriconazole.

All but 1 of these children also received inhaled corticosteroids (equivalent median dose of budesonide of 1000 mcg per day, range from 200 to 2000), but the dose did not change during treatment with voriconazole.

In this group as a whole, pulmonary function increased significantly over the period of treatment with voriconazole; FEV₁ by a median of 13.5% (95% CI 2.5–24.5; *p*=0.01), and FVC by 18.5% (95% CI 6.5–32; *p*=0.007). Total serum IgE fell from a median of 1898 to 854 IU/ml (median difference 887, 95% CI 389–1466; *p*=0.003).

3.2. Case 1

A 13 year old girl with CF presented with an increase in cough and wheeze, a fall in FEV₁ to 53% and FVC to 56% (from 64% and 83% respectively). There were new bilateral lower lobe infiltrates on chest radiography. She had experienced 2 previous episodes of acute ABPA in the preceding 2 years and had been given prolonged courses of oral prednisolone with good recovery. Despite treatment with intravenous antibiotics, her pulmonary function did not improve, and a recurrence of ABPA was diagnosed on clinical and serological grounds: total serum IgE 2089 IU/ml (previously 482), specific IgE on RAST against *A. fumigatus* 15.4 IU/ml. She refused oral corticosteroids on this occasion as she had gained significant weight with prior

Table 1
Patient characteristics

No	Age (years)	Genotype	ABPA past	ABPA active	AF ¹	PA ²	SA ³	Oral steroids	Dose of voriconazole (mg) ⁴	Weeks of therapy	ICS (mcg/day) ⁶	RAST IgE (IU/ml)	IgE on starting (IU/ml)	IgE at end (IU/ml)	FEV ₁ (% on starting)	FEV ₁ (% at end)	Adverse effects	Comments
<i>Patients with ABPA</i>																		
1	12.8	ΔF508/ΔF508	Y	Y	Y	N	N	N	100	41	2000	15.4	2089	999	53	75	No	2 courses
2	16.2	ΔF508/ΔF508	Y	Y	N	N	Y	N	200	32 ⁵	1000	65.0	2162	860	71	80	No	
3	12.2	ΔF508/ΔF508	Y	Y	Y	Y	N	N	100	50 ⁵	400	18.3	1138	601	42	58	Nausea and headache (stopped 1st course)	On methotrexate, 2 courses
4	13.8	ΔF508/ΔF508	Y	Y	Y	N	N	N	200	21 ⁵	800	18.6	1748	673	65	91	Photosensitivity (Stopped 1st course)	On IVIG ⁷ , 2 courses
5	5.4	ΔF508/ΔF508	N	Y	N	Y	Y	Y	100	36	800	16.9	1477	63	82	87	No	
6	15.7	ΔF508/ΔF508	Y	Y	Y	Y	Y	Y	200	19	800	31.5	2346	489	56	101	No	
7	9.8	ΔF508/ΔF508	Y	Y	Y	Y	N	Y	100	24	2000	18.8	536	166	70	87	Liver dysfunction (stopped)	
8	9.2	ΔF508/ΔF508	Y	Y	Y	Y	Y	Y	100	1	1600	23.0	1898	2306	29	29	Nausea (stopped)	
9	12.5	-/-	Y	Y	Y	Y	Y	Y	100	12	1600	10.7	607	367	66	98	No	
10	12.6	ΔF508/ΔF508	N	Y	Y	Y	Y	Y	200	26	800	59.3	4428	957	72	70	No	Developed IDDM ⁸ on prednisolone
11	7.3	ΔF508/G542X	Y	Y	N	Y	N	Y	100	22	2000	101.0	8922	9036	88	80	No	
12	12.9	ΔF508/ΔF508	Y	Y	Y	Y	N	Y	100	33	2000	47.9	2684	1879	67	55	No	
13	8.4	ΔF508/ΔF508	Y	Y	N	Y	Y	Y	100	15	0	37.1	1823	854	44	73	No	
Median	12.5		Y=11	Y=13	Y=9	Y=10	Y=7	Y=9	100	24	1000	23.0	1898	854	66	80	Y=4	
<i>Patients without ABPA</i>																		
14	10.2	G551D/-	N	N	Y	N	Y	Y	100	22	200	10.8	417	-	56	51	No	
15	13.4	ΔF508/ΔF508	Y	N	Y	Y	N	Y	100	7	800	0.3	57	49	37	53	Hair loss (stopped)	On alternate day prednisolone
16	11.3	ΔF508/ΔF508	Y	N	Y	N	Y	Y	200	29	800	2.0	268	126	62	43	Photosensitivity	On alternate day prednisolone
17	10.8	ΔF508/G542X	N	N	Y	Y	N	Y	100	2	1000	7.4	176	267	47	50	No	
18	9.2	ΔF508/ΔF508	N	N	N	N	N	Y	100	21	1600	1.0	30	98	41	56	No	
19	10.9	ΔF508/ΔF508	N	N	Y	Y	N	N	100	10	0	0.3	8	8	62	63	Photosensitivity	
20	7.5	ΔF508/R553X	Y	N	N	N	N	N	100	28	400	1.7	209	236	43	64	No	
21	14.8	-/-	N	N	Y	N	Y	N	200	4	800	0.3	36	40	54	48	No	
Median	10.9		Y=3	Y=0	Y=6	Y=3	Y=3	Y=5	100	16	800	1.4	117	98	51	52	Y=3	

Culture of ¹*Aspergillus fumigatus*, ²*Pseudomonas aeruginosa* and ³*Staphylococcus aureus* in the preceding 12 months.

⁴twice per day.

⁵patient still receiving voriconazole therapy.

⁶inhaled corticosteroids, total budesonide dose per day or equivalent.

⁷intravenous immunoglobulin.

⁸insulin dependent diabetes mellitus.

courses. For this recurrence she was given a one month trial of voriconazole as monotherapy with clinical and serological improvement at the end of this period (FEV₁ increased by 11% to 64%, and total IgE fell to 1468). 2 months later she became more symptomatic and her FEV₁ had dropped to 58%. Voriconazole was restarted and she had a sustained improvement in her status over a further 8 month treatment period (at the end of therapy FEV₁ was 75% and total IgE 874). Changes in FEV₁ and total IgE, over this 3 year period, including the 13 months since starting voriconazole, are shown in Fig. 1. Periods of treatment with intravenous antibiotics are also marked.

3.3. Case 2

A 16 year old boy with CF reported rapidly increasing cough and breathlessness. A chest radiograph showed a new large round opacification in the left lower lobe as well as bilateral lower lobe infiltrates. FEV₁ had fallen from 77 to 71% (FVC 96 to 87%). Sputum over the previous year had grown multiple isolates of *Stenotrophomonas maltophilia* and *Staphylococcus aureus* but not *A. fumigatus*. He had had 3 previous episodes of ABPA over the preceding 4 years that had been treated with oral prednisolone and itraconazole. A recurrence of ABPA was diagnosed (total serum IgE 2162 IU/ml, specific IgE to *A. fumigatus* 65 IU/ml). He refused oral corticosteroids because of cessation of growth during previous tapered courses. He was therefore given a trial of voriconazole as monotherapy. He has now remained on therapy for 7 months with a sustained clinical and

serological improvement (FEV₁ currently 80% and total IgE has fallen to 860 IU/ml) without any recourse to oral corticosteroids.

3.4. Children without ABPA

Eight children did not have evidence of active ABPA at the time of starting voriconazole. Six of these had grown *A. fumigatus* in the previous year. Of the other 2 children, one had had previous ABPA, and the other was admitted with severe acute wheezing which did not respond rapidly to oral corticosteroids. All had a recent clinical deterioration, which had failed to respond to conventional therapy, including multiple courses of oral and/or intravenous antibiotics. *A. fumigatus* was thought to be at least partly responsible for their deterioration. 2 children were given voriconazole without the prior use of itraconazole, and 5 were given concomitant oral corticosteroids. In this group pulmonary function did not change significantly (median FEV₁ increased by 2% ($p=0.31$), and forced vital capacity (FVC) increased by 6.5% ($p=0.42$)).

3.5. Adverse effects

Seven children (33%) experienced adverse affects attributed to voriconazole. Three children (14%) had a photosensitivity skin reaction, and in one this prompted withdrawal of medication, although the drug was subsequently tolerated without any reaction in a second course. Another child had persistent erythema of sun-exposed areas,

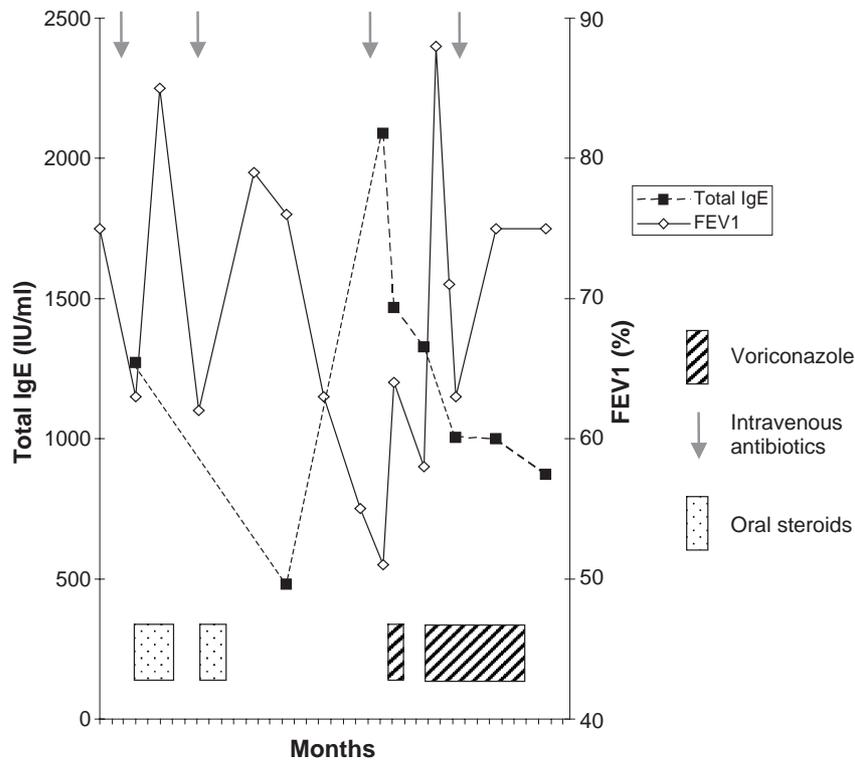


Fig. 1. Change in serum total IgE and FEV₁ (% predicted) during periods of therapy with voriconazole, oral steroids and intravenous antibiotics in case 1.

and the third experienced an acute photosensitivity reaction at the time of taking the drug with ciprofloxacin, despite taking the usual precautions against sun exposure. Two children (10%) complained of nausea and/or headaches, which led to cessation of therapy in both, although a second course was subsequently tolerated by one of these. One child had pre-existing CF related liver disease; voriconazole therapy was stopped following deterioration in his liver function tests after 5 months of treatment. One child had hair loss and therapy was stopped. Overall, therapy was discontinued due to adverse effects in 5 children (24%). No child had any overt symptoms or signs of adrenal insufficiency. One child who was on long-term alternate day prednisolone and 800 mcg of budesonide per day underwent formal investigation with a standard synacthen test and this was normal.

4. Discussion

This paper describes our clinical experience with a new antifungal agent, voriconazole, in children with cystic fibrosis. Over an 18 month period, 13 children received voriconazole for acute ABPA and 8 were treated for a clinical deterioration when *A. fumigatus* was thought to be a contributing factor. The most interesting finding was the apparent therapeutic effect of voriconazole in 2 children with ABPA without the use of oral corticosteroids.

The main limitation of this study is that it is an uncontrolled, open label, retrospective review. We decided it would be impossible to select suitable controls from the same or previous time periods. Managing a child with CF and ABPA, particularly with oral corticosteroids requires an individualised treatment regimen, and such children are not easily compared on simple clinical parameters. We have presented all children treated with voriconazole independent of length of therapy. It is therefore a mixed group, especially as it includes patients with and without ABPA. In addition, clinical and serological parameters at the two time points recorded do not solely reflect the effect of voriconazole therapy. It should also be acknowledged that spontaneous resolution of ABPA may occur, although the chronicity of the illness in the two children we describe makes this unlikely, and their response to voriconazole alone is suggestive evidence of its efficacy. There did not appear to be any benefit in those children without ABPA.

Several case series have reported the use of itraconazole as an antifungal in the therapy of ABPA. In a retrospective review of 21 CF patients aged 8–30 years with ABPA over a 5 year period, 12 patients received itraconazole as monotherapy and 9 patients received the drug in conjunction with oral corticosteroids [7]. Itraconazole was used in high doses (up to 600 mg per day) and for long periods (median 33 months, from 6 to 60 months). There appeared to be some reduction in culture of *A. fumigatus* and improvement in immunological status over this time period. In a separate

retrospective series of 16 CF patients aged 10–44 years with ABPA who had received prednisolone, 12 had been also been given itraconazole, and these were compared to the other 4 patients [8]. Patients given itraconazole received a lower dose of oral steroids and had a reduction in the number of acute exacerbations. Itraconazole has been studied in 2 randomised double-blind placebo controlled trials as therapy for ABPA, although both have been in adults with asthma and stable ABPA, and have not included patients with CF. In patients dependent on at least 10 mg per day of prednisolone, itraconazole over a 16 week period was associated with greater response rate in terms of steroid reduction, decrease in total IgE and improvement in pulmonary function or infiltrates compared to placebo [9]. In the second trial, again over 16 weeks and involving patients of whom the majority were not on oral corticosteroids, itraconazole therapy led to a greater decrease in sputum inflammatory markers and serum IgE compared to placebo [10]. It is however unclear whether antifungal therapy is beneficial in *A. fumigatus* infection in the absence of ABPA or invasive disease.

Itraconazole has the disadvantage of limited oral bioavailability, and this is particularly true for the capsule form, requiring an acidic environment for dissolution which is inhibited by antacid therapies [4]. The liquid formulation is better absorbed but is unpalatable. A pharmacokinetic study of the liquid formulation administered to 17 CF patients over 14 days showed marked inter-subject variability, with none of the 5 subjects under 16 years of age achieving the recommended trough steady-state concentration [12]. Our current practice is not to monitor serum itraconazole levels, and this was not performed in any of the children in this series. In contrast voriconazole has a high oral bioavailability exceeding 90%, and absorption is not affected by gastric pH [11]. The oral bioavailability may be lower in ill patients however, and some centres are determining voriconazole levels to ensure adequate blood concentrations. It has in vitro activity against *A. fumigatus* which has been found to be superior to or equivalent to itraconazole [13,14]. The mechanisms of action are similar, inhibiting cytochrome P450-dependent 14 α -sterol demethylation, a step required for fungal cell membrane synthesis.

Voriconazole is approved for the treatment of invasive aspergillosis, a serious complication in immunocompromised patients. In a large, open, randomised trial in invasive aspergillosis, patients treated with voriconazole had a greater rate of survival than those given intravenous amphotericin B [15]. Its use in invasive fungal infections in immunocompromised children has also been described [16]. A single case report has documented its success in treating an adult patient with CF and invasive aspergillosis and aspergilloma, refractory to itraconazole and amphotericin B [17].

Voriconazole appears to be generally well tolerated, but a transient disturbance in vision has been reported to occur in up to 30% of patients [11]. Skin reactions (rash or

photosensitivity) are the next most common adverse effect (reported in up to 15% of patients), and elevations in hepatic enzymes have been reported in up to 10% of patients [11,15,16]. No child in our series reported visual problems, but 3 children (14%) had a skin reaction. Only one child, with pre-existing liver disease, had an alteration in hepatic enzymes. Like other azoles, there is a significant potential for drug interactions due to its hepatic metabolism by CYP450 isoenzymes [11]. Itraconazole has been found to be associated with adrenal suppression when used alongside inhaled corticosteroids in CF [18–20]. Formal testing of the pituitary–adrenal axis in one child in our series was normal, however, in the absence of complete data on adrenal function, caution in the concomitant use of voriconazole and corticosteroids is advisable. Itraconazole has also been found to increase the plasma concentration of methylprednisolone, but not of prednisolone, and it is currently not clear if voriconazole has similar effects [21]. Similarly, we do not have any data on serum drug levels, which may or may not have been abnormally high in those children experiencing adverse effects.

Finally, voriconazole is expensive. One month of oral therapy of 200 mg twice per day costs approximately € 2700 (\$3600) [22]. This compares to approximately € 85 (\$110) for comparable treatment with itraconazole. Therefore, with the increased cost of voriconazole and its potential for adverse effects and drug interactions, the decision to start this therapy in CF needs to be made very carefully. However, the additional expense may be worthwhile if oral corticosteroids can be avoided or the dose minimised.

In conclusion, we report apparent benefit from the use of voriconazole in 2 children with CF and ABPA who demonstrated clear clinical and serological improvement without the use of further oral corticosteroids. We suggest that voriconazole should be considered as an alternative antifungal in ABPA, particularly when oral corticosteroids are deemed unsuitable.

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