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Case Reports

Terbinafine in the treatment of non-immunocompromised compassionate cases of bronchopulmonary aspergillosis

Terbinafin-Behandlung von Einzelfällen bronchopulmonaler Aspergillose bei abwehrkompetenten Patienten

G. F. Schiraldi[1], M. D. Colombo[2], S. Harari[1], S. Lo Cicero[1], G. Ziglio[1], M. Ferrarese[1], D. Rossato[1] and E. Soresi[1]

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Schlüsselwörter. *Aspergillus*, *Pseudallescheria boydii*, bronchopulmonale Aspergillose, antimykotische Chemotherapie, Allylamine, Terbinafin.

Summary. Conventional treatments of bronchopulmonary aspergillosis are often ineffective and result in associated side-effects. Terbinafine (a new allylamine derivative), although as active against *Aspergillus in vitro* as amphotericin B and itraconazole, is less effective in rodent models because of a rapid hepatic first-pass effect. As terbinafine is metabolized differently in humans, the aim of this work was to evaluate this drug, for the first time, in the treatment of seven immunocompetent patients with lower respiratory tract mycotic infections unresponsive to the usual antimycotic drugs. Diagnosis was based on identification of fungal isolates, worsening of respiratory function tests, chest radiographs and computerized tomographic (CT) scan changes, positive skin test, aspergillin precipitins and clinical history. Terbinafine was administered at doses ranging from 5 to 15 mg kg^{-1} day^{-1} depending on the clinical severity of the disease, and was given for 90–270 days depending on clinical progress and compliance. In three patients *A. fumigatus* was suppressed with resolution of signs and symptoms; four patients showed transitory *A. fumigatus* suppression with marked clinical and radiological improvement. During relapses no resistance to terbinafine was observed. No significant side-effects were detected. Terbinafine appeared to be as effective as amphotericin B and itraconazole in the treatment of bronchopulmonary aspergillosis in non-immunocompromised patients. These preliminary results suggest that controlled studies are warranted.

Zusammenfasung. Die herkömmlichen Behandlungsstrategien der bronchopulmonalen Aspergillose haben eine beträchtliche Versagerquote und sind belastet mit Nebenwirkungen. Das neue Allylaminderivat Terbinafin zeigte zwar *in vitro* Aktivität gegen *Aspergillus*, vergleichbar Amphotericin B und Itraconazol, versagte jedoch im Nagetier-Infektionsmodell wegen schnell einsetzender hepatischer Nebenwirkungen. Da Terbinafin jedoch im Menschen einen andersartigen Metabolisierungsgang zeigt, bot es sich an, diesen Wirkstoff erstmals auch in der Behandlung von 7 abwehrkompetenten Patienten mit Aspergillosen des tiefen Respirationstraktes einzusetzen, die auf herkömmliche Antimykotika nicht angesprochen hatten. Die Diagnose wurde gestellt über Pilziosolierung, Messung der respiratorischen Funktion, Röntgenbilder und CT, Hautteste, präzipitierende Antikörper und das klinische Gesamtbild. Terbinafin wurde in Dosen von 5-15 mg/kg/Tag entsprechend dem klinischen Schweregrad angewendet. Die Behandlungsdauer variierte von 90 bis 270 Tagen entsprechend der klinischen Entwicklung und der Compliance. Bei 3 Patienten wurde *A. fumigatus* unterdrückt mit Verschwinden der Symp-

[1]Department of Pneumology, Niguarda General Hospital, Milano, and [2]Sandoz Prodotti Farmaceutici SpA, Milano, Italy.

tome; bei 4 Patienten wurde *A. fumigatus* vorübergehend beseitigt verbunden mit deutlicher klinischer und radiologischer Besserung. Bei den Rückfällen wurde keine Resistenz gegen Terbinafin gesehen. Bedeutende Nebenwirkungen traten nicht auf. Terbinafin erwies sich somit bei bronchopulmonaler Aspergillose abwehrkompetenter Patienten als ähnlich wirksam wie Amphotericin B und Itraconazol. Diese vorläufigen Ergebnisse ermuntern zur Durchführung weiterer kontrollierter Studien.

Introduction

Bronchopulmonary aspergillosis includes a spectrum of different conditions from the harmless saprophytic state to rapidly fatal acute invasive conditions, encompassing allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing aspergillosis (CNA), acute invasive aspergillosis (AIA) and aspergilloma [1, 2]. The increasing frequency of these diseases is due to the widespread use of corticosteroid agents (topical and systemic) and other immunosuppressive drugs in a large population of immunocompetent patients to treat diseases such as chronic bronchitis, bronchiectasis, corticosteroid-dependent asthma, and post-TB pulmonary fibrous dystrophy [3–6]. Diseases of the lung caused by *Aspergillus* spp. are a major clinical problem because they are difficult to diagnose (diagnosis often being made post mortem) and treat. Now it is clear that hypersensitivity *Aspergillus* syndromes and other pulmonary infections are often present, both contributing to the clinical picture, and that there may be considerable clinical overlap among these syndromes [7, 8].

Conventional therapies may be ineffective in some patients, and may induce important side-effects that further complicate the evaluation [9–12].

For these reasons, seven patients with bronchopulmonary aspergillosis unresponsive to conventional treatment or with recurrence episodes have recently been treated at our institution with terbinafine, a classic allylamine antifungal agent. This drug, which interferes with the integrity of the cytoplasmic membrane of fungi by blocking membrane sterol synthesis, is fungicidal owing to intracellular accumulation of squalene [13–16]. Against *Aspergillus* species the *in vitro* action of terbinafine is similar to, or greater than that of amphotericin B, ketoconazole or itraconazole [17–21]. However, this activity is not so evident with *in vivo* experimental models. These poor *in vivo* results with *Aspergillus* as well as with other organisms may reflect the rapid metabolism (liver first pass) of terbinafine in rodents, which is different from its metabolism in man [22].

Therefore, on the basis of the above-mentioned evidence, we decided to treat with terbinafine a few patients who had been shown to be unresponsive to all conventional antifungal treatments, or who presented with recurrent flare-up episodes or had relevant untoward side-effects with available antifungal medications.

Diagnostic criteria

Diagnosis was based on evidence of fungi in serial samples of sputum or bronchoalveolar lavage fluid (BALF), histological confirmation of mucosal alterations due to fungi, pulmonary function tests (obstruction with superimposed reversible restrictive pattern), chest radiograph and CT scan modifications (central bronchiectasis, pleuropulmonary infiltrates), the presence of *Aspergillus* precipitins in serum, immediate positive skin tests to *Aspergillus*, elevated serum IgE levels [radioimmunoassay (RIA)], peripheral blood eosinophilia and clinical history [23–29]. All essential mycological and clinical parameters are shown in Tables 1 and 2 respectively. The skin tests were carried out using the bracco-Allergopharma allergenic extracts, BE/ml [30, 31]. The anti-AF precipitin titre was assessed by the gel double diffusion technique according to Ouchterlony, using a Bouty kit; the anti-*A. flavus*, *-nidulans*, *-niger* and *terreus* precipitins were assessed by a Pasteur kit [32–35]. IgE circulating levels were assessed by the Pharmacia Cap System IgE RIA [36, 37]. A Sabouraud glucose agar culture medium was used.

The various forms of pulmonary aspergillosis were classified according to the criteria suggested by J.E. Pennington and C. Iber [1], i.e. hypersensitivity syndromes (allergic bronchopulmonary aspergillosis), non-invasive infections (aspergilloma, suppurative bronchitis, empyema and pleural aspergillosis), invasive infections (invasive tracheobronchitis, acute invasive aspergillosis, chronic necrotizing aspergillosis).

Case reports

Patient 1

Patient 1 was a 52-year-old woman weighing 64 kg. In 1987, she had a right pneumectomy because of diffuse bronchiectasis and arteriovenous fistula. Mycotic aggregates were found on histological examination inside dilated bronchial specimens. A chronic empyema due to *Aspergillus fumigatus* and various other micro-organisms

Table 1. Mycological tests and fungal isolates

Patient no.		Mycetes			Precipitins*			IgE			Skin test		
		Before therapy	During therapy†	After therapy	Before therapy	During therapy†	After therapy	Before therapy	During therapy†	After therapy	Before therapy	During therapy	After therapy
1		AF+‡	AF−‡	AF−‡	4	2	0	0.40	0.39	<0.35	Neg	Neg	Neg
2	1^0	AF+§	AF−§	AF−§	3	1	0	<0.35	<0.35	<0.35	Neg	Neg	Neg
		PAB+§	PAB−§	PAB−§									
	2^0	PAB+§	PAB−§	PAB−§	0	0	0	<0.35	<0.35	<0.35	Neg	Neg	Neg
3		AF+§	AF+§	AF−§	3	2	1	50.3	49.2	6.20	2+	2+	2+
4		AF+§	AF−§	AF−§	3	2	2	48.2	47.0	7.40	2+	2+	1+
5		AF+§	AF+§	AF−§	3	1	0	<0.35	<0.35	<0.35	Neg	Neg	Neg
		AF spp.+¶	AF spp.−¶	AF. spp.−¶									
6		AF+‖	AF−‖	AF−‖	0	0	)	53	0.60	<0.35	3+	2+	1+
7		AF+§	AF−§	AF−§	5	4	3	4.0	0.57	0.53	1+	Not done	1+

* Arches.
† After 2–3 months' treatment.
‡ Pleural fluid.
§ BALF.
¶ Nasal plus.
‖ Sputum.
PAB, *Pseudallescheria boydii*; Af. spp., *Aspergillus* species; AF, *Aspergillus fumigatus*; −, negative; +, positive.
1^0 first and 2^0 second courses of therapy with terbinafine.

Table 2. Clinical data and outcome

Age/ sex	Diagnosis	Pre-T therapy	Total dose	Other pathogenes	Radiographic findings	Outcome	Relapses during T
52 F	Pleural empyema	AMP ITR	2816 mg 108 g	*Pseudomonas aeruginosa*	Pleural effusion	+++	Yes
50 F	Suppurative bronchitis	ITR MCZ AMP aerosol	144 g		Bronchiectasis	+++	Yes
28 F	CNA	AMP ITR AMP aerosol	200 mg 112 g	*Pseudomonas aeruginosa*	Honeycomb lung	+	No
31 F	CNA	AMP ITR AMP aerosol	300 mg 112 g	*Pseudomonas aeruginosa*	Honeycomb lung	+	No
22 F	CNA	NO		*Pseudomonas*	Multiple cavitary infiltrates	++	No
67 M	ABPA	NO			Lobectomy for aspergilloma	+++	No
44 M	CNA	AMP	300 mg	*Escherichia coli*	Peripheral cavitation and bronchiectasis	++	No

ITR = itraconazole.
MCZ = miconazole.
T = terbinafine therapy.
AMP = amphotericin B.

developed after surgery on the right side, requiring the insertion of a permanent pleural catheter. An oesophageal–bronchial–pleural fistula developed after a few months, which necessitated feeding through a nasogastric tube. The patient was given two courses of therapy with amphotericin B (60 days, 2816 mg total), followed by 12 months of oral itraconazole (300 mg daily), without benefit.

Beginning in 1991, the patient was given terbinafine 250 mg daily p.o. plus 250 mg daily directly into the pleural cavity. After 48 days of therapy with terbinafine, suppression of *Aspergillus* from the pleural cavity was recorded and progressive repair of the oesophageal fistula was seen. The patient was able to eat by herself. Four months later, because of relapse of the fistula, the oral terbinafine dose was doubled (500 mg p.o. plus 250 mg intrapleurally, to maintain the total daily dose at about 750 mg). *Aspergillus fumigatus* was suppressed again, the fistula healed and it was possible to perform a successful myo-omentomammoplasty; *Aspergillus fumigatus* precipitins and radioallergosorbent test (RAST) became negative. Corticosteroids were never given; courses of ranitidine were given for the overall period of treatment; at follow-up 3 years later, the patient was disease free.

Patient 2

A 50-year-old woman weighing 64.5 kg was diagnosed as having a 'suppurative bronchitis' associated with a *Pseudallescheria boydii* infection with bilateral bronchiectatic post-tubercular fibrodystrophy. She also had an unrelated mitral valvular defect.

The patient presented with cough, accompanied by a thick sputum and episodes of haemoptysis treated previously with oral itraconazole, 300 mg daily for 8 months, followed by amphotericin B via aerosol in doses of 2–5 mg daily for 2 months. A course of itraconazole was then repeated. At this point *Aspergillus fumigatus* had been suppressed and the precipitin level decreased. For a subsequent recurrence the patient was then treated with miconazole (600 mg daily for 10 days), which was stopped because of adverse reactions (anaphylactoid reaction, diffuse urticaria). The patient was admitted again after 2 years, in February 1991, in relapse. Treatment with oral terbinafine (750 mg day^{-1}) was given for 8 months, with successful suppression of *Aspergillus fumigatus* and *Pseudallescheria boydii* (the latter infection had never been suppressed with previous treatments) from the bronchial aspirate and decreased *Aspergillus fumigatus* precipitin levels. Cough and haemoptysis disappeared, and the sputum became thinner. A reinfection of *Pseudallescheria boydii* occurred after 14 months, but the infection was suppressed again after a new course of oral terbinafine (375 mg day^{-1}), with clinical improvement.

Patients 3 and 4

Two sisters, 28 and 31-year-old, body weight 56 and 48 kg, were investigated for ABPA and asthma

with episodes of haemoptysis that presented almost simultaneously. All criteria for ABPA were present (asthma, positive skin test for *Aspergillus fumigatus* and precipitins, positive IgE test, *Aspergillus fumigatus* in BALF, central bronchiectasis), but later the patients developed chronic necrotizing aspergillosis. Both of them were treated initially with oral itraconazole (300 mg day^{-1}) for 1 year and aerosolized amphotericin B for 1 month (parenteral amphotericin B was not tolerated) with a transiently improved symptomatic pattern.

Oral terbinafine treatment was started 1 year after itraconazole discontinuation. The schedules of treatment were for patient 3 750 mg day^{-1} for the first 34 days and subsequently 500 mg day^{-1} for 55 days and for patient 4 375 mg day^{-1} for 22 days and subsequently 250 mg/day for 62 days. This therapy was stopped after approximately 3 months owing to gastric discomfort not necessarily attributable to this drug, as many other drugs were used concomitantly. *Aspergillus fumigatus* was suppressed, haemoptysis stopped, precipitin titres and IgE levels reduced. Cough and sputum decreased. CNA recurred in both after 8 months. During terbinafine treatment patient 3 was given oral prednisone 375 mg day^{-1} for 15 days and later 25 mg day^{-1} for 30 days. Patient 4 was given beclomethasone spray 1000 μg day^{-1} for the whole therapeutic course.

Patient 5

A 22-year-old woman weighing 52 kg who was a mild smoker developed severe episodes of bronchopneumonia in the previous 3 years. Before coming to our attention, the patient, who had developed a further acute bronchopneumonia episode, was hospitalized in another institution but responded only transiently to a specific antibiotic treatment. Fever, chest pain, relevant mucopurulent sputum and dyspnoea were recorded at the time of admission.

Chest radiography and stratigraphy revealed inflammatory thickening of the middle lobe with scissural effusion, lingular thickening with hyperdiaphanous areas caused by an initial colliquation and three mildly padded peripheral hyperdiaphanous images of the upper lobe. A radiograph of the paranasal sinuses showed clouding of maxillary sinuses. Two fibrobronchoscopies (FBS) showed inflammation of the complete bronchial system with mucus plugs obstructing the lingula and right lower apical bronchus. BALF showed at our examination mucinoid material including granulocytes, fungal hyphae and spores and *Pseudomonas aeruginosa*. Lymphocytes subpopulations were with the normal range. In the nasal plug *Aspergillus* spp. were detected and anti-*Aspergillus* precipitins proved positive. Pulmonary function test (PFT) only showed a mild decrease in diffusion lung of carbon monoxide (DLCO). On the basis of this information, a diagnosis of chronic necrotizing aspergillosis was made. The patient accepted no further diagnostic invasive procedures or treatments with amphotericin B or itraconazole.

The patient was treated with terbinafine for 4 months; the schedule of treatment was 375 mg day^{-1} p.o. for the first 78 days and subsequently 500 mg for 42 days. The treatment was then stopped because of non-compliance. *Aspergillus fumigatus* was suppressed, precipitin titre was reduced and PFT increased.

A marked reduction of the parenchymal consolidation was observed; pleural effusions and endobronchial mucus plugs also improved. An overall amelioration of clinical symptoms was reported. At 1-year follow-up, recurrence of ABPA was recognized.

Patient 6

A 67-year-old man weighing 78 kg developed ABPA after middle lobectomy for aspergilloma. The medical history included residual angina after an aorto coronary bypass and chronic liver disease. Fibreoptic bronchoscopy was not carried out because of severe heart failure. The patient could not be treated with amphotericin B or itraconazole because of liver problems. The pressing symptoms were cough, thick sputum, wheezing and haemoptysis. *Aspergillus fumigatus* was found in serial sputum examinations. Serum IgE levels were elevated. Eosinophils were quite high (1279 mm^{-3}) and PFT revealed a severe obstruction. The patient treated with oral terbinafine (375 mg day^{-1}) for 9 months with disappearance of *A. fumigatus* and reduction of the levels of IgE and eosinophils (50 mm^{-3}). PFT and clinical symptoms improved at 8 months follow-up.

Patient 7

A 44-year-old man weighing 40 kg with multiple peripheral evolving infiltrates of the lung with cavitation, bronchiectasis and bullae was admitted to our institution for treatment of chronic necrotizing aspergillosis after bilateral upper lobectomy because of aspergilloma and tuberculosis.

Chronic respiratory failure required long-term oxygen therapy. The main complaints were cough, haemoptysis, mucopurulent sputum and chest pain. *Aspergillus fumigatus* was found in several BALF specimens. *Aspergillus fumigatus* precipitins and IgE were positive. Amphotericin B treatment was followed by severe liver and kidney failure.

Itraconazole treatment had to be stopped because of liver toxicity.

For the whole period of treatment, the patient was given prednisone 5 mg day^{-1}. Terbinafine was given at dosages of 250 mg day^{-1} for 73 days and subsequently 125 mg day^{-1} for 48 days. *Aspergillus fumigatus* was suppressed at 4 months and precipitin and IgE levels decreased; in addition, coughing stopped and episodes of haemoptysis were less frequent.

At 12 months follow-up the patient was aspergillosis free, but he died from massive haemophtysis. Post-mortem examination revealed that death was due to rupture of the tracheal artery caused by the decubitus of a tracheal cannula; no extant *A. fumigatus* infection was observed.

Terbinafine treatment in terms of daily and total doses is summarized in Table 3.

Discussion

Bronchopulmonary aspergillosis includes a spectrum of diseases with a low incidence in non-immunocompromised patients. These infections are becoming increasingly frequent because of the widespread use of corticosteroids and other immunosuppressant drugs. The diagnosis of bronchopulmonary aspergillosis is sometimes elusive, and problems are encountered both in patient management and in selecting an appropriate treatment. The prognosis depends entirely on the specific disease type sustained by *Aspergillus* and on the general condition of the patient. Moreover, as conventional treatments are often ineffective, a new approach to these diseases is undoubtedly required.

This pilot trial included seven patients, treated as compassionate cases but not affected by an evident systemic immunodepression, presenting with an anatomically injured bronchial system and mucociliary clearance impairment. Such dysfunctions do not enable radical and permanent drainage of the tracheo broncho pulmonary area, and predispose to overt infectious flare-ups.

The case of patient 1 was highly significant, being characterized by sterilization of the pleural cavity with subsequent corrective positive surgery and consequent prevention of a more severe and invasive aspergillosis as a possible post-operative sequel. Terbinafine was also effective against *Pseudallescheria boydii*, a fungus practically resistant to all antimycotic agents.

The dosage schedule we used was suggested by *in vitro* investigations as well by previous dermatological experiences. Although quite relevant, the incidence of reinfections might be explained by insufficiently prolonged treatment as well as by anatomical predisposition to relapses, as previously emphasized.

Suppression of *Aspergillus fumigatus*, albeit temporary, results in a clinical improvement, prevents the further progression of the underlying disease (empyema, bronchiectasis) and enables a more effective antibiotic treatment against all concurrently present pathogens, specifically *Pseudomonas aeruginosa*.

Terbinafine administration is definitely justified in cases of ABPA: in our opinion, the use of an anti-infectious agent is warranted not only by the high risk of overt aspergillar bronchopulmonary invasion but also on the grounds of the classic criteria ruling a hypersensitivity disease. This assumption is also supported by trials conducted with ketoconazole, natamycin and nystatin [38–41].

This pilot study demonstrates the clinical efficacy of terbinafine against *Aspergillus* species and *Pseudallescheria boydii* in bronchopulmonary infections unresponsive to a classical treatment. In one patient (no. 2) *Pseudallescheria boydii* reinfection was suppressed despite using a much lower terbinafine dosage than previously (i.e. 375 versus 750 mg). As the second new infection was diagnosed 14 months after the first and as terbinafine was equally effective despite the use of a lower dosage,

Table 3. Daily and total doses of terbinafine

Patient no.	Total days	mg day^{-1}	Total dose (mg)
1	155 (e.o.)	294	45 500
	155 (intrapleural)	444	68 750
2	242 (first treatment)	750	181 500
	244 (second treatment)	375	91 500
3	89	596	53 000
4	84	283	23 750
5	120	419	50 250
6	264	375	99 000
7	121	200	24 250

we assumed that the patient suffered a reinfection and not relapse of a previous infection.

Only minor untoward side-effects were encountered with this drug. In addition it is not excessively expensive and does not interfere with any other drug (e.g. cyclosporin A).

This positive profile suggests that further studies are warranted to evaluate the use of terbinafine in pulmonary fungal infections.

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