ORIGINAL ARTICLE

Terbinafine versus itraconazole: a long-term, randomized, double-blind, clinical trial in chronic pulmonary aspergillosis. A pilote study

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Abstract

Background: The frequency of pulmonary aspergillosis has been increasing for decades. Standard oral treatment is associated with tolerability problems and interactions with commonly used medications. Present data suggest that terbinafine may be a useful alternative for chronic forms.
Methods: A randomised, double-blind, multicentre trial compared terbinafine (500 mg b.i.d) with itraconazole (200 mg b.i.d.) with respect to successful outcomes for up to 6 months in 24 patients with chronic pulmonary aspergillosis. The primary end-point was a global clinical assessment using a 4-point rating scale, including (thorax) X-ray or Tc features. Secondary end-points were mycological response, duration of treatment and tolerability based on adverse events, haematology, biochemistry and urinalyses.
Results: The patients were randomly allocated to terbinafine or itraconazole. No patients discontinued terbinafine, while 2 of 12 patients discontinued itraconazole because of protocol violation (*n*=1) or withdrawal of consent (*n*=1). The mean ± SD duration of the treatment was longer in the terbinafine group (139.8 ± 43.6 days vs 120.5 ± 41.8 days). The clinical success rate was also higher with terbinafine (91.7% vs 70.0%), as was the eradication rate (100% vs 75%). The proportion of patients who reported adverse events was higher with itraconazole (7 of 12 vs 3 of 12).
Conclusions: Terbinafine (500 mg b.i.d. for up to 6 months) is an effective, well-tolerated antifungal agent for the treatment of chronic infectious forms of pulmonary aspergillosis, representing a valid alternative to treatment with itraconazole in these clinical forms, due to better clinical efficacy and safety and lower costs vs new azoles.

KEY WORDS: terbinafine; itraconazole; treatment; pulmonary aspergillosis; positron emission tomography.

Riassunto

Introduzione: La frequenza della aspergillosi polmonare è in aumento. Il trattamento orale standard è associato a problemi di tollerabilità ed a interazioni con altri farmaci comunemente usati. I presenti dati preliminari suggeriscono che la terbinafina possa rappresentare una valida alternativa per il trattamento delle forme croniche.
Metodi: Studio multicentrico randomizzato, in doppio cieco di confronto tra terbinafina (500 mg due volte al giorno) ed itraconazolo (200 mg due volte al giorno) somministrati fino al raggiungimento del successo terapeutico oppure per un massimo di 6 mesi in 24 pazienti con aspergillosi polmonare cronica. End-point primario era la valutazione clinica basata su una scala a 4 punti, che includeva anormalità osservate in radiografie e/o TAC. End-points secondari erano la risposta micologica, la durata del trattamento e la tollerabilità, valutata in base agli eventi avversi ed agli esami ematologici, biochimici ed urinari.
Risultati: 12 pazienti sono stati assegnati a terbinafina e 12 ad itraconazolo. Nessun paziente ha sospeso terbinafina, 2/12 hanno sospeso itraconazolo per violazione del protocollo (*n*=1) o ritiro del consenso (*n*=1). La durata media ± DS del trattamento è stata più lunga nel gruppo terbinafina (139.8 ± 43.6 giorni verso 120.5 ± 41.8 giorni). Il tasso di successi clinici è stato più elevato con terbinafina che con itraconazolo (91,7% vs 70%) e così pure il tasso di eradicazioni (100% vs 75%). Il numero di pazienti che ha segnalato eventi avversi è stato maggiore con itraconazolo (7/12 vs 3/12).
Conclusioni: Terbinafine (500 mg due volte al giorno per un massimo di 6 mesi) è un trattamento antimicotico efficace e ben tollerato in forme infettive croniche di aspergillosi polmonare e, in questi pazienti, rappresenta una valida alternativa all'itraconazolo per la sua miglior efficacia e ancor più, per il suo miglior profilo di tollerabilità e per il suo minor costo verso i nuovi azolici.

TAKE-HOME MESSAGE

Terbinafine, an allylamine fungicidal antimycotic agent, can be a valid alternative therapeutic option to itraconazole and new azole drugs for chronic pulmonary aspergilloses, as it exhibits good tolerability, efficacy and low cost.

Competing interests - none declared.

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INTRODUCTION

Pulmonary aspergillosis is an infection acquired by the inhalation of airborne spores of Aspergillus spp., a ubiquitous fungus found in organic debris, dust, compost, food and rotted plants. The infection results in a number of distinct pulmonary disorders. The classification is related to the patient's immune status and includes saprophytic forms, immunological forms, acute invasive aspergillosis (in the severely immunosuppressed patient) and chronic pulmonary aspergillosis (CPA) in patients with mild immunodepression. The frequency of these infections is increasing (in incidence and prevalence), and aspergillosis has been reported in teaching hospitals to be the second-most frequent fungal infection after candidiasis [1]. Factors leading to this increase are the widespread use of immunosuppressive drugs including corticosteroids as well as the increasing mean age of the population associated with a higher number of patients with other chronic pulmonary diseases, diabetes mellitus, renal insufficiency and liver diseases. Thus, pulmonary aspergillosis is also becoming more frequent in immunocompetent patients [1-3].

Schiraldi et al. [4-5] have proposed the novel diagnosis of "Chronic Pulmonary Aspergillosis (CPA)", defined as any chronic infection of the lower respiratory tract caused by Aspergillus spp. in patients with non-acute immune alterations; these infections differ completely from acute invasive forms, which are typical of immunosuppressed patients and are not a simple transition between the acute invasive and the saprophytic forms.

According to a further epidemiological study performed by the same group, the incidence of CPA may be more common than suspected [4]. The same authors with others also reviewed the literature in order to provide therapeutic guidelines for the novel diagnosis [6-13]. As long-term treatment is mandatory in chronic forms, all intravenous treatments (amphotericin B, itraconazole, voriconazole and echinocandins) are not indicated in CPA, for practical reasons and due to patient compliance. Switch therapy, that is, intravenous treatment followed by oral antifungal agents, may be indicated in severe cases [14]. Surgery may be beneficial in cases of aspergilloma, which generally does not respond to pharmacological treatment. These recommendations are consistent with the guidelines for disease caused by Aspergillus, produced by the Infectious Disease Society of America, which recommend amphotericin B for severe cases requiring intravenous treatment and itraconazole as an alternative for patients who can be treated orally [15].

Furthermore, oral formulations of voriconazole and posaconazole have been introduced, representing a valid alternative to itraconazole in the prolonged therapy of CPA [16,17]; unfortunately, voriconazole and posaconazole as well as itraconazole are hepatotoxic, can cause visual and neurological problems and are very expensive. Nevertheless, oral itraconazole is still considered the first-line option, mainly for economic reasons.

Itraconazole is also associated with tolerability issues. Its most common adverse effects are dyspepsia, abdominal pain, nausea, constipation, diarrhoea, headache and dizziness. Stevens-Johnson syndrome and an increase in transaminases, hepatitis, cholestatic jaundice, adrenal suppression and peripheral neuropathy have rarely been reported. Moreover, one has to consider the additional issue of interactions with drugs that are metabolised by hepatic microsomal enzymes (especially cytochrome P450), HIV protease inhibitors, drugs such as rifampicin or phenobarbitone and drugs that reduce gastric acidity such as proton pump inhibitors [2, 18]. Moreover, itraconazole resistance is increasing, often cross-resistant to voriconazole and posaconazole [19, 20]. Two preliminary studies were carried out [4] with oral terbinafine in 18 patients with chronic pulmonary aspergillosis; the results were positive (cure in 33% and improvement in 56% of the cases), and the authors recommend this agent as a possible alternative to oral itraconazole.

Terbinafine is an allylamine antimycotic agent with fungicidal activity due to the inhibition of ergosterol biosynthesis [21]. The

compound exhibits potent fungicidal action: *in vitro* against dermatophytes, *Aspergillus species*, *Scopulariopsis brevicaulis* and some dimorphic fungi (*Sporothrix schenckii*, *Blastomyces dermatitidis* and *Histoplasma capsulatum*) and in vivo (animal models) in dermatophytoses and aspergilloses [22, 23]. Positive results have also been observed (in animal models) against Pneumocystis carinii pneumonia [24, 25]. The clinical pharmacological profile of terbinafine is comparable to that of other antifungal drugs. The main difference is the low potential for drug-drug interactions, since terbinafine has only minor interactions with the cytochrome P-450 system [21]. Following commercialization for the treatment of dermatological fungal infections sustained by dermatophytes or Candida spp., data on adverse events of terbinafine have become available in over 2,000,000 subjects treated orally. Overall, the compound is well tolerated with few gastrointestinal adverse events and rare haematological or biochemical evidence of organ dysfunction. No effects on endocrine function or lipid metabolism have been reported [25]. The compound (at the usual dosage of 250–500 mg daily) has been shown to be well tolerated for extended periods of treatment (4 to 6 months), making it a suitable agent for the treatment of some systemic mycoses such as aspergillosis [26]. Moreover, high terbinafine concentrations have been found in pulmonary tissue (tissue: plasma ratio = 4) in subjects undergoing pulmonary surgery, after 3 days of treatment with oral terbinafine (250 mg b.i.d. or t.i.d.) [27-28].

The purpose of this randomized, double-blind, controlled clinical trial was to compare the safety and efficacy of terbinafine with that of standard oral antimycotic treatment (itraconazole) in patients with chronic pulmonary aspergillosis.

PATIENTS AND METHODS

This is a prospective, double-blind, randomized, parallel group, multicentre clinical trial comparing oral terbinafine (500 mg b.i.d.) with oral itraconazole (200 mg b.i.d.) per os.

Patient population

The study included patients of both sexes weighing ≥ 40 kg and suffering from chronic pulmonary aspergillosis, as defined by Schiraldi et al. (i.e. any chronic infection of the lower respiratory tract caused by the *Aspergillus species* in a patient with non-severe chronic immune alterations). Patients were included provided that they supplied written consent [4].

The main exclusion criteria were as follows: other clinical forms of aspergillosis, such as allergic bronchopneumonia, disseminated forms and forms localized elsewhere (eye, ear, central nervous system); life expectancy judged to be < 6 months; inability to take the study medication due to organ dysfunction or a history of adverse reactions; concomitant systemic antifungal therapy or the use of other antimicrobial investigational drugs within 2 weeks prior to the trial; amphotericin B or echinocandins for more than 7 days prior to the study entry; pregnancy or lactation and childbearing potential in women not using a suitable contraceptive method.

Study treatment

Blinding was achieved by putting 250 mg tablets of terbinafine into capsules identical to those containing 100 mg of itraconazole. Patients were allocated into one of the two treatment groups by dispensing one of the blinded study medications with the next consecutive number, which was prepared following a computer-generated balanced-block randomisation list. The trial drug was to be taken orally twice daily, preferably after a meal, until the treatment end. The treatment end was defined as either the time of complete or partial clinical response or treatment up to a maximum period of 6 months. Besides the clinical outcome, the mycological cure was taken into consideration.

Assessments

Patients returned to the centre every month for 6 months. At baseline, a full medical history was taken, physical examination was performed and women underwent a pregnan-

cy test. Aspergillosis was evaluated specifically by reporting every clinical finding related to the infection, by collecting biological material (sputum, bronchial lavage fluid and/or bioptic tissue when feasible and appropriate) for mycological assessments (microscopy and culture) and by performing a chest X-ray and/or CT scan when appropriate. These assessments were repeated at every visit, except for the chest X-ray and/or CT scan, which were repeated only at the end of the 6-month treatment period and/or whenever clinically indicated.

Safety was assessed by reporting adverse events and by performing routine haematology and biochemistry tests and urinalyses at every visit. An additional safety investigation was a 12-lead electrocardiogram, which was carried out at baseline and at the end of treatment.

End-points

The primary efficacy end-point was the number and percentage of patients with a positive outcome according to a global clinical assessment consisting of a 4-step rating scale referring to all symptoms, signs and imaging abnormalities related to aspergillosis, as follows:

1. complete response, defined as complete resolution;
2. partial response, defined as major improvement;
3. stable disease, defined as minor or no improvement; and
4. treatment failure, defined as a worsening of signs, symptoms or imaging related to aspergillosis to such an extent as to require alternative antifungal treatment or resulting in death.

The secondary efficacy end-points were as follows:

1. mycological response, defined as a cure: negative microscopy and culture; or failure: positive microscopy and culture; and
2. the duration of treatment with terbinafine or itraconazole.

Compliance was assessed by counting the capsules returned by the patients at the various visits.

Statistical analysis

This was an exploratory study, and the data were analysed only descriptively. The results were referred to the whole intention-to-treat population.

RESULTS

Patients

Twelve patients were randomly allocated to the terbinafine and 12 to the itraconazole group. In the itraconazole group, 10 completed the treatment, since 2 patients discontinued itraconazole early because of protocol violation (n=1) or withdrawal of informed consent (n=1). In the terbinafine group, all 12 completed the treatment.

The demography and baseline aspergillosis characteristics of the two treatment groups were similar, except for age (the patients in the terbinafine group being slightly younger) and sex (a higher proportion of males in the itraconazole group, 7 of 12 vs 5 of 12 in the terbinafine group). The most frequent symptoms were cough and purulent sputum, which were present at baseline in > 70% of the patients, usually associated with abnormal auscultatory findings. The incidence of the various symptoms at baseline was slightly higher in the terbinafine group.

Treatment

Compliance in general was satisfactory, except for the patient who withdrew his consent. The mean ± SD duration of treatment was slightly longer in the terbinafine group than in the itraconazole group (139.8 ± 43.6 days vs 124.5 ± 41.8 days).

Efficacy

Global clinical assessment

At the end-point, 91.6% of patients in the terbinafine group and 81.2% in the itraconazole

group had a positive clinical assessment, that is, a complete response, a partial response or stable disease. We include stabilization in the positive results of therapy, since in general, six months without effective therapies result in a clinical worsening of this kind of patient. Complete or partial responses were achieved in 66.6% of patients in the terbinafine group and in 60% in the itraconazole group. Furthermore, 25% patients in the terbinafine group vs 10% in the itraconazole group demonstrated a stabilization of the disease. Overall, there were only 8.33% treatment failures in the terbinafine group and 30% in the itraconazole group (Fig.1, 2).

Mycological examinations

At the end-point, the eradication rate was higher in the terbinafine group (8 of 8; 100%) than in the itraconazole group (6 of 8; 75%).

Subgroup analysis

- CPA in patients with Aspergilloma

  The difference in positive clinical assessments in patients with aspergilloma suggests that in this form of pulmonary aspergillosis, terbinafine was more effective than itraconazole. Moreover, mycological eradication was achieved with terbinafine in all three cases in which the presence of Aspergillus spp. was documented, whereas itraconazole produced eradication in only one of the three cases of its group in which the infection was documented. However, no complete responses were obtained in either group. One patient treated with terbinafine, with pleural aspergilloma with partial response, who underwent F-FDG PET/CT, showed positive results with 3.4 SUV consistent with active phlogosis. PET/CT seems to be a reliable support tool, providing additional information on the metabolic activity, accurate anatomic localization and extent of the disease. Studies are ongoing [29].

- CPA in patients without Aspergilloma

  The positive clinical assessment rate was 100% with both treatments. Both treatments achieved a 100% eradication rate. A global overview of these results is provided in Table 1.

Safety

A greater number of patients experienced adverse events in the itraconazole group than in the terbinafine group; one patient treated with itraconazole discontinued the study treatment because of adverse events related to the treatment (moderate oedema in lower limbs and severe nausea).

Minor and/or temporary adverse events (gastrointestinal disturbances, rash, insomnia, abdominal pain) were observed in 3 of 12 patients in the terbinafine group and in 7 of 12 in the itraconazole group.

DISCUSSION

The results of this study suggest that terbinafine, given orally at the dosage of 500 mg b.i.d. for up to 6 months, is an effective and well tolerated antifungal agent in the treatment of these infections. It should be noted that the study did not have power enough for statistically based statements. Nevertheless, the success rate was better in the terbinafine group (91.7%) than in the itraconazole group (70%); positive outcomes with itraconazole in the literature amount to 62–98% [4]. In summary, we can state that terbinafine showed a better response than itraconazole in patients with aspergilloma, although no complete response was achieved in these patients either with terbinafine or with itraconazole. This was to be expected. It is almost impossible to achieve a complete resolution of symptoms (complete response) in patients with aspergilloma, a result wich is generally only achieved following surgical intervention. In the subgroup of chronic pulmonary aspergillosis in patients without aspergilloma, the results were more or less comparable, although a "complete" response was achieved in more cases with terbinafine than with itraconazole. According to the eradication rates, it must be considered that in the aspergilloma subgroup, although the data were necessarily limited, a

better terbinafine eradicating effect was demonstrated (mycological eradication in 3 of 3 with terbinafine but in 1 of 3 with itraconazole). In the non-aspergilloma subgroup, the eradication effect of both drugs was excellent (100%). The lack of follow-up data documenting the relapse rate is a limitation of this study. A four-month follow-up period was planned, but very few patients entered this phase, and no meaningful data were collected. The tolerability of terbinafine was good, as there were no withdrawals due to intolerance, and no new safety issues were identified. This is an important result, as terbinafine was given at a high dose, i.e. 1,000 mg daily, which is 2–4 times the approved dosage for the dermatological indications. Moreover, treatment lasted for 6 months, which is twice as long as the recommended maximum duration of treatment with respect to the dermatological indications. In contrast, our safety data highlighted the gastrointestinal relative intolerance of itraconazole, which is a well-known issue related to this drug [30]. The known liver toxicity of itraconazole was not an issue in any of our patients.

In conclusion, the study suggests that terbinafine, given at the dosage of 500 mg b.i.d. for up to six months, is an effective and well tolerated antifungal agent for the treatment of chronic infectious forms of pulmonary aspergillosis.

We may add that it has shown some relatively better clinical and microbiological results than itraconazole. Its better tolerability contributes to the suggestion of terbinafine as a valid alternative therapeutic option to itraconazole, and its low cost must be considered a remarkable advantage in comparison to other new oral azoles and other novel agents; this is a non-secondary issue today, especially in "emergent" countries. Furthermore, terbinafine can be safely used during pregnancy [31].

Table 1. Positive Mycological results and positive clinical assessments by treatment and diagnosis category (ITT population)

	Terbinafine (*n*=12)	**Itraconazole (*n*=10)**
Aspergilloma		
Mycology – eradication	3/3*	1/3*
Clinical assess.	5/6	2/5
Complete response	0	0
Partial response	3	1
Stabilization	2	1
CPA without Aspergilloma		
Mycology – eradication	5/5*	5/5*
Clinical assess.	6/6	5/5
Complete response	5	3
Partial response	0	2
Stabilization	1	0

* number of cases with adequate microbiological documentation

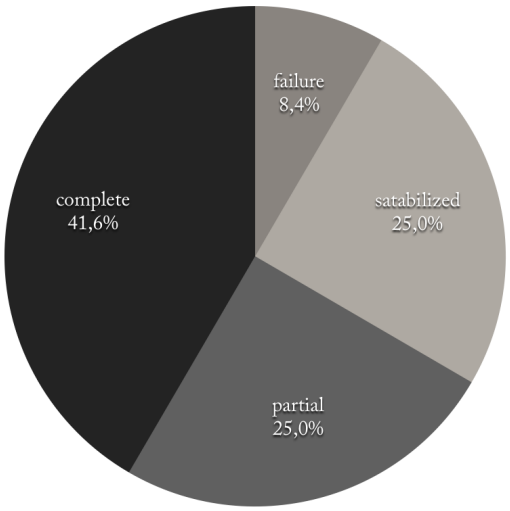

Figure 1. Terbinafine: outcome of global clinical assessment by treatment
(proportion of patients - 12)

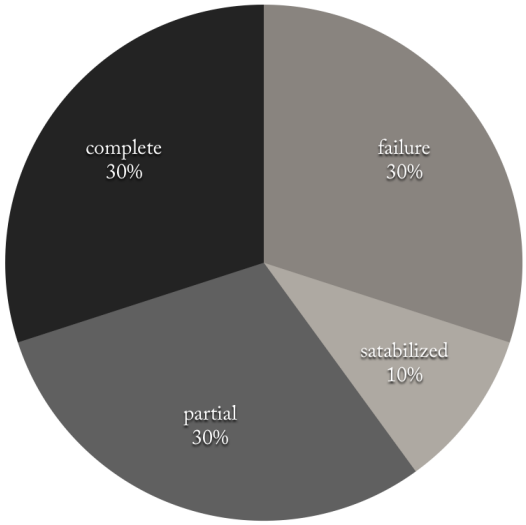

Figure 2. Itraconazole: outcome of global clinical assessment by treatment
(proportion of patients - 10)

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