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Clinical efficacy and tolerability of terbinafine in patients with pityriasis versicolor

Klinische Wirksamkeit und Verträglichkeit von Terbinafin bei Patienten mit Pityriasis versicolor

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Schlüsselwörter. Pityriasis versicolor, antimykotische Chemotherapie, Allylamine, Terbinafin, Bifonazol.

Summary. The antifungal efficacy and tolerability of 1% terbinafine cream vs. 1% bifonazole cream were assessed in a single blind randomized trial in patients with pityriasis versicolor. Terbinafine, a drug of the allylamines group, a new class of antimycotic agents, blocks sterol biosynthesis in the pathogen through inhibition of squalene epoxidase and consequent squalene accumulation, a primarily fungicidal process. Forty pityriasis versicolor patients, (18 M, 22 F; mean age 32.4 years; min. 16, max. 65), used 1% terbinafine cream or 1% bifonazole cream for a maximum of 4 weeks. All patients were followed-up weekly both clinically and mycologically. Clinical cures, defined as negativization of each clinical parameter, were recorded for 20 terbinafine patients (100%) and 19 bifonazole patients (95%), with routine microscopy and Wood's light tests both negative. By the 2nd week of treatment, 2 terbinafine patients were mycologically cured (10%). By the 3rd week, 14 terbinafine patients (70%) and 5 bifonazole patients (25%) were mycologically cured. The present controlled clinical trial consequently demonstrates that terbinafine is rapidly effective and well tolerated for treatment of pityriasis versicolor.

Zusammenfassung. In einer randomisierten Einfachblindstudie an Patienten mit Pityriasis versicolor wurde die antimykotische Wirksamkeit und Verträglichkeit einer 1%igen Terbinafin-Creme versus 1%iger Bifonazol-Creme untersucht. Terbinafin, ein Allylamin, blockiert die Sterolbiosynthese im Erreger über die Hemmung der Squalenepoxidase mit anschließender Squalenakkumulation, ein primär fungizider Vorgang. Vierzig Pityriasis versicolor-Patienten (18 m, 22 f; Altersmittel 32,4 Jahre; Altersbereich 16–65 Jahre), applizierten die Terbinafin-Creme oder Bifonazol-Creme maximal vier Wochen lang. Alle Patienten wurden anschließend sowohl klinisch als auch myokologisch wöchentlich kontrolliert. Die klinische Heilung, definiert als völlige Normalisierung sämtlicher klinischer Parameter, wurde bei 20 Terbinafin-Patienten (100 %) und 19 Bifonazol-Patienten (95 %) beobachtet; hierbei waren sowohl die mikroskopische Untersuchung als auch der Woodlicht-Test negativ. In der zweiten Woche der Behandlung erwiesen sich zwei Terbinafin-Patienten (10 %), in der dritten Woche 14 Terbinafin-Patienten (70 %) und fünf Bifonazol-Patienten (25 %) als mykologisch saniert. Die vorgelegte kontrollierte klinische Studie zeigt daher, daß Terbinafin ein schnell wirksames und gut verträgliches Medikament für die Behandlung der Pityriasis versicolor darstellt.

Introduction

Pityriasis versicolor is a common superficial chronic fungal infection of the skin caused by a fungus known as *Malassezia furfur* that typically affects young adults in warm climates [1].

Although topical imidazole agents can cure the great majority of patients, recurrences are common. Therefore, there is an active search for new effective antifungal agents [2].

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The allylamines, a new class of antimycotic agents, differ from all other imidazole antimycotics in their mode of action [3, 4]. Allylamines block sterol biosynthesis in the pathogen by inhibition of squalene epoxidase with consequent squalene accumulation, a primarily fungicidal process [5]. Squalene epoxidase is not a cytochrome P450-dependent enzyme. Unlike azoles, allylamines do not bind to cytochrome P450 from mammalian steroidogenic tissues [6]. This characteristic may provide a greater selectivity of action, with less toxicity to mammalian tissues. In fact, mammalian squalene epoxidase and cholesterol biosynthesis systems *in vitro* are inhibited only at concentrations much higher than the therapeutic ones [7].

This paper reports a controlled study of the clinical efficacy of terbinafine, a new agent of the allylamines group, exclusively in patients with pityriasis versicolor infestations. Terbinafine is highly active against a wide range of fungi after both oral and topical administration [8, 9].

Whether it is regarded fungicidal or fungistatic depends on the test strain used. The drug is particularly effective for the treatment of dermatomycoses [10–12].

Previous non-comparative clinical studies have suggested that terbinafine is effective against *Pityrosporum ovale (Malassezia furfur)*. The aim of this controlled clinical trial was to compare the effects of terbinafine with those of bifonazole in patients with pityriasis versicolor only.

Material and methods

Forty adult patients of both sexes, affected with pityriasis versicolor diagnosed by clinical, microscopic and culture tests and/or by Wood's light, were admitted to the trial. The trial was carried out according to a randomized, single-blind, between-patients design comparing 1% terbinafine cream with 1% bifonazole cream.

Patients with clinically overt skin superinfections, or under treatment with topical or systemic antimycotic and/or antibiotic or corticosteroid drugs, or who had discontinued them for less than 2 weeks, patients with established or assumed pregnancy, non-cooperative or possibly noncompliant were excluded from the trial.

After giving informed consent, the patients were assigned on the basis of a computerized randomization list to treatment with terbinafine or bifonazole, applied twice daily to the affected area, because this is the modality of treatment in our clinic with other antifungal drugs.

Treatment, obviously depending on the clinical course, was for 2–4 weeks. To evaluate the efficacy of the drug, both clinical and mycological examinations were performed before starting the study and at the end of each week of treatment. Clinical evaluation included all signs and symptoms of the disease (achromia, hyperchromia, desquamation, itching and others) scored on a 4-item semi-quantitative rating scale (1 = absent, 2 = mild, 3 = moderate, 4 = severe). Mycological examinations looked for pathogens, evidenced by microscopic, culture and/or Wood's light tests. Pictures of the lesion, taken both before and at each weekly follow-up, were obtained for cases for which they were of specific interest.

A patient was considered mycologically cured when culture, Wood's light and microscopic findings were negative, and clinically cured when all the clinical parameters considered were negative, with the possible exception of mild achromia.

At the end of the treatment period, the patient was asked to come for a follow-up visit 2 weeks later to check for any possible recurrence.

Tolerability was evaluated by classic biochemical parameters, (i.e. Hb, RBC, WBC, mean corpuscular volume, serum creatinine, bilirubin, SGOT, SGPT and urinalysis), assessed both before and at the end of the study.

All possible untoward side effects, either systemic or local, as assessed by the investigator or complained of by patient, were also recorded in detail.

Quantitative data were analyzed by the Student *t*-tests for paired and unpaired data. Qualitative data were analyzed by the χ^2-test, Friedman's and Wilcoxon's tests, as appropriate. Data are reported as mean $\pm$ SE. A *P*-level of < 0.05 was considered significant.

Results

Forty out-patients (18 M, 22 F), mean age 32 years (range: 16–65 years), were enrolled, and none was removed after assignment. The personal and clinical data were comparable for the two groups. Mycological and clinical diagnosis of pityriasis versicolor was established for all cases. The current mycoses were relapses for 10 terbinafine (50%), and 10 bifonazole patients (50%). The mean duration of the disease was 16 $\pm$ 8.8 months for the terbinafine group and 10 $\pm$ 4.6 months for the bifonazole group.

Mycological cures were obtained after 3 weeks of treatment for 14 (70%) terbinafine and 4 (20%) bifonazole patients ($\chi^2 = 8.12$, $P < 0.05$). At the end of the study, all 20 terbinafine patients and 19 of the 20 bifonazole patients had negative mycological tests (Figs 1 and 2). The mean duration of treatment, until negative microscope and Woods' light findings, was 3.1 $\pm$ 0.1 weeks for terbinafine and 3.7 $\pm$ 0.1 weeks for bifonazole patients. These durations were significantly different ($P < 0.05$).

Clinical cures, defined as all clinical parameters negative, were observed for 20 (100%) terbinafine and in 19 (95%) bifonazole patients at the end of the study. Sixteen (80%) terbinafine patients and 7 (35%) bifonazole patients ($\chi^2 = 8.29$, $P < 0.05$) were already cured by the 3rd week of treatment (Fig. 3).

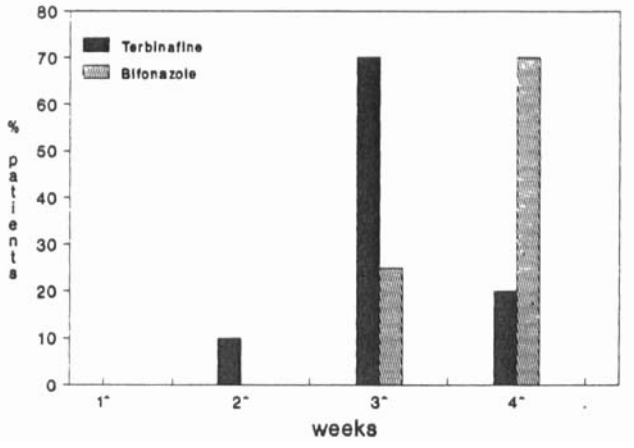

Figure 1. Percentage of negative microscopy at each week of treatment.

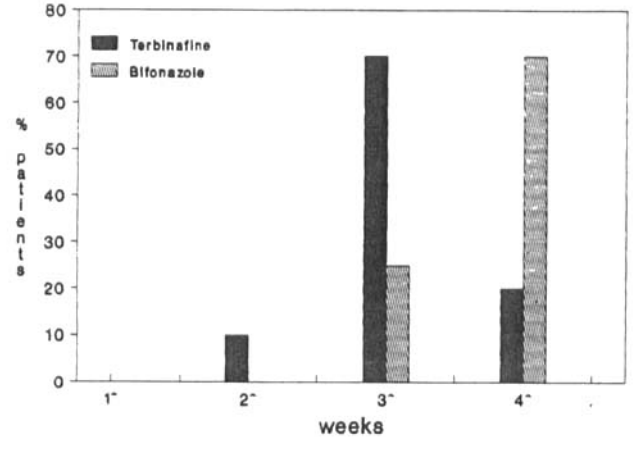

Figure 2. Percentage of negative Wood's light test.

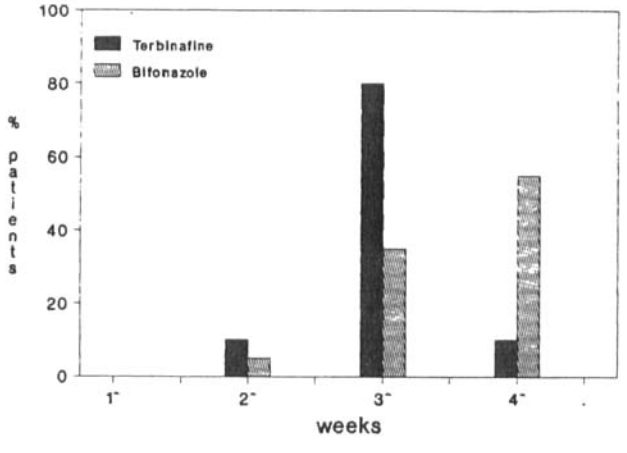

Figure 3. Clinical cure rate.

Desquamation was the most common symptom of all the clinical parameters. At the end of the treatment, this had disappeared in all the terbinafine and in 19 (95%) of the 20 bifonazole patients (Figs 4 and 5). Hyperchromia, observed in 17 terbinafine and in 18 bifonazole patients, had disappeared in all terbinafine (100%) and in 16 (89%) of the 18 bifonazole patients. (Figs 6 and 7). Itching, recorded with the same frequency in both experimental groups, had subsided after treatment in all cases. Achromia persisted in all patients in spite of my-

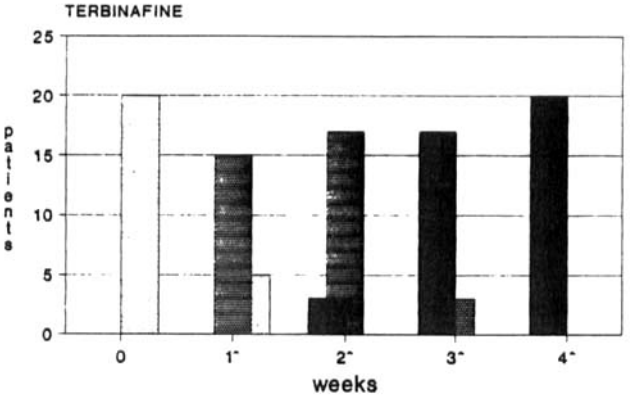

Figure 4. Desquamation pattern on terbinafine treatment.

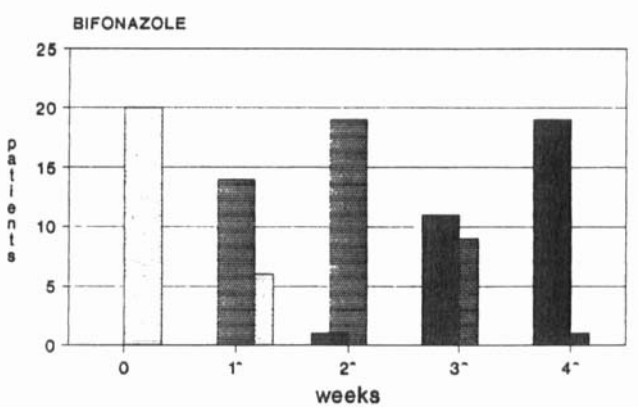

Figure 5. Desquamation pattern on bifonazole treatment.

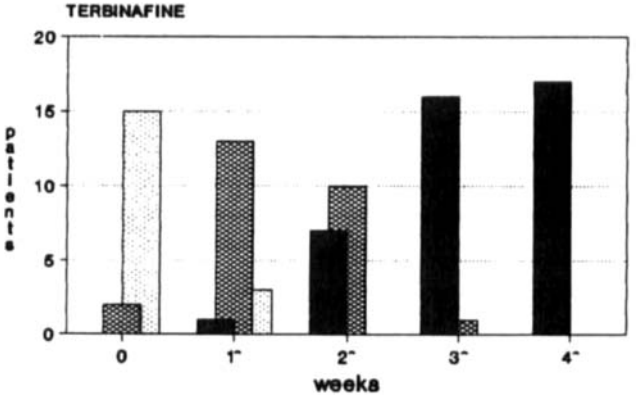

Figure 6. Hyperchromia pattern on terbinafine treatment.

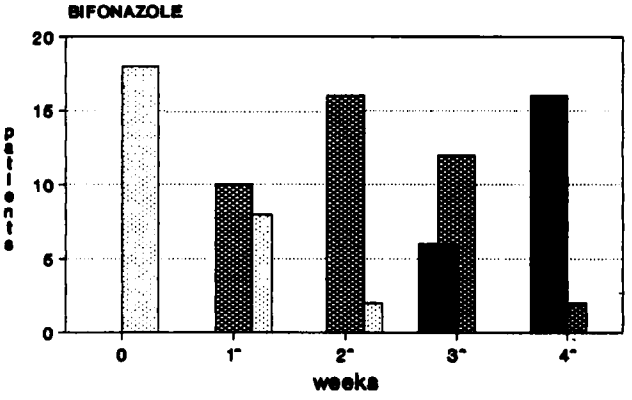

Figure 7. Hyperchromia pattern on bifonazole treatment.

cological cure and recovery from all other clinical signs of infection. Both drugs were well tolerated and no patient reported side effects. Laboratory diagnostic tests were in the normal range.

Discussion

The development of effective and well tolerated antifungal agents has produced significant progress in the treatment of pityriasis versicolor. In fact, new topical antifungal drugs have made the treatment of this mild but therapeutically difficult skin disease much easier and safer than with galenic treatment [2, 13, 14]. However, new classes of antifungal agents might offer even further therapeutical progress, provided they have at least comparable efficacy and tolerability, and may possibly demonstrate faster curative effects.

In the present study, terbinafine was compared with bifonazole, a well established imidazole antifungal agent in patients with pityriasis versicolor. It was considered unethical to perform a placebo-controlled study on the efficacy of terbinafine, although not done so far, because of the inconvenience for the patients and the availability of well accepted therapeutic agents. The design of the present trial, centered on a single disease and a single pathogen, is a method-of-choice in medical mycology to obtain reliable data about drug efficacy, duration of treatment and patient compliance.

Negativization of all microscopic and Wood's light findings seems to be the most significant evidence to state a real mycological cure of pityriasis versicolor. Culture examination were not deemed necessary. Negativization of all clinical parameters was an additional end point of the study, used to prove that there had been a cure. Achromia, although persisting in most patients at the end of the treatment period, was not included as a parameter of efficacy since it may persist for several months after an overt mycological cure. Mycelial forms are assumed to invade both intracellular and extracellular areas of the stratum corneum, disrupting melanocytes and inhibiting tyrosine production, with the resulting achromia commonly observed in this condition [15–17].

At the end of the investigation, cure was observed in all subjects and after both treatments, except for a single bifonazole patient. In addition, treatment was shorter for the terbinafine group, since, as early as the 3rd week, 70% of the terbinafine patients had negative microscopic and Wood's light examinations, compared with 25% of the reference group. The same was true for negativization of clinical symptoms observed within 3 weeks in 80% of terbinafine and 35% of bifonazole patients.

These results demonstrate the better clinical efficacy of terbinafine. However, longer follow-up studies are needed to verify whether this efficacy might also result in a reduced relapse rate of pityriasis versicolor.

These results of the present trial indicate that topical terbinafine, a new allylamine drug, is effective, rapid in action and optimally tolerated.

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