

Research Article

Ciclopirox HPCH Nail Lacquer after Failure of Topical Treatment with Amorolfine

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Abstract

According to a recent controlled study, about 85% of patients with onychomycosis fail to respond to a standard treatment with amorolfine 5%. An 8% ciclopirox nail hydrolacquer, based on hydroxypropyl chitosan technology (P-3051), has been shown to improve efficacy in topical treatment of onychomycosis. No comparative studies between P-3051 and amorolfine were hitherto published. It has been investigated the efficacy of P-3051 in patients with onychomycosis who did not respond to amorolfine. This was a non-interventional, multicentre study. Patients with mild-to-moderate onychomycosis, who had failed to respond to a previous 6-month treatment course with amorolfine twice weekly, were treated daily for 24 weeks with P-3051. The primary endpoint was the success rate of treatment, defined as conversion to negative of KOH of the target nail. Secondary endpoints included clinical effectiveness, defined as negative mycology (culture and KOH) and $\geq 90\%$ clear nail. Overall, 70 patients were included in the Full Analysis Set (FAS) and 66 completed the study. Success at primary endpoint was achieved by 41 patients (58.6% of FAS, 95% CI 46.17%; 70.23%). The null hypothesis that success rate is $\leq 15.7\%$ taken from literature was rejected ($P < 0.0001$). Clinical effectiveness was obtained in 21.4% of patients. The study showed that treatment failures to amorolfine, subsequently treated with P-3051 for 24 weeks, resulted in a high statistically and clinically significant success rate. The high response rate observed suggested that P-3051 may be efficacious in amorolfine treatment failures as an alternative prior to oral therapy.

ABBREVIATIONS

ADR: Adverse Drug Reaction; **CPX:** Ciclopirox; **FAS:** Full Analysis Set; **GCP:** Good Clinical Practice; **HPCH:** Hydroxypropyl Chitosan; **ICH:** International Conference on Harmonisation; **NIS:** Non-Interventional Study; **SD:** Standard Deviation

INTRODUCTION

Onychomycosis is a common, age related, fungal infection of the nail, affecting approximately 12-13% of the general population [1-5]. Two topical compounds, amorolfine and ciclopirox are currently used in several countries in Europe, in nail lacquer formulations, aimed at allowing drug delivery to nails [6]. In three large, non-controlled studies, mycological cure was achieved in 52.1% of the toenail mycoses and in 64.3% of the fingernail mycoses [7].

Recently, a controlled study with topical terbinafine was published using amorolfine as comparator for a 48-week treatment on 1029 patients. In this study amorolfine nail lacquer showed a complete cure rate of 0.96%, a response of 15.7% in terms of mycological eradication and a mycological cure failure of 84.3% [1].

Ciclopirox (CPX) is currently available on the market in the form of two different nail lacquer preparations: one is based on a formulation in an insoluble nail lacquer base and the other is a new 8% ciclopirox nail hydrolacquer (P-3051) based on hydroxypropyl chitosan (HPCH). HPCH is a water-soluble semisynthetic biopolymer, which renders the new hydrolacquer permeable to moisture and air and the film non-glossy and non-sticky, revealing superior properties in terms of affinity to keratin, nail permeation and ease of use. In the pivotal, controlled study of this new formulation [8], statistically significant superiority of P-3051 vs. the reference old CPX was shown at the end of the 12-week follow up, after a standard 48-week once a day treatment.

It is common knowledge that topical therapy of onychomycosis is less effective than oral therapy and after a failure with a topical product the patient is generally treated by an oral agent, in most cases terbinafine or itraconazole is given after the failure of a standard amorolfine treatment.

On the basis of such assumptions and previous results, the present study aimed to verify whether a drug with an improved nail penetration, such as P-3051, can be useful in daily practice in those patients with persistent onychomycosis that failed to respond to a topical treatment with amorolfine.

MATERIALS AND METHODS

Study Design

A total of 10 German sites participated in the present non-interventional study (NIS), conducted from June 2011 to January 2013. The study was performed under the exclusive therapeutic responsibility of the physician. The study was fully GCP and ICH compliant and the protocol was approved by the institutional ethics committee of Munich according to the local regulations. All patients enrolled provided their written informed consent before starting any protocol procedure. In compliance with the approved labelling, all patients of the study had been treated for distal lateral subungual onychomycosis. Treatment failure in clinical or mycological outcome was defined according to Scher et al [4]: positive KOH test with onychomycotic dystrophy leaving more than 10% of nail plate, in at least one toenail or one fingernail, chosen as target nail. Eligible patients had to have failed a previous topical antimycotic treatment based on amorolfine which had lasted at least 6 months and had terminated no longer than one month before the inclusion into the NIS. The inclusion of the patient into NIS was considered after the decision of the investigator for treatment of P-3051 was made. No concomitant oral treatments for onychomycosis were allowed. Each patient underwent a study visit at three different time points, chosen in accordance with the usual clinical setting in this indication.

Patients who had failed an amorolfine treatment defined as above were selected for the study. The evaluation of the enrolment was considered as the baseline time point (Visit 1). The failure of previous treatment was proven clinically and by routine laboratory examination, including nail-scrapings for mycological assessments, placing the specimens in a drop of Calcofluor stain, mounted with a cover slip, and examined at 40x under a fluorescent microscope (KOH microscopy) and - but not compulsory - the culture examination, by plating onto general and inhibitory media the nail-scraping. After an incubation period of 4 weeks, the identification of the filamentous fungi is based on an evaluation of their colony characteristics and microscopic morphology [9]. Patients fulfilling inclusion criteria were instructed to start the daily application of the P-3051 nail lacquer (Ciclopoli® gegen Nagelpilz, Taurus Pharma GmbH, Germany) for 24 weeks. KOH assessment (primary endpoint) of the target nail was repeated by the investigator at Visit 3 (end of treatment).

For those patients with a clinical and mycological evaluation available both at baseline and at the end of treatment, the conversion to negative mycological examination, defined as composite evaluation of KOH and culture, was assessed. Moreover, the following secondary endpoints were assessed: 1) clinical effectiveness rate, defined as composite of negative KOH microscopy, negative culture and < 10% residual involvement of the target nail; 2) complete cure rate, defined as negative KOH microscopy, negative culture and no residual clinical involvement of the target nail.

Statistical analysis

The estimated sample size consisted of 70 evaluable patients allocated to the open-label arm of P-3051. The Full Analysis Set (FAS) included all patients with at least one application of

P-3051 and at least one visit with documentation of response data. Patients with violation of major inclusion/exclusion criteria (negative KOH microscopy, concomitant oral treatments for onychomycosis) were excluded from efficacy analysis. The analyses of the primary and secondary endpoints were based on the FAS population. All tests were explorative and they were performed "two-sided" using a α -level of 5%; no alpha adjustment was performed.

The primary endpoint was achieved for a patient if the KOH-test was negative at visit 3 (week 24).

In the FAS analysis, patients with missing KOH test at Visit 3 were considered as "failure". Confirmatory analysis for robustness was performed in the Per Protocol population (PP), defined as all patients who fulfilled the mandatory protocol procedures and had the KOH test available at the Visit 3.

The relative frequency of primary and key secondary endpoints achievement together with its 2-sided 95% confidence interval was calculated using the binomial distribution and five different methods.

Null and alternative hypotheses were: $H_0: P - p_0 \leq 0$ and $H_a: P - p_0 > 0$, where P represents the observed response rate from a subsequent treatment with P-3051 after unsuccessful treatment with topical amorolfine and p_0 the hypothesized response rate from a subsequent treatment with placebo after unsuccessful treatment with topical amorolfine (i.e. 15.7% as per randomized, controlled trial on amorolfine) [1].

The comparison of investigators' satisfaction between previous amorolfine and present P-3051 treatment was performed using Wilcoxon-Signed-Rank test (FAS).

RESULTS AND DISCUSSION

Demography and baseline characteristics

Overall, 70 patients were enrolled in this non-interventional study. Four patients prematurely discontinued after 12 weeks: out of these, 3 were lost to follow up and the last one abandoned due to an adverse event not related to study drug (broken leg). None of the enrolled patients was excluded from the efficacy analysis. At baseline, patient's mean age was 59.2 ± 13.2 years. The patients were Caucasian (98.6%) or African (1.4%) and there was a higher proportion of females (58.6%) compared to males (41.4%) (Table 1). All 70 patients in the FAS complied with the eligibility criteria.

The majority of target nails (94.3%) were located on the toes, with 85.7% on the big toe. Only 5.7% (4 of 70 nails) were fingernails with a comparable distribution at the 1st, 2nd and 3rd finger and mostly on the right side. The distribution of toenails between the left and right side was comparable (48.6% on the left and 45.7% on the right). The 4th and 5th toe or finger was never selected as a target nail. Culture was available at baseline in 48 patients: all were positive to dermatophytes, out of them 64.6% for Trichophyton spp. (*T.rubrum/T.mentagrophytes*), 20.8% for undefined Dermatophytes and 8.3% for mixed fungi. Positivity for *Scopulariopsis brevicaulis*, undefined moulds or undefined yeasts was reported for one (2.1%) patient each. The average affected area of target nail at baseline was 38.1% with a standard

deviation (SD) of 20.2%.

Efficacy

The response rates for treatment with P-3051 are presented in (Table 2): 41 patients responded successfully to treatment, while 25 patients failed to respond. Four further patients had missing values for the KOH-test at Visit 3.

In the FAS analysis, the estimate of the response rate for the primary endpoint was 58.6% with a 2-sided 95% confidence interval ranging from 46.17% to 70.23% (Clopper-Pearson Exact method). Because the hypothesized minimal response rate of 15.7% falls outside the confidence intervals, this result is highly statistically significant ($P < 0.0001$).

The analysis on PP population confirmed that on FAS set: primary endpoint was achieved by 62.1% of patients (95% CI: 44.34% - 73.78% Clopper-Pearson Exact method). Again, the hypothesized minimal response rate of 15.7%, falls outside the confidence interval ($P < 0.0001$).

As secondary endpoints, the culture examination pre- and post-treatment was available in 28 patients. Out of these, the mycological culture was converted to negative in 25 patients (89%), while only in 3 patients it was not (10.7%). Furthermore, 17 out of those patients, were also negative to the direct KOH microscopic examination. Those patients, defined as "mycological cure", (i.e. as negative microscopy and negative culture) were in proportion 60.7% of all patients with pre- and post- mycotic culture available (95% CI: 40.58%-78.50%, $P < 0.0001$, Clopper-Pearson Exact method).

At the end of treatment, the percentage of responders, defined as negative KOH microscopy and negative culture and $< 10\%$ residual involvement of the target toenail, was 21.4%, matching those patients where the decrease of the residual involvement of the target nail area was $\leq 5\%$. The complete cure rate (defined as composite of negative KOH microscopy and negative culture and no residual clinical involvement of the target toenail) was obtained in 10.7% (95% CI: 2.27%-28.23%; $P < 0.0001$, Clopper-Pearson Exact method).

A gradual, clear decrease of diseased target nail area was shown during treatment (Table 3).

No adverse drug reactions (ADRs) were reported during the observational period of this NIS. Only one patient discontinued the observation prematurely due to an event (broken leg) that

Table 1: Demographic data.

Variable	Statistical parameter	Treatment with P-3051 (N=70)
Ethnic origin		
Caucasian	N (%)	69 (98.6)
African	N (%)	1 (1.4)
Gender		
Male	N (%)	29 (41.4)
Female	N (%)	41 (58.6)
Age [years]		
	Mean $\pm$ SD	59.2 $\pm$ 13.2
	Min-Max	26.0-83.0

Table 2: Response rates to P-3051 treatment at visit 3.

Result of KOH-test at Visit 3 / Response rate of the target nail after treatment	Patients	
	N	%
In total	70	100.0
success	41	58.6
failure	25	35.7
missing values	4	5.7
FAS population	70	100.0
success	41	58.6
failure	29	41.4
PP population	66	100.0
success	41	62.1
failure	25	37.9

Table 3: Percentage of diseased target nail surface (FAS).

	Baseline N=70	Month 3 (V 2) N=67	Month 6 (V 3) N=66
Mean $\pm$ SD	38.1 $\pm$ 20.2	29.3 $\pm$ 19.4	22.8 $\pm$ 20.4
Min-Max	10 - 100	5 - 100	0 - 90
Difference vs. baseline	—	-9.0 $\pm$ 11.1	-15.6 $\pm$ 17.9
Min-Max	—	-50.0 - 5.0	-90.0 - 20.0

was categorized as not related to the treatment.

This study, even within the limits of the small patient number and the NIS design (KOH microscopy as primary mycology assessment and lack of an active reference comparison), showed a clinical benefit with P-3051 in patients who failed to respond to an onychomycosis treatment with amorolfine. The non-interventional nature of the study reflects the normal clinical practice of the country in which the study had to be performed: in particular German Ethical Authorities approved the study with the recommendation to perform culture and KOH at baseline to confirm the diagnosis of onychomycosis and to follow the outcome of direct examination by KOH microscopy. Therefore culture was not considered compulsory at each visit and the assessment of culture was used as secondary endpoint as not always performed. In clinical practice, KOH microscopy is easier, faster and cheaper, and it is known that culture evaluation gives many false negative results, due to subjectivity in collecting nail specimens. Instead, KOH gives much fewer false negatives and "absence of a proof is not a proof of absence" [4]. A weak point of this study was the lack of an active reference comparison. On the other hand, as the selected patients were resistant to amorolfine, no therapeutic option was available other than ciclopirox, and randomising part of the patients to placebo would not have been an option from the ethical point of view.

Amorolfine is commonly believed to be an effective treatment of onychomycosis but the scientific data are controversial [1,7,10-11]. Even a combination of amorolfine used topically in conjunction with oral terbinafine gave contradictory results in terms of benefit to the patient [12-14]. Although it is a potent anti-fungal agent in *in vitro* studies [15], amorolfine shows a very poor penetration into the nail plate both in *in vitro* models and *in vivo* studies in healthy volunteers [16-18] and a high

failure rate (even if probably underestimated) was reported in the only available controlled randomized study [1]. According to therapeutic guidelines and common clinical practice [6,19-22], those failed patients should undergo a subsequent active treatment with oral terbinafine or itraconazole despite cross resistance among amorolfine, terbinafine and itraconazole, due to a similar mechanisms of action, having been recently described in an *in vitro* study [23].

Conversely, Ciclopirox has no resistance potential and does not show cross resistance with the membrane ergosterol biosynthesis inhibitors [23] and has already showed a statistically significant clinical efficacy when formulated with hydroxypropyl chitosan technology (P-3051) [8].

The present study showed that treatment failures with amorolfine 5%, subsequently treated with P-3051 for 24 weeks, resulted in a statistically and clinically significant high success rate.

The effect of P-3051 was revealed in terms of mycological cure (composite endpoint including both conversion to negative of the KOH and conversion to negative of culture) in 60.7% of the restricted population analysed. Mycological cure is a strong independent endpoint for evaluating topical anti-fungal treatment and is superior to the evaluation of culture only, as positivity to KOH overcomes the false negative results of culture [9].

Moreover, a clear clinical improvement of the target nail has been shown for P-3051 after a 24-week treatment, compared to baseline.

CONCLUSION

In conclusion, our study gives hints that a second line course of treatment with P-3051 in amorolfine failures could be of benefit. This would represent an advantage for patients both in terms of cost to benefit and risk to benefit ratio.

Of course, further, randomized and controlled studies with larger patient numbers are required to confirm the role of Ciclopirox HPCH topical treatment in the management of onychomycosis.

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Conflict of Interest

There is not any significant interest in the Study Sponsor

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