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Retrospective observational study in patients with onychomycosis treated with Mycoclear and ciclopirox

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Abstract

The prevalence of onychomycosis in adults varies considerably between countries. In a recent survey conducted in Italy, the prevalence of onychomycosis in subjects aged >65 years was found to be as high as 35%. The most prevalent clinical variant of onychomycosis is distal and lateral subungual onychomycosis (DLSO), which affects both finger and toenails in 58–85% of cases. The fungus (usually dermatophytes) enters the nail through the distal subungual and lateral nail groove. The primary objective of this observational, retrospective study is to evaluate the effectiveness of Mycoclear, a medical device widely used as an antifungal in outpatient clinical practice, by the Clinical Cured Index, compared with ciclopirox, an antifungal drug commonly used as a therapeutic option in dermatology. The data collected pertains to patients who were treated at the Department of Dermatology at the IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola in Bologna, Italy, between January 1, 2019, and April 30, 2023. The primary outcomes are the Investigator Global Assessment of Efficacy, mycological assessment, and healthy nail growth. In accordance with the clinical practice of the involved center, patients are evaluated using the Clinical Cure Index as follows: complete cure, partial cure, or no cure. Secondary outcomes are the Patient Global Assessment of Efficacy, the Patient Assessment of Usability, and the incidence of adverse events. Included patients are men and women aged 18 years or older with distal and lateral subungual onychomycosis (DLSO) (≤30% involvement of the nail plate of at least one of the great toenails) evaluated as mild to moderate following OSI. In addition, patients must have positive microscopy (direct KOH) and a positive fungal culture for dermatophytes. It is not permitted for patients to have used systemic antifungal agents within the previous six months or topical antifungal agents on toenails within the previous six weeks. Patients were treated for a period of six months, in accordance with the clinical practice of the center, and were visited at baseline, week two, four, 12, and 24 (final visit). The calculated sample size for the study is 40 patients per group. This study is not funded by any grants.

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Code and version

2 Code of the study: ONYCO/23
Protocol version: 1.0
Date: May 15, 2024

Title

3 Retrospective, observational study in patients with onychomycosis treated with Mycoclear and ciclopirox

Background and rationale

4 The prevalence of onychomycosis in adults varies considerably between countries, ranging from 1.9 to 6.8% in the USA[1], 8.4% in the Finnish population,[2] 8.9% (95% CI: 4.3-13.6) for the hospital-based studies, and even may be as high as 35% in the subjects > 65 years, as evidenced recently in a survey performed in Italy[3]. Although onychomycosis is rarely life-threatening, its high prevalence, the frequency of incomplete cure, have a negative impact on the quality of life of patients and make this pathology an important public health problem. As the nail unit acts as a barrier to exogenous substances, its physiological characteristics impede drug penetration, making the treatment of onychomycosis
a challenge. In addition, the nail plate has a very slow growth rate, and treatments usually required to achieve significant improvement of the infection have a long duration. Dermatophytes are the most frequently implicated causative agents in onychomycosis (approximately 90% in toenail and 50% in fingernail). The dermatophyte *Trichophyton rubrum* (*T. rubrum*) is the most common causative agent followed by *T. mentagrophytes*[4]. Distal and lateral subungual onychomycosis (DLSO) is the commonest clinical variant (58–85% of all cases)[5] affecting both finger and toenails in which the fungus enters via the distal subungual and lateral nail groove. This clinical presentation of onychomycosis is usually caused by the dermatophytes and may develop on the fingernails, toenails, or both, with infection of the toenails being much more common than infection of the fingernails. Currently, both oral and topical antifungal treatments are available, systemic antimycotics being the most effective and those indicated
in moderate and severe forms. However, use of systemic treatments (terbinafine and itraconazole) must be balanced against the risk of drug interactions and adverse effects,

the most frequent of which are gastrointestinal effects, headache, and minor rashes. Oral antifungals should be administered for 2 months in fingernail disease and 3 months in toenail onychomycosis. Topical antifungals (ciclopirox olamine and amorolfine in nail lacquers) are effective in mild forms of onychomycosis (involving less than 30% of one or 2 nails) and require daily or weekly application for a long time: 6 months for fingernails and 12 months for toenails.[6] The safety of ciclopirox is demonstrated by data in the medical literature showing that approximately 3% of the applied product is excreted in the urine within 48 hours of application, with a renal elimination half-life of approximately 5.5 hours[7]. Although ciclopirox is classified by the FDA as pregnancy category B and no problems have been reported with topical application during pregnancy, treatment of onychomycosis with this product should be delayed in pregnant and breastfeeding women[8]. Mycoclear acts as a mechanical film-forming barrier that fills the nail surface and isolates the nail from external and environmental aggressors. It is registered as a medical device and has no pharmacological activity. Consequently, no data are collected on its bioavailability after topical administration. The safety level of Mycoclear and the acceptability of its risk/benefit ratio are demonstrated by the results published in the medical literature[9] and the PMS data collected by the manufacturer.

Importance of the study and its clinical relevance

5 The antifungal activity of Mycoclear is demonstrated by both in vitro tests and articles on individual device components. This evidence was also supported by data from the published literature on the medical devices considered equivalent to Mycoclear under the Medical Device Directive (MDD). Although Mycoclear appears to be widely used in clinical practice, and its efficacy in antifungal treatment is recognized by both prescribers and patients, there is only one open-label study published in the literature[9] and no controlled clinical trials on its efficacy. The present study aims to fill this gap by analyzing the efficacy of Mycoclear in a normal outpatient clinical setting and in comparison with a commonly used antifungal agent such as ciclopirox, which is also included in international guidelines as a key recommendation for topical treatment of mild to moderate nail infections[6]

Primary Objective

6 The primary objective of the study is to evaluate the effectiveness of Mycoclear, a medical device widely used as an antifungal in outpatient clinical practice, by the Clinical Cured Index[10] (see definition reported in section 8), compared with ciclopirox[11], that is an antifungal drug commonly used as therapeutic option in dermatology.

Secondary Objectives

7 Patients' assessment of usability, subjective evaluation, and safety of the tested products will be secondary objectives. Regarding the safety, the favourable safety profile of ciclopirox was demonstrated by a wide use as drug for more than 40 years and in several trials. Since it is topically applied, side effects are localized including periungual erythema and erythema of the proximal nail fold (5%), nail disorders (1%), reactions and/or burning of the skin (1%) in the application site, and periungual erythema (1%)[12,13]. The safety profile of the medical device Mycoclear was evidenced by the post-marketing data showing only two adverse events reported out of about 200.000 pieces sold, and by the number of adverse events reported in the medical literature for a medical device with similar ingredients (two cases)[14].

Outcomes

8 All outcomes utilized in this study are validated by the medical literature and used in normal clinical dermatology practice.

Primary outcome

- The primary objective will be assessed by the following outcomes:

Investigator Global Assessment of Efficacy (IGAE)[15]: It is the assessment of target nail colour, surface, and thickness using a 3-point scale (0=no change; 1=moderate improvement; 2=excellent improvement) at baseline and 4-, 12-, and 24-week visits.

- Mycological assessment: mycologic evaluations will be performed at baseline and at the 2-, 4-, 12-, and 24-week visits. This will include KOH staining[16] and collection of a sample for culture. The investigator will assess the clinical change of onychomycosis of the target nail according to the following categories: negative culture= cure; positive culture= failure.

- Healthy nail growth: on measuring in mm the distance a scratch-mark on the nail. The procedure is performed by the investigator at baseline and at 4-, 12-, and 24-week visits. The nail measurement represents a standard and widely used tool in most clinical trials evaluating the effectiveness of therapy for toenail onychomycosis.

As for clinical practice, patients will be evaluated using the Clinical Cure Index[10] with the following scores:

- Complete cure: defined as negative fungal culture on collecting sampling, no growth of dermatophytes in culture examination, progressive growth of normal nail (at least 4 mm), and resolution of all clinical symptoms (excellent improvement using the IGAE) at 24-week visit.
- Partial cure: defined as negative fungal culture on collecting sampling, no growth of dermatophytes in culture examination, progressive growth of normal nail (at least 4 mm), and partial resolution of all clinical symptoms (moderate improvement using the IGAE) at 24-week visit.
- No cure: it is any other mycologic and/or clinical evaluation.

Secondary outcome

- Patient Global Assessment of Efficacy (PGAE)[17]: patients will perform a global assessment of treatment efficacy using a 4-point scale (0=no change; 1=moderate improvement; 2=good improvement; 3=excellent improvement) at the final visit (week 24).
- Patient Assessment of Usability (PAU)[18]: the patient will respond to a usability questionnaire specifically designed to assess the usefulness, ease of use, ease of instruction, satisfaction, and tolerability of the tested medical device. The questionnaire items (ranging from 1-10: 1 = poor rating, 10 = excellent rating) will be completed at the final visit (week 24).
- Incidence of adverse events (AEs), serious adverse events (SAEs), adverse device effects (ADEs), and serious adverse device effects (SADEs) for the two products. These parameters will be collected by Investigators only if they are not reported as part of clinical practice in the previous visits performed on the patients.

Study Type

9 Retrospective Cohort Study
Monocenter Study at the Department of Dermatology at the IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola (Bologna, Italy)

Study Design

10 This is an observational, spontaneous, monocentric, retrospective, non-inferiority, drug versus medical device clinical trial that requires the collection of data from two cohorts of patients affected by DLSO, treated according to current clinical practice with the drug ciclopirox or with the medical device Mycoclear, and visited the Department of Dermatology at the IRCCS Azienda Ospedaliero-Universitaria
Sant'Orsola (Bologna) during the period from January 1, 2019 to April 30, 2023 The research hypothesis (or null hypothesis) states that the Mycoclear nail fungal solution treatment is not inferior to the ciclopirox topical solution by more than the 'non-inferiority margin ' indicated in the sample size section.

Study Population

11 The study population will be outpatients affected by mild to moderate onychomycosis as for onychomycosis severity index (OSI)[19]. Any patient who had a dermatology visit at the Dermatology Department at the IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola (Bologna) from January 1, 2019 to April 30, 2023 and was treated with Mycoclear nail fungal solution or ciclopirox topical solution could be enrolled and his/her data could be retrospectively collected in the study.

Inclusion criteria

12 Patients will be eligible for inclusion if ALL the following criteria are respected:

- Age ≥ 18 years old.
- Patients, otherwise healthy, clinically diagnosed with DLSO (≤30% involvement of the nail plate of at least one of the great toenails) and evaluated as mild to moderate following OSI[6].
- Patients presenting positive direct potassium hydroxide (KOH) microscopy and positive fungal culture for dermatophytes.
- Patients visited in the involved site from January 1, 2019 to April 30, 2023 and able to do self-administration at home of the tested products (Mycoclear or ciclopirox), for the whole duration of the treatment.
- Patients able to communicate adequately with the Investigator and understand the questions contained in the questionnaire.
- Patients able to understand and who can provide valid signed informed consent to the study.

Exclusion criteria

13 Patients fulfilling one or more of the following exclusion criteria will NOT be included in the study:

- Other clinical types of onychomycoses.
- Subjects who used systemic antifungal agents within 6 months or topical antifungal agents on toenails within 6 weeks of screening.
- Pregnant woman, lactating woman, and woman of childbearing potential who is planning a pregnancy.

Number of patients and sample size calculation

14 The target sample size is based on the IGAE [15] evaluated at 24 weeks after the start of treatment, which is the primary endpoint with expected values as reported in similar studies[20,21]. We performed a meta-analysis of the primary outcome for ciclopirox, with the values obtained from Gupta K[20]. The reported results from nine trials yielded a clinical response rate of 64.8% (ratio of subjects reporting any clinical improvement to the total number of subjects). We assumed that Mycoclear will achieve a clinical response rate of 52.5%. Our hypothesis was that Mycoclear is not inferior to ciclopirox by a margin of 15%. Consequently, by performing a binomial test of proportions between the clinical response rates of the two products, with a significance level of 5% and a power of 20%, we calculated the required sample size of 40 patients for each group as necessary.

Study duration and Timing

15 The starting date of data collection is planned for year 2024, but in any case it must be after the approval of the Ethic Commette and the issuance of the authorization (nulla-osta) of the General Director of Bologna IRCCS. The observational retrospective period is from January

1, 2021 to April 30, 2023. The study duration will be 18 months (also considering the statistical analysis).

Treatments, visits and examinations

16 The medical device Mycoclear and the drug ciclopirox (and any concomitant medication given) were
administered from January 1, 2019 to April 30, 2023 as indicated in the respective instructions for use of the products and the patients were visited at baseline and at 2, 4, 12, 24-week visits according to the clinical practice of the site.

Flow Chart

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Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Baseline				End of Study
	from week -5 to day -1	day 0	week 2 (± 2 days)	week 4 (± 2 days)	week 12 (± 4 days)	week 24 (± 7 days)
Inclusion Criteria	X					
Exclusion Criteria	X	X	X	X	X	X
Demographics and Medical History	X					
Physical examination and Vital signs	X	X	X	X	X	X
Concomitant treatments and medications assessment	X	X	X	X	X	X
Indication of the DLSO chosen as target nail	X					
Photos of target nail		X	X	X	X	X
Mycologic evaluation	X		X	X	X	X
Healthy nail growth measurement (by Investigator)		X		X	X	X
Investigator Global assessment of efficacy (IGAE)		X		X	X	X
Patient Global assessment of efficacy (PGAE)						X
Patient assessment of usability (PAU)						X
Clinical Cure Index				X	X	X
Tested Products supply		X				
Tested Products collection						X
AE, SAE, ADE, SADE These parameters will be collected by Investigators only if they are not reported as part of clinical practice in the previous visits performed on the patients		X	X	X	X	X

Table 1. Flow Chart

Assessments

18 The first visit assessments are:

- Clinical history/current therapy
- Previous therapies
- General evaluation
- Laboratory tests
- Outpatient visits and/or specialized examinations
- Photos of the target nail

The follow up visits assessments are:

- Laboratory tests
- Outpatient visits and/or specialized examinations
- Administration of questionnaires
- Photos of the target nail

Timing of the follow-up visits

19 The data collected are related to patients seen in the standard 'usual care' that took place at Dermatology Department at the IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola (Bologna), and therefore patients were seen at the intervals provided by the normal clinical routine of the centre regardless of their participation in the study. Patient data will be collected retrospectively and numbered following a chronological order. Each patient retrospectively enrolled will be identified by the patient number, a five digits code (e.g., 01.001), which will be the only identification element and will be used only for the purposes of this study. This code will consist of the Centre number (01 corresponding to the Bologna Centre) and of the sequence number of the patient (e.g., .001, which means the 1st patient enrolled). Only the patients fulfilling the eligibility criteria can be enrolled. The standard clinical practice of the Centre required the following procedure for each patient visited for onychomycoses:

- In the initial standard dermatological visit the medical doctor defined the DLSO chosen as target nail, made the initial assessment of the nail growth, and performed the mycological examination (direct KOH microscopy and mycologic culture). The medical doctor also took photographs and provided the initial assessment of treatment efficacy.
- At the week 2± 2 days (visit 3) the medical doctor performed the mycological evaluation and photographs of target nail.
- In the visits at week 4 ± 2 days (visit 4) and week 12 ± 4 days (visit 5) the medical doctor performed the mycological evaluation, healthy nail growth measurement, IGAE, and photographs of target nail.
- In the final visit at week 24 ± 7 days (visit 5) the medical doctor performed the mycological evaluation, healthy nail growth measurement, IGAE, PGAE, PAU, and photographs of target nail.

Funding

20 This study is not funded by any grants.

Data management

21 The clinical data required by the protocol will be collected in anonymized form by personnel designated by the Principal Investigator in a Case Report Form (CRF) and will be managed through the REDCap UNIBO platform.

Statistical Analysis Plan: Methodology of analysis

22 A two-sided p-value of 0.05 or less will be used to declare statistical significance for all analyses. Similarly, all confidence intervals will be calculated at the 95% level. If a patient is missing information for one or more variables, the missing data will not be replaced. All statistical analyses will be performed using the R statistical software (v 4.2.1; R Foundation for Statistical Computing), or the latest stable version at the time of statistical analysis. The overall type I error rate will be preserved at 5%. All tests will be two-sided. Statistical analysis will be performed on patients whose data have been collected retrospectively from all visits specified in the protocol, without any protocol deviation affecting the assessment of key variables (as per protocol). The quality and completeness of the collected data will be evaluated preliminarily compared to data analysis. If a patient is missing information for one or more variables, the missing data will not be replaced. If a patient has been involved in violation of inclusion/exclusion criteria, the respective data will be excluded from the analysis. Quantitative variables (i.e., demographic) if normally distributed will be described through media, standard deviation (SD); non-normally distributed variables will be described using median and range of interquartile. The Student's t-test and the Mann-Whitney U will be employed to perform comparative analysis in accordance to the distribution of these variables. Categorical variables will be finally described using frequencies and percentages and comparative analysis will use the $\chi 2$ test. The safety analysis will be done on the safety population. Minor deviation from the original statistical plan (SAP) will be considered acceptable (e.g., due to non-parametrical form of the data, statistical tests will be adjusted accordingly). Major deviations from the SAP will result in clinical trial protocol amendments and will be evidenced in the final report. Additional details about statistical analysis will be documented in the Statistical Analysis Plan (SAP), enclosed to the Trial Master File.

Statistical Analysis Plan: Risk factors, confounders and effect modifiers

23 Considering this retrospective study on the treatment of onychomycosis and the existing medical literature, we can categorize the following variables as potential risk factors, confounders, or effect modifiers:

Sex

Role: Can be considered an effect modifier.

Explanation: Sex may influence how individuals respond to the treatment, as there could be gender-related differences in the prevalence and presentation of onychomycosis.

Age range

Role: Can be considered a risk factor.

Explanation: Age is often associated with an increased risk of onychomycosis, as the condition is
more common in older individuals. It's a risk factor that can affect the likelihood of developing the condition.

Nail involvement

Role: Can be considered a risk factor.

Explanation: The extent of nail involvement (e.g., the percentage of the nail affected) can impact the severity of onychomycosis and potentially the treatment outcome. Greater nail involvement is a risk factor for more severe cases.

Healthy nail growth (mm)

This parameter is also an outcome of the study.

Role: Can be considered an effect modifier.

Explanation: The rate of healthy nail growth can affect the evaluation of treatment success. It may be an effect modifier if it influences the response to treatment.

Nail appearance (transparency, surface, thickness)

Role: Can be considered confounders.

Explanation: Nail appearance characteristics like transparency, surface, and thickness could confound the assessment of treatment outcomes. They may influence the perception of treatment efficacy, so it's essential to account for them in the analysis.

KOH staging

Role: Can be considered an effect modifier.

Explanation: KOH (potassium hydroxide) staging is a diagnostic criterion for onychomycosis and may influence the response to treatment. It may be an effect modifier if it affects how individuals respond to the treatment.

Mycological culture

Role: Can be considered a confounder.

Explanation: Mycological culture is a diagnostic test for confirming the presence of the fungal infection. It may confound the treatment outcome assessment if it is not accounted for in the analysis.

For these parameters, we will conduct the appropriate statistical analysis after the database is locked. It should be noted in a pragmatic sense that the small sample size of the enrolled population hindered the ability to identify risk factors, confounders, or effect modifiers.

Statistical Analysis Plan: Criteria for selecting and matching controls

24 Patients treated with ciclopirox and used as the control group in this retrospective study will be the subjects who were seen according to 'usual care' at the Department of Dermatology at the IRCCS Azienda Ospedaliero-Universitaria Sant'Orsola (Bologna). Therefore, the

patients in the control group (such as those treated with Mycoclear) were also seen at the usual clinical routine schedules at the centre regardless of their participation in the study.

Strategies for disseminating results and enabling reproducibility of research

25 The Investigator agrees to publish the results at the end of the study. For this purpose, the clinical study will be registered on an open science platform (e.g., the present protocols.io, and/or OSF,). Any formal submission or publication of data derived from this study should be considered a publication by the Investigator.

Strategies for disseminating study results

26 During the project the Investigators will develop a dissemination plan to clarify the target audience, and determine the scope, objectives, format, style, and wording of the communication as well as the appropriate tools for dissemination.

Data access policy

27 Data from this study will be made available to other researchers only as anonymous aggregated data.

Administrative procedures and statements

28 **Informed Consent and consent to personal data processing**
This section is not applicable, since in the present retrospective study will be collected anonymous data only.
Amendments to the protocol and changes to the conduct of the study
Any changes to the protocol will be made in the form of an amendment, to be submitted to the Ethics Committee. No other mode of amendment to the protocol is allowed during the study period. Any unexpected changes in the conduct of the study will be recorded in the "Clinical Study Report".
Study conclusion
The Investigator agrees to report completion of the study and to send at least one abstract or publication derived from the study to appropriate.
Archive of documentation
The Investigator is responsible for storing and preserving essential study documents before, during the conduct and after the completion or termination of the study, in accordance with current regulations and GCP and related timelines. The data collected in the CRF will be in a strictly anonymous form, and the subject will only be identified with a number/code.
Audits and Inspections
If a Regulatory Authority requests an inspection, the Investigator should immediately notify the Ethics Committee.
Contact Persons

The phone numbers and emails of the contact persons for conducting the study can be found in the Investigator Folder at the centre.

List of abbreviations

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A	B
ADE	Adverse Device Effects
AE	Adverse Events
AOU	University Hospital Corporation (Azienda Ospedaliera Universitaria)
ASADE	Anticipated Serious Adverse Device Effect
CRF	Case Report Form (Scheda Raccolta Dati)
CRO	Contract Research Organization
GCP	Good Clinical Practice (Norme di Buona Pratica Clinica)
DLSO	Distal and Lateral Subungual Onychomycosis
IGAE	Investigator Global Assessment of Efficacy
IRCCS	Scientific Institute for Hospitalization and Therapy (Istituti di Ricovero e Cura a Carattere Scientifico)
PGAE	Patient Global Assessment of Efficacy
MDD	Medical Device Directive
PAU	Patient Assessment of Usability
SADE	Serious Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
KOH	Potassium hydroxide
SAP	Statistical Analysis Plan

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