An open, single center pilot study of efficacy and safety of topical MOBO15B in the treatment of distal subungual onychomycosis

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Introduction

Distal subungual onychomycosis (DSO) is a fungal infection that results in thickening, discoloration and splitting of the finger/toe nails, and lifting of the nail from the nail bed. The prevalence of DSO in Western adult populations is 2–14% [1] and incidence increases with age [2]. Difficult to treat, DSO can significantly affect a patient's self esteem. The difficulty in treating DSO results from the deep-seated nature of the infection within the nail unit (nail plate, nail bed and surrounding tissue) and the inability of drugs to penetrate all sites effectively.

Although they are the most effective treatment for DSO, only 20–50% of patients respond to oral systemic drug therapy which can trigger adverse drug reactions and drug interactions.

MOB015B is a topical treatment for DSO that contains 10% terbinafine, a well known anti fungal agent. In vitro, it has been demonstrated that MOB015B can effectively penetrate the nail tissue and deliver terbinafine at sufficient efficacious concentrations into the nail and through the nail [3; data on file, Moberg Pharma].

We report here the clinical outcome data with MOB015B in a well designed, Phase IIa pilot study in patients with DSO. We also describe for the first time results from biopsies of nail and nail bed tissue to determine drug concentration from patients undergoing treatment for DSO.

Objectives

To evaluate the efficacy and safety of topical MOB015B in adults with DSO.

Methods

Study design: An open, single centre Phase IIa pilot study of 48 weeks of MOB015B topical treatment in adults ≥18 years with DSO. Diagnosis of DSO was confirmed by fungal culture positive for dermatophytes on a target great toenail with 25–75% nail involvement and >2 mm of unaffected proximal nail. The study comprised a screening visit, baseline visit, five treatment period visits (4, 12, 24, 36 and 48 weeks) and one post treatment follow up visit/wash out period (at 60 weeks). A control was not used as the primary efficacy variable was an objectively assessed parameter.

Treatment: MOB015B, in the form of a moderately viscous solution was applied once daily to affected nails at bedtime for 48 weeks.

Analysis: The primary analysis of the study was the proportion of patients with mycological cure defined as negative fungal culture and direct microscopy, at 60 weeks in the target nail. Secondary analyses included number of patients with negative fungal culture, negative direct potassium hydroxide [KOH] microscopy, and physician's global evaluation score [GES] = 4 or 5; patient's subjective score; and terbinafine concentration in the nail and nail bed and plasma.

Punch biopsies: A treated non target nail was carefully cleaned with alcohol and following local anaesthesia, a nail sample was obtained using a 4 mm punch biopsy. Following this, a 3 mm punch biopsy was introduced into the hole and a tissue biopsy was obtained from the nail bed.

Results

Patients' baseline characteristics. Twenty five patients received at least one application of MOB015B and 24 (96%) completed the trial. All patients were male and Caucasian.

The inclusion criteria allowed for target nails with 25–75% affected nail area, but post hoc analysis of the target nail photographs at baseline revealed that 17 (68%) patients had more than 50% affected nail area at inclusion.

Week	All patients (N=25) n (%)
12	6 (24%)
24	10 (40%)
36	11 (44%)
60	13 (52%)

n=number of patients.

Table 1. Number (%) of patients with mycological cure of target nail following treatment with MOB015B. The number of patients with mycological cure of target nail increased throughout the study period. Mycological cure was achieved by 13 (52%) patients at 60 weeks.

Week	All patients (N=25) n (%)	
	Negative fungal culture	Negative direct KOH microscopy
12	24 (96%)	6 (24%)
24	24 (96%)	10 (40%)
36	25 (100%)	11 (44%)
60	25 (100%)	13 (52%)

n=number of patients; KOH= potassium hydroxide.

Table 2. Number (%) of patients with negative fungal culture and/or negative direct KOH microscopy of the target nail following treatment with MOB015B. Almost all patients (24/25; 96%) achieved negative fungal culture at the first assessment time point (12 weeks); all 25 patients had negative fungal culture from 36 weeks onwards. The proportion of patients with negative direct KOH microscopy increased steadily over the study period and reached 13 (52%) at 60 weeks.

Number (%) of patients with negative fungal culture, negative direct KOH microscopy and physician's GES = 4 or 5*. The number of patients with mycological cure and excellent clinical improvement or cure increased from 0 at 12 weeks, 1 (4%) at 24 and 36 weeks to 7 (28%) at 60 weeks.

*GES = global evaluation score, 1 no change (no detectable improvement from screening evaluation), 2 slight improvement (<50% clearance of clinical signs of disease), 3 moderate improvement (at least 50% but less than 75% clearance of clinical signs of disease), 4 excellent clinical improvement (at least 75% but less than 100% clearance of clinical signs of disease), 5 cured (100% clearance of clinical signs of disease).

Week	Score	All patients (N=25) n (%)
24	1	5 (20%)
	2	6 (24%)
	3	12 (48%)
	4	2 (8%)
	5	0
36	1	4 (16%)
	2	11 (44%)
	3	8 (32%)
	4	2 (8%)
	5	0
48	1	5 (20%)
	2	10 (40%)
	3	7 (28%)
	4	3 (12%)
	5	0
60	1	6 (24%)
	2	5 (20%)
	3	8 (32%)
	4	4 (16%)
	5	2 (8%)

n=number of patients.

Table 3. Patient's subjective score* following treatment with MOB015B.

The patient's subjective score increased during the study with 14 (56%) patients reporting at least a substantial improvement in DSO at 60 weeks.

*1=no improvement (no signs of improvement/worsening), 2=some improvement (some improvement, but not of any relevance for the patient), 3=improvement (substantial improvement and reduction of patient's symptoms), 4=almost cured (most symptoms have disappeared), 5=cured (completely cured without any symptoms).

Terbinafine concentration in nail plate and nail bed at 24 weeks and in plasma at 4 weeks

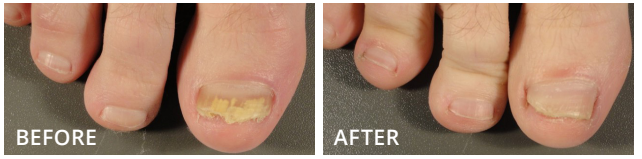
High concentrations of terbinafine were detected both in the nail plate (median: 1610 µg/g; N=8) and nail bed (median: 45 µg/g; N=8) tissue.

Low concentrations of terbinafine were detected in plasma (median: 656 pg/mL; N=8).

Safety

Two (8%) patients experienced one adverse event each of periungual skin irritation assessed as probably related to MOB015B. One AE of skin irritation of moderate intensity led to patient withdrawal at week 36.

Figure 1. Photographs of a patient's target nail before and after MOB015B treatment.



Discussion

Mycological cure of DSO was achieved by 13 (52%) patients and was higher than those previously shown for topical onychomycosis treatments which have typically ranged from 29 to 35% [4, 5]. Recently published data for tavaborole and efinaconazole show mycological cure rates of 36–55% [6]. However, these studies included target nails with a lower degree of disease involvement than in this study (the majority of our patients had >50% disease involvement). In the case of efinaconazole, the mean area of target nail involvement was 36% [7].

Excellent clinical improvement or cure of the target nail, in conjunction with mycological cure, was observed in 7 (28%) patients. Notably, all patients had negative cultures at the follow up visit, 12 weeks post treatment (60 weeks).

We are the first to describe results from punch biopsies performed on patients undergoing treatment for DSO. High terbinafine concentrations were detected in both the nail plate and the nail bed, indicating effective MOB015B penetration into the nail unit with several orders of magnitude over the minimum inhibitory concentration for dermatophytes (0.001–0.1 µg/g). Low concentrations of terbinafine were detected in plasma, which were ~1000x lower than following orally administered terbinafine [8].

As might be expected for a topical treatment, two patients experienced transient irritation of the skin around the treated nails. This could be due to excessive application of MOB015B and leakage onto periungual skin. These convincing Phase II data warrant further investigation in randomised, controlled Phase III studies.

Conclusions

Daily topical administration of MOBO15B was an efficacious treatment for DSO leading to mycological cure in over half the patients.

Clinically significant improvement of the target nail in conjunction with mycological cure was observed in a high proportion of patients.

High terbinafine concentrations in nail and nail bed tissue and low plasma concentrations were observed.

MOB015B was safe and well tolerated.

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