Efficacy and tolerability of amorolfine 5% nail lacquer in combination with systemic antifungal agents for onychomycosis: A meta-analysis and systematic review

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1 | INTRODUCTION

Onychomycosis is a common, disturbing and difficult-to-treat medical problem (Midgley et al., 1994). It not only causes cosmetic disfigurement, but also may have an impact on patients’ emotional, social and occupational functioning, thus affecting the overall quality of life (Elewski, 1998). It accounts for at least 30% of superficial fungal infections and for up to 50% of all consultations for nail disorders (Scher, 1994). Despite the advent of new systemic antifungal agents, treatment of onychomycosis remains challenging. Treatment failures including lack of immediate response and high incidence of relapse. Therefore, it is worthwhile to consider the combination of systemic and topical antifungals to improve the cure rates further, prevent the recurrences and to reduce the duration of systemic treatment as well as the associated risks and cost. Amorolfine is a morpholine derivative with antifungal and fungistatic activity, introduced in 1981 (Zuag & Bergstraesser, 1992). It interferes with the production of ergosterol in the fungal cell membrane by inhibiting 14α-reductase and 7,8 isomerase (Borgers, 1980). The highest activity is exerted against dermatophytes, but it is also active against yeasts and molds. Although combination therapy combining oral and topical treatments is thought to be the most effective method and is already widely adopted by a large amount of clinicians, but it is not well evidence-based because of a lack of comprehensive statistical data to support it. So as to get a better knowledge about amorolfine in combination with other systemic antifungals, we performed a meta-analysis of the efficacy and adverse effects of these combinations in treating onychomycosis, based on published randomized, controlled trials (RCTs).

2 | MATERIALS AND METHODS

2.1 | Inclusion criteria

We retrieved all the randomized controlled trials comparing combination of amorolfine 5% nail lacquer and systemic antifungal agents with monotherapy of systemic antifungal agents or other combinations in patients with a diagnosis of onychomycosis (≥11 years of age).

2.2 | Outcome measures

The primary outcome is complete clearance (defined as achieving both clinical cure and mycological cure). Secondary outcomes were adverse events and cost-effectiveness.
2.3 | Literature search

Databases used for searching relevant studies were Pubmed, Ovid, The Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI). The following keywords were used to search in all databases: (amorolfin OR antifungal combination) AND (onychomycosis).

2.4 | Quality assessment and data extraction

Two researchers assessed the methodological quality of included trials independently according to the Jadad Scale (all the five articles we choose were >4). Disagreements on validity assessment were resolved through discussion or consultation with a third researcher. Basic information obtained from each eligible study included the proportion of patients achieving complete clearance after a relatively long enough treatment course, the proportion of patients with any adverse event, and the average cost-effectiveness of each method.

2.5 | Statistical analysis

Statistical analysis was performed in Review Manager Software (Review Manager Version 5.2 software for Windows; The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, England). Heterogeneity of results between each trial was tested using the chi square test ($p > .1$, $I^2 < 50\%$). Meta-analysis was performed in the fixed effect model if no heterogeneity was found between subgroups, otherwise the randomized effect model was used, and comparison of the effects between two groups was expressed by OR and its 95%CI (Feng et al., 2014; Light & Pillemer, 1984).

3 | RESULTS

Five articles met all the entry criteria and were included in the study (Baran et al., 2000, 2007; Jaiswal, Sharma, & Garg, 2007; Lecha et al., 2002; Rigopoulos et al., 2003). The study flow diagram is shown in Figure 1. A total of 713 patients were included; the cohort for efficacy analysis was composed of 382 in the experimental combination group and 400 in the controlled group. The cohort for adverse events was composed of 217 in the combination group and 225 in the controlled group.

3.1 | Meta-analysis of efficacy

The combination of amorolfine nail lacquer and systemic antifungal agents appears to show a statistically significant difference compared with the monotherapy of systemic antifungal agents, which indicated that amorolfine nail lacquer in combination with oral antifungals can get a much higher percentage of complete clearance than those treated with monotherapy of systemic antifungal agent like terbinafine and itraconazole (OR = 1.97, 95%CI = 1.44–2.69) (Figure 2). From this study, we are unable to obtain enough evidence to identify if amorolfine nail lacquer in combination with oral antifungals is more effective than the combination of ciclopirox olamine 8% and oral antifungals.

3.2 | Meta-analysis of safety

There were only two trials we can adopt for pooled analysis, which showed no statistically significant risk of adverse events between the combination group and the monotherapy group (OR = .96, 95%CI = .56–1.63, $p = .95$) with low heterogeneity ($p = .76$, $I^2 = 0\%$) (Figure 3). Most of the adverse events were found to be related to the systemic antifungal drugs, the most frequent complaints were gastrointestinal disturbances (nausea, abdominal pain) and slight to moderate increases in liver function enzymes which occurred early in the course of treatment. Addition of amorolfine nail lacquer to systemic therapy did not present an increase in safety risk. Adverse events related to amorolfine may be in-grown toenail and constipation. And in the trial conducted by Jaiswal et al. found that adverse events related to topical ciclopirox were observed in 2 patients, while none observed on the application of amorolfine (Jaiswal et al., 2007).

4 | DISCUSSION

To the best of our knowledge, this study is the most comprehensive evidence-based review to date of the combination of amorolfine nail lacquer and systemic antifungal agents in the treatment of onychomycosis, with the data on 713 patients ($\geq$11 years old) from five RCTs. In this meta-analysis, we only extract the related information about the
FIGURE 2  Forest plot analysis of percentage of patients who achieve the complete clearance; M–H, Mantel–Haenszel. Pulse therapy: each pulse was 1 week long, with 3 weeks between successive pulses.

FIGURE 3  Comparison of incidence of adverse events in RCTs between combination group and controlled group.
number of whom get complete clearance which is defined as mycologically clear (including both negative direct microscopy and negative culture) and clinically clear (as disappearance of all lesions or residual disease of no more than 10% of the original total suffering surface). It is recommended that topical treatment administration should continue for at least 1 year and, if necessary, up to 18 months which could produce a better clinical outcome that reflects true nail pathology (Ghanoun, Isham, & Catalano, 2014; Ghannoun et al., 2015). Furthermore, to avoid the diagnostic bias, a significantly longer washout period (e.g., 3–6 months) might be necessary to ensure complete removal of nonviable fungal cells, subungal debris, and residual topical medication before assessing the final outcome (Scher et al., 2007). Based on the mentioned reasons, we employ the treatment course and follow-up time as long as every trial could get which is not standardized yet and different from each other.

Evidence-based guidelines state that the two most effective antifungals for the treatment of dermatophyte onychomycosis are orally administered fungicidal terbinafine and fungistatic itraconazole, of which the success rates vary from 20% to 80% in monotherapy (Ameen et al., 2014). While oral systemic therapy is widely used for the more severe cases of onychomycosis, lengthy systemic treatments are not short of side effects or risk of toxicity and are often accepted reluctantly by the patients (Lecha, 2001). The most effective topical antifungals, according to recent guidelines, are 5% amorolfine hydrochloride lacquer and 8% ciclopirox lacquer (Ameen et al., 2014). But it also indicates a limited role for topical antifungals as a monotherapy for onychomycosis, topical medicines are recommended only for preventing recurrence, as a part of a combination therapy, or for treating mild to moderate toenail onychomycosis (Gupta, Daigel, & Foley, 2014) as they minimize drug exposure, drug interactions and adverse events (AEs). Chen et al. reported a case report of a 16-month-old boy who had been successfully treated by 5% amorolfine nail lacquer after the diagnosis of onychomycosis, as systemic treatment with itraconazole and terbinafine in children is not approved by the Food and Drug Administration (FDA) (Chen et al., 2014). Amorolfine nail lacquer as a novel monotherapy regimen in the treatment of Neoscytalidium onychomycosis which is considered recalcitrant could also provide superior efficacy than topical urea cream with occlusion in every aspect (Bunyaratavej et al., 2016). Urea ointment under occlusion is applied as atraumatic chemomechanical maceration of the diseased nail, however, the clinical success of it alone is poor, better cure rates can be found with the combination of antifungal agent and nail removal, such as the combination of bifonazole 1% and urea ointment 40%, the efficacy of which is slightly lower than that of amorolfine 5% lacquer (Niewerth & Korting, 1999). As for fluconazole, the data for onychomycosis are limited, since its systemic use is not FDA-approved for skin or nail infections (Tan & Joseph, 2004), an in vitro study (Seidl et al., 2015) shows that amorolfine and ciclopirox had the same sporidical efficacy and kinetics for the spores predominantly occur in onychomycosis. Both were more effective than fluconazole and bifonazole against dermatophytes as well as slightly more potent against candida than terbinafine after 4 days of incubation and at concentrations of ≥10 µg/ml, although the specific sporidical mechanism for the different antymycotics is still unknown. In a vitro nail penetration model (Ghannoum, Sevin, & Sarkany, 2016), it shows that even small amounts of amorolfine alone reaching the nail bed inhibit or kill the pathogens, its use is far more better than three acid-based devices which turns out the PH cannot be low enough to be fungicidal. And in another in vitro study (Seidl et al., 2015), amorolfine demonstrated significant sporidical effectiveness on dormant T. rubrum and C. albicans cells even at the lowest tested concentration of 1µg/ml.

About 90%–95% of nail infections are caused by dermatophytes which can be treated by terbinafine, while itraconazole has also been shown to be effective in the management of dermatophytes, Candida species, and molds (Gupta & Del Rosso, 2000). No matter what kind of fungus is found the cause of the onychomycosis, 5% amorolfine nail lacquer may prove useful by increasing the efficacy of systemic drugs, offering more rapid cure and preventing relapses. Tamura et al. conducted a vitro trial (Tamura et al., 2014) which makes the combination of amorolfine and itraconazole as representative external and internal drugs for dermatophytes. It was found that this combination had synergistic or additive effects on most dermatophytes, and had no antagonistic effects, amorolfine applied on the nail plate goes into the nail keratin and then through the nail bed, whereas systemic antifungals reach the nail via the nail bed and matrix by diffusion from the dermal vessels and via the matrix by incorporation into the growing onychocytes (Finlay, 1992), the multiple drugs with different antifungal mechanisms should be used to treat refractory dermatomycoses, especially onychomycosis. In the current study, we adopt amorolfine as the representative of topical treatments, because abundant, reliable information was available on the feasibility, outcomes, and potential side effects of amorolfine in the treatment of onychomycosis (Auvinen et al., 2015). There are some other topical antifungals available in the market, but it is difficult to assess their efficacy in monotherapy due to the different criteria of recruiting patients for investigations, different study periods and post-treatment assessment (Tabara et al., 2015), there is one article which put amorolfine and ciclopirox in separate combination in comparison, it turns out that ciclopirox in combination is more efficient than amorolfine in combination, but we still need more evidence to verify it. Iorizzo et al. supported that P-3051 (a water-soluble ciclopirox 8% formulation in hydroxypropyl chitosan technology) should be considered as the gold standard for the topical treatment of onychomycosis (Iorizzo et al., 2016). Furthermore, a network meta-analysis of onychomycosis treatments (Gupta, Daigel, & Foley, 2015) pointed out that newly developed topicals (like efnaconazole topical solution 10% and tavaborole topicalsolution 5%) have improved ORs of mycological cure, but these ORs were not significantly greater than those of preexisting topical treatments (like amorolfine and ciclopirox). While topical 30% resin lacquer also showed the similar efficacy as amorolfine for treating onychomycosis (Auvinen et al., 2015).

Furthermore, lacquer is a form of drug which can maintain proper concentration of the active substance on the nail surface, and it just need to be applied once or twice weekly, which is of great convenience. And cosmetic nail varnishes would not affect the antifungal
efficacy and can be applied concomitantly with amorolfine in the treatment of onychomycosis (Sigurgeirsson et al., 2010). Long-term use of amorolfine lacquer, once every 2 weeks, was found to be effective in prophylaxis of onychomycosis recurrence in patients earlier treated with terbinafine in monotherapy or combined with amorolfine (Sigurgeirsson et al., 2016). A clinical study (Zhang et al., 2016) also suggested that combination therapy of a fractional 2,940-nm Er: YAG laser and 5% amorolfine lacquer is an effective, safe, and convenient treatment method for onychomycosis. Indeed, a combination of treatments that are effective in the long term is more cost-effective than a treatment used for a shorter period but with lower long-term efficacy, which will bring about possible complications related to the relapse or chronicity of the disease, as a consequence, adding to the patient’s overall healthcare costs (Lecha et al., 2002).

There are some limitations in our meta-analysis. Firstly, there have been few related studies published about the combination, only five RCTs were eligible and included, and little study put different combination therapies in comparison. So from this meta-analysis, we can only come up with the conclusion that the combination therapy is better than monotherapy, but whether the combination of amorolfine is preferable than the other combinations still needs more trials to confirm it. Secondly, this meta-analysis is comparatively simple, we only extract part of the results of the RCTs which are the most realistic and rigorous factors, such as efficacy, safety and cost-effectiveness. Thirdly, every trial we included did not adopt a same treatment course which have not been standardized yet, although the results we synthesized appeared to be positive, it may more or less affect the conclusion.

5 | CONCLUSION

Several factors must be considered before choosing therapy for onychomycosis: kind of pathogen, onychomycosis subtype, matrix involvement, number of invaded nails, location (toes or fingers), thickness of nail plate and coexistence of other mycoses with different location. Combination therapy has been demonstrated to be an effective and safe alternative treatment approach in patients who do not respond to monotherapy or as first-line therapy for patients who may benefit from a more aggressive therapy (Borgers, 1980). In conclusion, combined therapy of amorolfine nail lacquer and systemic antifungal agents can increases efficacy of the treatment and shortens duration of oral antifungal drug intake, so it is an effective and safe treatment modality for onychomycosis. Further clinical verification is also required, it should be tested by more large scale clinical trials.

CONFLICT OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

ACKNOWLEDGEMENT

We thank Xie Jinwei from West China Hospital, for providing language help and writing assistance. No sources of funding were used to assist in the preparation of this manuscript. All authors have no financial or personal relationships with other people or organizations that could inappropriately influence this work.

REFERENCES


How to cite this article: Feng X, Xiong X, Ran Y. Efficacy and tolerability of amorolfine 5% nail lacquer in combination with systemic antifungal agents for onychomycosis: A meta-analysis and systematic review. Dermatologic Therapy. 2017;30:e12457. https://doi.org/10.1111/dth.12457