Relative impact of traditional vs. newer oral antifungals for dermatophyte toenail onychomycosis: a network meta-analysis study

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Abstract

Background There is a paucity of evidence regarding the relative therapeutic efficacy of treatments for onychomycosis.

Objectives We determined the relative efficacy of monotherapies for dermatophyte toenail onychomycosis with Bayesian network meta-analyses (NMAs).

Methods We searched PubMed, Scopus, EMBASE (Ovid) and CINAHL to identify studies that investigated the efficacy of monotherapy with oral antifungals for dermatophyte toenail onychomycosis in adults. In this paper, ‘regimen’ corresponds to a given agent and its dosage. The relative effects and surface under the cumulative ranking curve (SUCRA) values of the various regimens were estimated; evidence quality was assessed at the study level and across networks.

Results Data from 21 studies were used. Our two efficacy-related endpoints were: (i) mycological and (ii) complete cure at 1 year; safety-related endpoints were: (i) 1-year count of any adverse event (AE), (ii) 1-year odds of discontinuation due to any AE, (iii) 1-year odds of discontinuation due to liver issues. Thirty-five regimens were identified; the newer agents among these included posaconazole and oteseconazole. We compared the efficacy of newer regimens with traditional ones like ‘terbinafine 250 mg daily for 12 weeks’ and ‘itraconazole 200 mg daily for 12 weeks’. We found that an agent’s dosage was associated with its efficacy; for example, the 1-year odds of mycological cure with terbinafine 250 mg daily for 24 weeks (SUCRA = 92.4%) were significantly greater than those of terbinafine 250 mg daily for 12 weeks (SUCRA = 66.3%) (odds ratio 2.62, 95% credible interval 1.57–4.54). We also found that booster regimens can increase efficacy. Our results showed that some triazoles could be more effective than terbinafine.

Conclusions This is the first NMA study of monotherapeutic antifungals – and their various dosages – for dermatophyte toenail onychomycosis. Our findings could provide guidance for the selection of the most appropriate antifungal agent, especially amid the growing concerns about terbinafine resistance.

What is already known about this topic?

• Numerous oral antifungal agents are available for the treatment of dermatophyte toenail onychomycosis.
• However, the relative efficacy of many of these agents and their dosages has not been determined.

What does this study add?

• We have produced statistical evidence on the relative efficacy of various dosages of traditional and newer antifungals: some of the newer regimens are as efficacious as the older ones, while other newer agents are more efficacious than the traditional ones.
• Some of the newer agents, for example posaconazole, may exhibit greater efficacy than terbinafine; however, they may be associated with more adverse events that lead to discontinuation of the drug.

Onychomycosis is the most common infection of nails affecting approximately 6–10% of the North American population.1–3 It frequently occurs in the elderly,4 persons with diabetes,2 those with peripheral vascular disease, and individuals who smoke.5 The most common infecting organisms are dermatophytes.6,7 Terbinafine and itraconazole have been approved for the treatment of onychomycosis since the 1990s.8–11 Fluconazole is not approved for this indication in the UK, nor in North America.12 The itraconazole pulse regimen was introduced by de Doncker et al.;13 terbinafine pulse therapy is used off-label in many countries.14 More recently, there
has been interest in the efficacy of the newer antifungals for onychomycosis, as there have been reports of terbinafine resistance.\textsuperscript{15–21}

The objective of our work was to determine the relative efficacy of oral monotherapy regimens for dermatophyte toenail onychomycosis through network meta-analyses (NMAs). In this paper, regimen corresponds to a given agent and its specific dosage. To the best of our knowledge, this is the first NMA on the relative efficacy of newer antifungals and traditional therapies and their various dosages, in terms of mycological and complete cure at 1 year.

Materials and methods

Our work was guided by the 2022 recommendations of Guelimi et al.\textsuperscript{22,23} and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Appendix S1; see Supporting Information).\textsuperscript{24} We prospectively registered the protocol for our work under the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) ID no. 2022240157 (https://inplasy.com/inplasy-2022-4-0157/); ethics board approval was not required as human subjects were not involved.

Eligible studies for quantitative analyses

The peer-reviewed literature was initially searched on 10 March 2022; an updated search was conducted on 30 November 2022. The searches had no date restriction. Details regarding search terms are provided in Appendix S2 (see Supporting Information).

Using the patient/problem/population–intervention–comparator–outcome (PICO) framework, trials that were eligible for quantitative analyses were those that investigated the efficacy of an oral monotherapy regimen (I/C) for adults (i.e. aged 18 years or above) with toenail onychomycosis caused by dermatophytes (P), in terms of 1-year mycological and/or complete cure rates (O). We excluded trials that were published in a non-English language and did not verify the occurrence of mycological cure with both negative microscopy and negative culture. Complete cure occurs when both mycological and clinical cure are attained; so, for a 1-year complete cure rate, we discarded estimates that were not based on clinical cure being defined as complete (i.e. 100%) absence of signs and symptoms. Our quantitative analyses used randomized and nonrandomized data; we did not analyse outcome data from combination therapy. Our secondary outcomes of choice were safety-related, namely, 1-year odds of discontinuation due to (i) any AE and (ii) liver-related issues, and (iii) 1-year count of any AE. For discontinuation due to liver-related issues, a hepatic condition corresponded to whatever the respective authors deemed them to be; in other words, we had no strict definition for this secondary outcome.

In this paper, a ‘regimen’ is the composite of (i) the antifungal agent and (ii) its dosage, where the latter is a compilation of the dose, frequency of administration, and duration.

The two stages of screening titles/abstracts and full text were done independently by two authors (M.V. and M.A.B.); any discrepancies between the two authors were resolved through discussion with a third author (A.K.G.). We used Rayyan software\textsuperscript{25} for the two stages of screening; data were extracted by two authors (M.A.B. and M.V.) and organized into spreadsheets. Extracted information pertained to authorship/publication details, regimen examined, sample size, patient sex and age.

Assessment of evidence quality

The evidence quality across the networks for 1-year complete and mycological cure rates was evaluated using Confidence in Network Meta-Analysis (CINeMA) software, the framework of which is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.\textsuperscript{26} This tool enables the qualitative judgment of all possible pairwise comparisons across a network. The CINeMA framework evaluates data in terms of six domains, namely, (i) study-level risk of bias, (ii) reporting bias (which can correspond to publication bias), (iii) incoherence (i.e. the consistency between direct and indirect evidence), (iv) heterogeneity (i.e. the variation in the effect of a given treatment across studies), (v) indirectness (i.e. relevance of eligible studies to research objective) and (vi) imprecision. With the CINeMA tool, the quality of evidence for a pairwise comparison can be given – similarly to GRADE – one of four evaluations, namely, ‘very low’, ‘low’, ‘moderate’ and ‘high’. In our CINeMA analyses, we deemed our data to have no reporting bias. Study-level risk of bias assessment was also conducted using the Cochrane Collaboration’s Risk of Bias (RoB) assessment tool.\textsuperscript{27}

Networks

For each outcome, we created network plots to depict the nexus of interventions that have been compared directly across trials. All analyses were performed with RStudio software; we conducted our NMAs using the multinma package;\textsuperscript{28–31} $\alpha$ (i.e. significance level) was set to 5%.

For each outcome of interest, we conducted a Bayesian NMA, from which the regimens’ relative effects and surface under the cumulative ranking curve (SUCRA) values were determined. Relative effects – which are often presented in ‘league tables’ – correspond to the pairwise comparisons across a network, while a regimen’s SUCRA is its overall rank for efficacy.

For our analyses, uniform priors were used, in addition to having 1000 burn-ins, 10 000 adaptations, and Markov chain Monte Carlo sampling.

Results

Eligible studies

Twenty-one unique studies were eligible for quantitative analyses. The Cochrane Collaboration’s RoB assessment for each study are presented in Figure 1; the characteristics of the eligible studies are presented in Table S1 (see Supporting Information); and Figure 2 depicts the schematic for our identification of eligible studies. We investigated two outcomes for efficacy and a separate network meta-analysis was done for each outcome.
Our analysis of per protocol 1-year mycological cure rate used data from 20 papers14,32–50 across which 36 interventions (including placebo) were investigated. For this endpoint, we included papers where mycological cure corresponded to both negative microscopy and culture; therefore, in trials where this outcome was confirmed by only microscopy, only culture or only Periodic Acid Schiff stain was excluded.

Our analysis of per protocol 1-year complete cure rate analysed outcome data from 11 papers – across which 28 interventions (including placebo) were investigated36,40,42–47,49–51.

Networks, evidence quality and analyses

Network plots for our efficacy-related outcomes (i.e. mycological and complete cure) are presented in Figures 3 and 4, while those for safety are in Figures S1 and S2 (see Supporting Information). We assessed evidence quality only across the networks of the efficacy-related outcomes (i.e. mycological and complete cure); our evaluations are presented in Tables S2 and S3 (see Supporting Information).

Firstly, we ran both a fixed- and random-effects NMA for networks pertaining to our primary outcomes (i.e. 1-year mycological and complete cure rates); we used leverage plots to determine which of the two had a better model fit. The fixed-effects analyses had a slightly better model fit as evidenced by the lower posterior mean of residual deviance (Dres) (i.e. the lower the value of lower Dres, the better the model fit). The leverage plots are presented in Appendix S3 (see Supporting Information). So, all our analyses were based on the fixed-effects model. Furthermore, by virtue of our analyses being at the level of ‘the dosage’, we de facto eliminated sources of heterogeneity – or selection bias – that would result from the amalgamation of various doses of a given agent. For example, across the 36 interventions that were identified for 1-year mycological cure rate, we distinguished ‘terbinafine 250 mg daily for 12 weeks’ from, say, ‘terbinafine 250 mg daily for 24 weeks’; hence, these two interventions were represented by distinct nodes (Figures 3 and 4), unlike other studies52,53 that amalgamated different dosages into one node.

We also conducted a node-splitting analysis of inconsistency for the primary outcomes; the results thereof are presented in Appendix S4 (see Supporting Information). There was no significant (P>0.05) difference between direct and indirect evidence (Appendix S4). We attempted to investigate whether gender is an effect modifier by conducting a network meta-regression; however, information on sex distribution (e.g. proportion male/female) was absent for many of the eligible studies.

Relative efficacy and safety

The SUCRAs of the regimens – as per the efficacy-related outcomes – are presented in the Kilim plot in Figure 5. The Kilim plot is a visual tool that was developed for the efficient presentation of NMA outputs, such as relative effects and SUCRAs.54,55

The league tables in Figures 6 and 7 present the relative effects of mycological and complete cure at 1 year, respectively, as per selected regimens (i.e. agents that are commonly used in clinical practice). The relative effects for
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The standard regimen for dermatophyte toenail onychomycosis is terbinafine 250 mg daily for 12 weeks. Our NMA showed that the odds of mycological cure at 1 year is significantly lower than with ‘terbinafine 250 mg daily for 12 weeks’ (SUCRA = 82.7%) (OR 0.21, 95% CI 0.11–0.42) (Figures 5 and 7). Additionally, the odds of complete cure at 1 year with terbinafine 250 mg daily for 12 weeks was significantly lower than with ‘terbinafine 250 mg daily for 8 weeks, followed by no treatment for 12 weeks and then followed by 250 mg daily for 4 weeks’ (OR 0.24, 95% CI 0.12–0.46) (Table S5).

Terbinafine booster therapy: The odds of complete cure at 1 year was significantly greater with some booster therapy regimens. For example, continuous terbinafine for 12 weeks (SUCRA = 45.6%) was less effective than ‘terbinafine 250 mg daily for 12 weeks, followed by no treatment for 12 weeks and then followed by 250 mg daily for 4 weeks’ (SUCRA = 82.7%) (OR 0.21, 95% CI 0.11–0.42) (Figures 5 and 7). Additionally, the odds of complete cure at 1 year with terbinafine 250 mg daily for 12 weeks was significantly lower than with ‘terbinafine 250 mg daily for 8 weeks, followed by no treatment for 12 weeks and then followed by 250 mg daily for 4 weeks’ (OR 0.24, 95% CI 0.12–0.46) (Table S5).

Terbinafine pulse therapy: The efficacy of some pulse regimens did not differ significantly from that of terbinafine 250 mg daily for 12 weeks (Figure 6; Tables S4 and S5). For example, the 1-year odds of mycological cure with terbinafine 250 mg daily for 12 weeks did not differ from those with

Figure 2 Schematic for the identification of studies for quantitative analyses. The flow chart summarizes the search process for the identification of studies that were eligible for quantitative analyses.
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Terbinafine 500 mg daily for 1 week in a month for 12 weeks (three pulses), nor from those with terbinafine 250 mg daily for 1 week in a month with nail abrasion for 24 weeks; comparative safety data as per the 1-year odds of discontinuation due to any AE was not available for these two pulse regimens (Tables S4, S5, S8 and S9).

Itraconazole continuous vs. pulse therapies: The efficacy of the pulse did not differ significantly from that of the continuous regimen (Table S4); likewise, pulse and continuous did not differ in terms of the two safety-related measures (Figures S3 and S4).

Itraconazole pulse therapy vs. regimens with terbinafine: We found that terbinafine 250 mg daily for 16 weeks was more efficacious – as per 1-year mycological cure rate – than itraconazole 400 mg daily (i.e. 200 mg twice daily) for 1 week in a month (i.e. 7 days on, 21 days off) for 12 weeks (i.e. 3 pulses) (OR 3.5, 95% CI 1.16–11.35); similarly, terbinafine 250 mg daily for 24 weeks was also more efficacious (OR 4.17, 95% CI 1.77–9.86) (Table S4).

Safety of antifungals: In terms of odds of discontinuation due to any AE, terbinafine 250 mg daily for 12 weeks is significantly safer than (i) albaconazole 400 mg weekly for 36 weeks (OR 0.018, 95% CI 0.001–0.628), (ii) oteseconazole 600 mg daily for 2 weeks (then 600 mg weekly for 10 weeks) (OR 0.0083, 95% CI 0.000057–0.64), (iii) posaconazole 200 mg daily for 24 weeks (OR 0.001, 95% CI 0.001–0.481) and (iv) fluconazole 300 mg weekly for 12 months (OR 0.013, 95% CI 0.001–0.477) (Figure S3). Itraconazole was significantly safer than posaconazole in terms of discontinuation due to any AE (OR 0.0014, 95% CI 9.2 × 10⁻⁷ to 0.72) (Figure S3) and liver-related issues (OR 2 × 10⁻⁶, 95% CI 1.25 × 10⁻⁶ to 0.2) (Figure S4). When considering counts of AEs at 1 year, there was no significant difference between posaconazole, oteseconazole and placebo. These data were not available for albaconazole.

Discussion

We determined the relative efficacy of monotherapy with various oral antifungal regimens for dermatophyte toenail onychomycosis.

This current study is not without limitations. A common limitation across many systematic reviews – including ours – is the exclusive inclusion of evidence communicated in only one language. Furthermore, the absence of information on patient sex distribution across some studies limited us from statistically determining whether gender is an effect modifier. We also acknowledge that our networks were sparse because there are more nodes than there are available numbers of studies. Our network was sparse also because the nodes were defined at the dosage level. The limitation of
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Sparseness is why inconsistency analyses constituted few comparisons, and this limitation could also explain the wide credible intervals of some comparisons. Hence, results of our analyses ought to be interpreted in light of these limitations.

For safety, we chose the two aforementioned endpoints as they are, relatively speaking, more ‘objective’ than many. For instance, we did not select occurrence of ‘headaches’ or ‘gastrointestinal issues’ as these are more subjective. Similarly, for efficacy, we did not choose patient-reported outcomes as we deemed these to be more subjective than cure rates. Notwithstanding that, an extension of our work could include examining the relative efficacy of such regimens on quality of life. Future studies could also include investigating the relative efficacy of combination therapy with oral and/or topical agents (e.g. laser therapy); results from such studies would further contribute to the comparative effective evidence base for this condition.

While the ‘traditional’ oral agents, namely terbinafine and itraconazole, are more effective than griseofulvin and ketoconazole, the complete cure rates are still – on average – relatively low (terbinafine: complete cure 38%, mycological cure 70%; itraconazole: complete cure 14%, mycological cure 54%). Failure with terbinafine therapy could result from terbinafine resistance; in such an instance, minimum inhibitory concentration (MIC) testing of the causative agent to a battery of antifungal agents and investigating for the presence of squalene epoxidase gene mutations are advised. However, MIC values may not always be the best indicator of resistance.

The present NMA is the first study to evaluate the relative efficacy and safety of the traditional and newer antifungal agents according to their mycological and complete cure rates, as well as discontinuation due to any AE and liver-related issues. The results of our work are congruent with previous findings. However, these previous NMAs did not include the newer triazoles and the tetrazole, oteseconazole. When looking at the NMA of monotherapies for onychomycosis by Fávero et al., we see notable contrasts between our work and theirs. Firstly, their definition of mycological cure was less stringent as they defined the outcome by the occurrence of either negative microscopy or negative

**Figure 4** Network plot for complete cure at 1 year. This network plot is for the 1-year rate of complete cure. See Figure 3 for a general description of a network plot.
Figure 5 Kilim plot of the overall rank of the regimens for efficacy as per 1-year mycological and complete cure rates. This kilim plot presents the surface under the cumulative ranking distribution curve (SUCRA) values for various regimens for mycological (left) and complete (right) cure rates at 1 year. Note: The regimen for fosravuconazole was given at a dose that is equivalent to 100 mg of ravuconazole. Given that it would be of clinical salience to compare the impact of fosravuconazole with ravuconazole, we made an exception by including the pro-drug because Watanabe et al. verified the occurrence of mycological cure with only a negative potassium hydroxide result.

Figure 6 Pairwise comparison for relative efficacy as per 1-year rate of mycological cure. This figure presents the relative effects for 11 of the 35 regimens that were identified for mycological cure rate within 1 year. The relative effects are quantified as odds ratio and its corresponding 95% credible interval (in parentheses). The cells with bold text correspond to pairwise comparisons that are statistically different; for example, ‘terbinafine 250 mg per day for 12 weeks’ is significantly more effective than ‘itraconazole 200 mg per day for 12 weeks’; this is represented by the odds ratio of 2.41 and corresponding 95% credible interval of 1.63 to 3.58.
Terbinafine continuous therapy: Terbinafine 250 mg daily given continuously for 24 and 16 weeks had been shown to be more effective than the labelled duration of 12 weeks; the findings from the current study are consistent with this. We recommend that any off-label use beyond 12 weeks be accompanied by regular monitoring.

Terbinafine booster therapy: Some booster regimens may be more effective than continuous terbinafine (Figures 5 and 7). An advantage of booster therapy is that it enables the physician to stop the treatment and monitor for clinical and laboratory adverse effects; it also allows for a degree of customization with booster therapy. One subgroup that would benefit are those who are poor responders at 6 or 9 months from the start of treatment.

Terbinafine pulse therapy: In this NMA the pulse regimens we selected had similar efficacy to continuous regimens. Additionally, there was no advantage of pulse over continuous in terms of safety – this could be due to limited clinical data. Pulse dosing, although higher in dosing level on a daily basis, provides a lower overall dose which may reduce risk of AEs.

Itraconazole: The pulse therapy regimen is 200 mg twice daily for 1 week on, 3 weeks off × 3 pulses for toenails. The cumulative amount of itraconazole in the pulse regimen is one-half of that used in the continuous regimen. In the present NMA there was no significant difference in the efficacy between the continuous and pulse regimens. There is no reported significant difference in safety between the itraconazole continuous and pulse regimens and our NMA supports this. With terbinafine-resistant organisms, itraconazole is a consideration if the causative organism has a low MIC to itraconazole.

Fluconazole: This triazole has shown some efficacy in dermatophyte toenail onychomycosis. In our NMA, terbinafine 250 mg daily for 12 weeks had a superior mycological cure rate to fluconazole 300 mg weekly for 12 months. Fluconazole may be considered in cases of terbinafine failure or if the causative organism is of the Candida species.

The newer azoles: There are several azole candidates that have been evaluated for the off-label management of dermatophyte toenail onychomycosis. While some of them may have superior mycological or complete cure rates compared with the traditional agents, their use needs to be monitored carefully for AEs, especially hepatic dysfunction and possible drug interactions.

Fosravuconazole: This is a pro-drug of ravuconazole that has been approved in Japan. In our NMA, the efficacy of fosravuconazole (equivalent to ravuconazole 100 mg daily) for 12 weeks was similar to pulse and continuous itraconazole, and continuous terbinafine. As per this NMA, terbinafine 250 mg daily for 12 weeks is safer than fosravuconazole with regard to discontinuation due to any AE within 1 year (Table S8).

Posaconazole: This triazole is indicated for some systemic fungal infections with one phase II study reported for the treatment of toenail onychomycosis. In this NMA, posaconazole 200 mg daily for 24 weeks had a higher complete cure rate than the standard terbinafine continuous therapy regimens.
regimen. Conversely, in our NMA, posaconazole 200 mg daily for 24 weeks was more likely to cause discontinuation due to any AE than terbinafine and itraconazole continuous therapies.

**Albaconazole**: In one phase II study the two most effective regimens were 400 mg weekly for 36 weeks and 400 mg weekly for 24 weeks. In our NMA, albaconazole had higher odds of mycological cure than itraconazole (continuous and pulse therapies), fosravuconazole and fluconazole 300 mg weekly for 12 months (Figures 5 and 6). With regard to discontinuation due to any AE within 1 year, the standard terbinafine continuous regimen was safer than albaconazole 400 mg daily for 36 weeks.

**Oteseconazole (VT-1161)**: This triazole is approved for some systemic mycoses. Oteseconazole 600 mg daily for 2 weeks followed by 600 mg weekly for 10 weeks was an effective regimen in a phase II study evaluating toenail onychomycosis. In the NMA, this regimen had greater odds of mycological cure than fluconazole 300 mg weekly for 12 months (Figures 5 and 6). With regard to discontinuation due to any AE, terbinafine continuous regimen was safer than this regimen of oteseconazole (Figure S3).

**Voriconazole**: This triazole is approved by the US Food and Drug Administration for some systemic mycoses; however, to our knowledge, there are no randomized controlled studies using voriconazole to treat dermatophyte onychomycosis in immunocompetent individuals and therefore it was not included in the NMA.

In conclusion, terbinafine 250 mg daily for 12 weeks is the gold standard regimen for the treatment of dermatophyte toenail onychomycosis. Some terbinafine booster therapy regimens may be more effective than continuous therapy. While certain newer azoles (e.g. posaconazole and albaconazole) may have higher cure rates than the standard terbinafine and itraconazole regimens their use is off-label and we recommend careful monitoring for AEs, especially hepatic dysfunction.

The practitioner must remain vigilant for terbinafine-resistant organisms; in such instances MIC testing to a battery of antifungal agents and molecular biology evaluation looking for squalene epoxidase gene mutations can help to confirm that the organism is terbinafine-resistant. The triazoles are considerations in such a scenario.

Whether or not any particular oral antifungal agent gets prescribed to treat dermatophyte onychomycosis for any particular patient depends on many factors including its efficacy, spectrum of action, safety of the dosage regimen, approval status, cost of the regimen, and patient/physician/insurance payer preferences. Increased use of the newer antifungal agents will establish their safety and efficacy in the general population, and provide guidance regarding the most appropriate choices for the management of onychomycosis.

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**Conflicts of interest**

The authors have no conflict to declare.

**Data availability**

The data underlying this article will be shared on reasonable request to the corresponding author.

**Ethics statement**

Not applicable.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher’s website.

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