The Efficacy And Safety Of Pulse Vs Continuous Therapy For Dermatophyte Toenail Onychomycosis

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BACKGROUND

• Onychomycosis is a persistent fungal infection of the nails and adjacent skin, manifesting as discoloration, thickening of the nail, and onycholysis. It is the most common nail pathology, accounting for 90% of toenail infections worldwide.

• The goal of treatment is to completely eradicate the fungal organism and return the nail to a clear and healthy baseline. Cure is evaluated by the following endpoints: mycological cure (-ve KOH preparation and -ve fungal culture) and complete cure (100% clear nail + mycological cure).

• Some of the most effective treatments are oral antifungals, namely terbinafine, itraconazole, and fluconazole, which generally have high mycological cure rates and are considered safe. They can be used continuously for several weeks or intermittently (pulsed) at a higher dose.

• Previous meta-analyses of pulse and continuous therapies have generated ambiguous results. There are few head-to-head clinical studies and no meta-analyses comparing regimens of terbinafine to regimens of itraconazole.

• This is the first study using network meta-analysis (NMA) to compare pulse and continuous systemic therapies for toenail onychomycosis.
METHODS

- Systematic review and NMA followed PRISMA 2015 checklist
- Inclusion criteria: randomized controlled trials of oral antifungal treatments for toenail dermatophyte onychomycosis, aged 18+, English language; diagnosed by KOH and culture
- Outcomes: mycological cure, complete cure, adverse events, dropout rates
- Literature search conducted on PubMed Feb 27, 2019: (onychomycosis OR tinea unguium) AND (oral* OR systemic*). References were mined for additional studies
- Treatment effects were based on intention-to-treat (ITT) cure rates. Ketoconazole and griseofulvin were excluded due to no longer indicated. Fluconazole results were collapsed due to equal efficacy of different doses
RESULTS

• 22 studies from 20 publications, 4205 randomized patients; mycological cure and adverse events results included, complete cure excluded (lack of studies)

• Comparing monotherapies to placebo resulted in significantly greater risk ratios (RRs) of achieving mycological cure with all treatments.

• The most successful treatments compared to placebo were continuous terbinafine, 250 mg daily for 24 weeks* with RR=11.00 (CI 6.08, 19.30) and continuous terbinafine, 250 mg daily for 16 weeks**, RR=8.90 (CI 4.16, 16.40).

<table>
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<tr>
<th>Treatment</th>
<th>SUCRA</th>
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<tbody>
<tr>
<td>Terb250_24w *</td>
<td>95.97</td>
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<tr>
<td>Terb250_16w **</td>
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<td>Terb250_12w</td>
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<td>Terb500_p*3</td>
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<td>ITR400*3</td>
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<td>ITR400*4</td>
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<td>ITR200_12w</td>
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<tr>
<td>Flu_9-12</td>
<td>32.25</td>
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<tr>
<td>Placebo</td>
<td>0.005</td>
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</tbody>
</table>

SUCRA values for Mycological Cure (MC)

A higher value = more likely to achieve MC

• The risk of experiencing adverse events in patients receiving any treatment was not significantly different from that of placebo

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<tr>
<th>Treatment</th>
<th>SUCRA</th>
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</thead>
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<tr>
<td>Flu_9-12</td>
<td>24.61</td>
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</table>

SUCRA values for Adverse Events (AE)

A higher value = lower number of AEs
DISCUSSION

- Although continuous terbinafine 250 mg for 24 weeks was significantly more likely to produce mycological cure than continuous itraconazole 200 mg for 12 weeks and weekly fluconazole (150–450 mg), it is not significantly different from the other included treatments.

- Considering the fungal life cycle, pulse therapy should theoretically be as effective as, or more effective than, continuous therapies: the sudden high concentration of an antifungal drug eliminates hyphae, sparing already-present spores. During the ‘off’ portion, these spores may germinate and be eliminated during the next pulse. Continuous therapy spares the spores, allowing them to germinate once treatment ends.

- In practice, neither continuous nor pulse therapy is necessarily better – It is possible that the drug concentration in the nail is maintained during the ‘off’ period of pulse therapy. In both therapies, it may be that residual spores that have not been eliminated by the end of therapy are left to germinate, possibly contributing to the recalcitrant nature of onychomycosis.

- Ultimately, the published evidence demonstrates that there are no differences in efficacy or safety between pulse and continuous regimens of terbinafine and no differences between pulse and continuous regimens of itraconazole.