Management of Nail Disease in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

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ABSTRACT. Objective. Nail psoriasis is common, impairs fine motor finger functioning, affects cosmesis, and is associated with a lower quality of life. This review updates the previous Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for nail psoriasis.

Methods. This systematic literature review of the PubMed, MEDLINE, Embase, and Cochrane databases examined the updated evidence since the last GRAPPA nail psoriasis treatment recommendations published in 2014. Recommendations are based on preformed PICO (Patient/Population - Intervention - Comparison/Comparator - Outcome) questions formulated by an international group of dermatologists, rheumatologists, and patient panel members. Data from this literature review were evaluated in line with Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

Results. Overall, there is insufficient evidence to make any recommendation for the use of topical corticosteroids, topical calcipotriol, topical tazarotene, topical cyclosporine, dimethyl fumarates/fumaric acid esters, phototherapy, and alitretinoin. There is a low strength of evidence to support the use of calcipotriol and corticosteroid preparations, topical tacrolimus, oral cyclosporine, oral methotrexate, intralesional corticosteroids, pulsed dye laser, acitretin, Janus kinase inhibitors, and apremilast.

Conclusion. The highest strength of supporting evidence is for the recommendation of biologic agents including tumor necrosis factor inhibitors, and interleukin 12/23, 17, and 23 inhibitors.

Key Indexing Terms: GRAPPA, psoriatic arthritis, psoriasis
Nail psoriasis is common, impairs fine motor finger functioning, affects cosmesis, and is associated with a lower quality of life. The scope of this manuscript is to provide an update and support the overall Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) nail psoriasis treatment recommendations, previously published in 2014, to assist clinicians in planning treatment for patients affected with nail psoriasis.

**METHODS**

An international working group consisting of 13 dermatologists and rheumatologists and 2 patient panel members was formed and consensus was reached on a literature review of agreed PICO (Patient/Population - Intervention, Comparison/Comparator - Outcome) questions. The search terms "nail," "psoriasis," and "PICO treatment" were used. A systematic literature review of the PubMed, MEDLINE, Embase, and Cochrane databases was performed.

Full-text articles published in the English language between January 1, 2013 (briefly overlapping with the previous GRAPPA nail psoriasis recommendations), and August 31, 2020, were eligible. The inclusion criteria were (1) studies with > 5 adult patients with psoriasis or psoriatic arthritis (PsA) and any degree of nail psoriasis; and (2) observational studies, case series, and clinical trials.

The data extracted for each PICO question were evaluated for quality of evidence, in line with GRADE criteria by individual reviewers, and then used to formulate a treatment recommendation by the respective reviewer and lead author (DL).2 Treatment success was judged according to each publication’s narrative and heterogenous measures of outcome. A holistic overall view was extrapolated, taking into account the data showing improvement in the patients’ symptoms, signs, and/or adverse events.

For the purposes of this review, the definition of nail psoriasis was taken as any degree of clinical involvement, be it more or less than 3 nails affected and with or without associated PsA.3

**Ethics and consent.** Ethics and consent approvals were not necessary for the conduction and preparation of this review article and manuscript, which involved the extraction and review of already published, ethically approved, and consented data.

**RESULTS**

**Literature review.** A total of 50 published articles met the review criteria across all posed PICO questions. The strength of recommendation ratings, and the respective symbols used, are summarized in Table 1 to assist with the subsequent narrative. Table 2 shows a summary of each treatment agent category cross-referenced with its strength of recommendation.

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**Table 1.** Strength of recommendation ratings, symbols used in subsequent statements, and their corresponding definitions.

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>**</td>
<td>High-quality body of evidence from robust, large, well-conducted trials, where benefits of treatment outweigh risks and adverse effects.</td>
</tr>
<tr>
<td>Conditional</td>
<td>*</td>
<td>Low-quality body of evidence from smaller studies and risks of bias where benefits of treatment, risks, and adverse effects are closely matched.</td>
</tr>
<tr>
<td>No recommendation</td>
<td>X</td>
<td>Insufficient evidence.</td>
</tr>
<tr>
<td>Against</td>
<td>Negative</td>
<td>Sufficient body of evidence where risks of treatment outweigh benefits.</td>
</tr>
</tbody>
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Overall, there is insufficient evidence to make any recommendation for the use of topical corticosteroids, topical calcipotriol, topical tazarotene, topical cyclosporine, dimethyl fumarates/fumaric acid esters, phototherapy, and altretinoin. The majority of these treatments have singular studies with low numbers of patients or no eligible studies from which to extract data.

There is a conditional strength of recommendation to support the use of calcipotriol and corticosteroid preparations, topical tacrolimus, oral cyclosporine, oral methotrexate (MTX), intralesional corticosteroids, pulsed dye laser, acitretin, Janus kinase inhibitors (JAKi), and apremilast. With the exception of pulsed dye laser, oral cyclosporine, and oral MTX, all the other aforementioned agents again had singular studies to extract data from, with low numbers of patients.

The strongest recommendation based on the quality of the supporting evidence is for the use of biologic agents including tumor necrosis factor inhibitors (TNFi) and interleukin (IL)-12/23, 17, and 23 inhibitors. This was supported by multiple international studies, with larger numbers of participants, consistently, for each treatment category.

All eligible studies demonstrated considerable heterogeneity in terms of disease threshold entry criteria, treatment regimes, objective and quantified disease measurement and methodology, duration of treatment, and follow-up. Extrapolation of the data for metaanalytical purposes was not possible.

**Revised PICO questions.** Twelve PICO questions were rephrased and recommendations ratings given (see Table 1 for rating definitions), as shown below. This is to be used in conjunction with the GRAPPA nail psoriasis review published in 2014.2

1. (a) In patients with nail psoriasis, is there insufficient evidence (X) to make a recommendation for the use of topical corticosteroid (no eligible literature to comment on or reference).

(b) In patients with nail psoriasis, is there insufficient evidence (X) to make a recommendation for the use of topical calcipotriol (no eligible literature to comment on or reference).

(c) In patients with nail psoriasis, is there an additional and cumulative conditional strength recommendation (‘) for the use of topical combination calcipotriol/betamethasone dipropionate?5,6

(d) In patients with nail psoriasis, is there an additional and cumulative conditional strength recommendation (‘) for the use of topical tacrolimus?7
In patients with nail psoriasis, there is insufficient additional evidence (X) to make a recommendation for the use of topical cyclosporine (no eligible literature to comment on or reference).

(f) In patients with nail psoriasis, there is insufficient additional evidence (X) to make a recommendation for the use of topical tazarotene.

2. (a) In patients with nail psoriasis, there is a conditional strength recommendation (*) for the use of intralesional corticosteroids.

(b) In patients with nail psoriasis, there is an additional and cumulative conditional strength recommendation (*) for the use of pulsed dye laser.

3. In patients with nail psoriasis, there is an additional and cumulative conditional strength recommendation (*) for the use of oral MTX and cyclosporine (as monotherapies).

4. In patients with nail psoriasis, there is insufficient evidence (X) to make a recommendation for the use of oral dimethyl fumarate/fumaric acid esters.

5. In patients with nail psoriasis, there is insufficient evidence (X) to make a recommendation for the use of phototherapy (including ultraviolet A and B with psoralens).

6. (a) In patients with nail psoriasis, there is insufficient evidence (X) to make a recommendation for the use of a combination of cyclosporine and phototherapy.

(b) In patients with nail psoriasis, there is a conditional strength recommendation (*) for the use of acitretin.

7. In patients with nail psoriasis, there is an additional and cumulative strong strength recommendation (**) for the use of TNFi.

8. In patients with nail psoriasis, there is strong strength recommendation (**) for the use of IL-12/23 inhibitors.

9. In patients with nail psoriasis, there is strong strength recommendation (**) for the use of IL-23 inhibitors.

10. In patients with nail psoriasis, there is strong strength recommendation (**) for the use of IL-17 inhibitors.

11. In patients with nail psoriasis, there is a conditional strength recommendation (*) for the use of JAKi.

12. In patients with nail psoriasis, there is a conditional strength recommendation (*) for the use of apremilast.

DISCUSSION
This GRAPPA systemic literature review strongly supports the use of biologic agents in the treatment of nail psoriasis. Another recent systematic review has also produced similar results with respect to systemic agents. All other reviewed interventions had conditional or insufficient evidence for efficacy. It was out of the scope of this guideline to assess the effect of interventions on other associated conditions such as PsA.

Treatment of psoriatic nail disease is challenging, and despite the scarcity of evidence for many of the nonbiologic therapeutic options for psoriatic nail disease, these therapies continue to feature prominently in the armamentarium of clinicians. This may be driven by the extrapolation of anecdotal evidence or historical therapeutic algorithms and the perceived risk-benefit profile of these therapies. The existing evidence base for these therapies has been potentially hamstrung by publication and research bias, and large well-designed studies are needed to further evaluate the efficacy and safety of these agents.

Cost and access are also important considerations. While the evidence base for biologic agents is strong, it is important to recognize that some patients with nail psoriasis may not be able to access such agents. Even in state-funded healthcare systems across the world, access to these agents is typically governed by the body surface area affected, severity of symptoms, disability, or the coexistence of disease activity in other domains of psoriatic disease. Some patients affected by nail psoriasis may not qualify for such agents despite this study’s recommendations.

There are a number of limitations in this review. Our search strategy focused on updating the evidence gathered in the...
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The key aim of this review was to provide an easily interpreted account of the current literature for use in the clinical setting when making decisions about patients’ treatment. All contributing authors followed the GRADE methodology, in which rigid, nonlinear, categorical recommendations are derived from the analysis of a body of evidence. Such categorization, although necessary to translate data into clinical recommendations, does not lend itself to a freely flowing narrative that highlights subtle differences in efficacy and adverse events between agents that have been placed in the same category of recommendation. Importantly, however, the significance of such differences is in itself difficult to adjudicate given the differences in study design and heterogeneity in outcome measures used across studies.

REFERENCES


Nail psoriasis treatments review


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