SIGNIFICANCE OF NAIL SYMPTOMS ASSOCIATED WITH PSORIASIS AND COMPARISON OF THE EFFICACY OF TREATMENTS USED IN NAIL PSORIASIS

PhD thesis

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INTRODUCTION

The nail as a special appendage of the epidermis is often affected in psoriasis. The prevalence of nail psoriasis is around 50%, but can be as high as 70-80% in case of psoriasis-associated joint involvement [1]. Psoriatic nail symptoms are caused by inflammation of the nail matrix and/or nail bed. The matrix under the proximal nail fold is responsible for the formation of the nail plate. The proximal part of the matrix produces the superficial part of the nail plate, while the distal part forms the lower half of the nail plate. The nail bed lies directly beneath the nail plate, with epithelial cells as the lower row of cells of the nail plate, ensuring the adhesion of the nail plate to the nail bed. Nail matrix abnormalities include pitting, leuconychia, red spot in the lunula and crumbling, while nail bed abnormalities include oil spot, onycholysis, hyperkeratosis and splinter haemorrhage [2][3][4].

Psoriasis-associated nail lesions manifest with varying degrees of severity (mild - moderate - severe). Different scoring systems have been developed to determine the severity of psoriatic nail symptoms, but objective assessment of symptoms remains a challenge to date. The most commonly used numerical, validated, objective scoring system is the NAPSI (NAil Psoriasis Severity Index) [5], which allows the identification of 8 symptom characteristic of nail psoriasis: the nail is divided into 4 equal quadrants, with 1 point per quadrant for the presence of nail matrix and nail bed symptoms. A maximum of 8 points per nail can be awarded, giving a total of 80 points for hand fingers and 160 points for hand and toes.

Studies have shown that the presence of nail symptoms among psoriatic patients has a negative impact on patients' health-related quality of life [6]. It not only appears as a cosmetic disorder, but also makes it difficult to perform household chores and hinders daily routines and social interaction [7][8]. Nail symptoms can cause pain to patients and inhibit hand and foot function. Occasionally, depression and suicidal thoughts may also be associated with the disease. In many cases, patients with nail symptoms are marginalized, with the perception of the outside world that psoriatic lesions on the skin surface and nails are the basis of stigmatization [9].

Recent studies have shown the presence of nail symptoms to be a predictive marker of psoriatic arthritis (PsA) [10]. This is probably due to the fact that the nail apparatus is considered a functional part of the musculoskeletal system. The nail has a close microanatomical relationship with the articular apparatus, being functionally connected to the distal phalanx and several interphalangeal articular structures, including extensor tendons and collateral ligaments [11]. Mcgonagle hypothesized that enthesitis may underlie some of the psoriatic nail symptoms [12].

Despite considerable progress in the treatment of psoriatic skin symptoms, nail psoriasis has remained a therapeutic challenge for both patients and physicians [13]. Most therapies used to treat psoriatic skin symptoms and joint involvement affected by psoriasis are ineffective or only moderately effective in treating nail symptoms, topical therapies tend to have poor penetration into the treated areas, and most of the available treatments are not evidence-based [14][15][16]. The treatment of nail psoriasis is largely determined by whether it occurs alone - possibly in association with minimal skin symptoms and/or joint involvement-, or in association with moderate to severe skin symptoms and/or joint involvement. For moderate skin and/or joint symptoms, systemic DMARD or biological therapy is usually considered, whereas for nail lesions with mild skin/joint symptoms, the number of affected nails and the type of nail symptoms are the primary factors in the choice of therapy. According to recent recommendations, for 1-3 nail involvement, topical steroids and vitamin D analogues or intralesional steroids should be the first choice. Systemic treatment may include methotrexate (MTX, 15-25 mg/week), acitretin (0.2-0.4 mg/kg/day), cyclosporine (3-5 mg/kg/day) - the choice of therapy depends on comorbidities, possible contraindications and the nature of the nail involvement (matrix vs. nail bed) [17]. Biological therapies (TNFα inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors) and small molecules targeting the PDE4 and JAK 1/3 pathways have shown good efficacy in the treatment of moderate to severe psoriatic nail symptoms.

AIMS

I. Comparison of the objective severity and the esthetic perception of nail symptoms in psoriasis

Although a lot is known about the development of psoriasis, the esthetic perception of nail symptoms among psoriatic patients and the general population is only partially investigated. First of all we would like to evaluate the esthetic impact of nail psoriasis amongst psoriatic patients and healthy individuals. Therefore, the purpose of our study was to determine the correlation between the severity of psoriatic nail changes (as determined by NAPSI) and the esthetic assessment of nail psoriasis. Furthermore, we assessed whether age, gender, or professional medical knowledge of the assessors would influence the result.

II. Comparison of biological therapies for moderate-to-severe psoriatic nail lesions according to their efficacy using a network meta-analysis model

Evidence-based therapeutic principles for the treatment of psoriatic nail symptoms are available in the literature, but there is no information on which therapy is recommended as the first-line treatment for moderate-to-severe psoriatic patients with nail symptoms. The aim of our study was to perform a network meta-analysis to determine the efficacy of biologics and small molecules inhibiting the PDE4 and JAK pathways in nail psoriasis. Our primary objective was to compare the efficacy of the therapies based on the change in NAPSI% and the achievement of NAPSI50. Our secondary objective was to determine the efficacy of therapeutic agents based on NAPSI75 and NAPSI100 metrics.

METHODS

Objective and subjective severity assessment of psoriatic nail symptoms

A cross-sectional survey using an online questionnaire was set up to investigate the differences of the subjectively esthetic evaluation of nail psoriasis between psoriasis patients and the general population. The online questionnaire was distributed among psoriasis patients and a group of healthy volunteers (including medical students, medical workers and nonmedical workers). Respondents were asked to specify their age, sex, medical history, and in case of psoriasis patients, the absence/presence of nail psoriasis and current or previous systemic anti-psoriatic drug administration (the latter information was used to characterize moderate to severe psoriasis). Participants were then asked to evaluate 19 nail photos subjectively and to score all images based on how disturbing they consider them, using numeric rating 0 (no esthetic disturbance) to 10 (maximal esthetic disturbance). Objective severity of nail psoriasis was determined by calculating the NAPSI scores (0-8 point original scoring was used). Nail photos were selected to represent all nail psoriasis severity grades: healthy and mild (NAPSI 0-3), moderate (NAPSI 4-6), and severe (NAPI 7-8). The nail photo sequence was randomly assigned.

Statistical analysis was carried out using Graphpad Prism v7 and R v3.5.1. For differences between groups of two or more groups, Mann-Whitney U test and Kruskal-Wallis test were used. Spearman correlation and linear regression were calculated using cor.test and Im R function. For statistical evaluation, p-value below 0.05 was considered significant.

Network meta-analysis model

Network meta-analysis is a popular method for comparing randomized trials with the same content, including the relative effectiveness of multiple treatments or interventions. To assess

the risk of bias, we followed the principles of the Cochrane Risk of Bias Tool. The network meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews), an international database of systematic reviews. The systematic review was prepared according to the PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses [18].

Selection of publications, search process, data collection

The publications were searched in MEDLINE (PubMed), CENTRAL and Embase databases up to April 2019 with the following search key "nail" OR "psoriasis" AND random*. The included randomized controlled trials compared the efficacy of TNFα, IL-17, IL-12/23, IL-23 and JAK and PFE4 inhibitors with placebo or active comparator in psoriatic patients with nail involvement. Interventions included biologics (ixekizumab [19][20], etanercept [21], infliximab [22], ustekinumab [23][24], tofacitinib [25][26][27], apremilast [28][29][30], secukinumab [31], adalimumab [32], guselkumab [33][34][35], golimumab [36] and risankizumab [37]). The severity of nail psoriasis was assessed by the objective scale of the NAPSI. Trial objectives were to assess target fingernail (usually the most severe nail, NAPSI 1-8) or overall fingernail (all fingernail, NAPSI 1-80). Trials were selected and assessed independently by 2 investigators in 3 phases by title, abstract and full texts. Interventions were evaluated based on NAPSI percentage improvement compared with baseline, with measure of dispersion at week 10-16, and the number of patients achieving at least 50%, 75% or 100% reduction in NAPSI, with measure of dispersion at week 10-16.

Statistical analysis

A Bayesian model was used to perform pairwise meta-analyses and NMA with the random effect model. The network model was performed under consistency assumption based on deviance information criterion (DIC, a measure to test model fit) since that proved to be equivalent to the consistency model (DIC: 63.91) and the inconsistency model (DIC: 64.09). Risk ratios (RR) for NAPSI 50 and mean difference (MD) for NAPSI percentage improvement (continuous) with 95% credible intervals (CrI), were used. Therapeutic agents were ranked by probability using SUCRA "Surface Under Cumulative Ranking".

RESULTS

I. Comparison of objective and subjective severity ratings of nail symptoms associated with psoriasis

1. Distribution of demographic data among respondents

Between October 10, 2015 and February 25, 2016, 362 psoriasis patients and healthy volunteers completed the questionnaire. Data of 68 respondents were excluded from the analysis: 14 respondents scored all nail photos with the same score, and 54 respondents scored all asymptomatic nail photos as severe (8-10 points). The data of 28 medical workers were also excluded, due to low sample size and significant age heterogeneity within the group. Altogether, data of 106 psoriasis patients (29% of respondents) and 160 respondents from the general population (86 medical students and 74 non health-care workers) were included in our analysis. Of the 266 respondents included in our analysis, 175 (66,0%) were female, and 91 (34,0%) were male. Mean age of the respondents was 38.4±16.7 years. In terms of age distribution, 14.2%, 57,6% and 28,3% of participants were <30 years, between 30 and 60 years, and >60 years, respectively. Among psoriasis patients, 75.5% had nail psoriasis, and, based on the history of anti-psoriatic drug use, 28,3% had severe psoriasis.

2. Subjective scoring of nail images

The 19 nail images were scored by all respondents with a 0-10 score based on how disturbing the participant found the image esthetically. For nails with asymptomatic (0) and severe (6-8) NAPSI scores, the subjective scores given by respondents showed a good correlation with the objective (NAPSI) score. However, significant heterogeneity was observed for the subjective scores of nails with moderate lesions (NAPSI 2-5), i.e. there were also nails in this group that were rated as less and more esthetically disturbing.

3. Correlation of the subjective scoring of nails and age of respondents

Next, we compared the subjective scores of the 19 nail images with the age of the respondents. Age showed robust positive correlation with the subjective assessment of nail symptoms both within the psoriasis patients and the general population. Participants over 60 years assessed nails with the highest points, followed by patients between 30 and 60 years and <30 years.

4. Differences in the subjective assessment of nail severity between subgroup of participants

We aimed to compare the subjective assessment of nails between different subgroups (patients with psoriasis and several psoriasis vs. general population, patients with severe vs. mild psoriasis and patients without vs. with nail psoriasis). For this, we calculated the mean subjective scores of all 19 nails of several subcategories. No difference was found between the subjective assessment of psoriasis patients and the general population. As a trend, patients with

severe psoriasis assessed nails esthetically more disturbing than patients with mild psoriasis or the general population; however the differences were statistically not significant. Psoriatic patients with nail symptoms also scored somewhat higher than patients without nail symptoms, but the difference was not significant.

Furthermore, we carried out linear regression analysis of subjective scoring and age between sexes in the complete study cohort. As a general trend, females showed higher scoring than males. As age increases, the subjective perception of the severity of nail symptoms increases, which is particularly observed in the female population.

Finally, we investigated whether professional medical knowledge influences the subjective scoring of the nail images. For this, we compared data of medical students and participants from the general population aged <30 years. On average, medical students showed a trend of lower severity scoring however with no statistical difference.

II. Network meta-analysis results

1. Characterisation of the randomized controlled trials included in the analysis

Altogether 14247 results were identified, and after the removal of the duplicates, the titles and the abstract of the randomized controlled trials, the selection has been implemented based on the search keyword. After that 34 studies were included in the systematic review, 17 of which (with a total of 6053 patients) fit the network. At baseline, the mean age of patients ranged from 41 to 54 years, males 34,4-100%, patients with PsA 0-100%, target fingernail 3,3-6,0 and overall NAPSI ranged from 18,7-47,9. Fifteen interventions, including placebo treatment enrolled in the network regarding NAPSI percentage improvement at week 10-16 and 9 interventions (including placebo) were analyzed regarding NAPSI 50 at week 12-16. The majority of the studies assessed the primary endpoints at week 10, 12 or 16.

2. Relative efficacy

Regarding NAPSI percentage improvement (week 10-16), ixekizumab 80 mg every 4 weeks and ixekizumab 80 mg every 2 weeks were more effective than infliximab 5 mg/kg, ustekinumab 45 mg, ustekinumab 90 mg, adalimumab 40 mg, guselkumab 50 m, guselkumab 100 mg and apremilast 30 mg. Not surprisingly, placebo was significantly worse than all biologics included in the analysis

3. Ranking of treatment options by efficacy

Regarding NAPSI percentage improvement (week 10-16) given in SUCRA, ixekizumab 80 mg every 4 weeks had the highest probability of being the best treatment, followed by ixekizumab 80 mg every 2 weeks and ixekizumab 75 mg. The other interventions yielded lower SUCRAs; not surprisingly, placebo proved to be the worst option. Regarding NAPSI 50 (week 12-16) etanercept 50 mg twice and once weekly had the highest efficacy indicated by the ranking table probability, followed by adalimumab 40 mg every 2 weeks. The other interventions yielded lower SUCRAs; not surprisingly placebo had the lowest probability of being the best option for treating nail psoriasis.

DISCUSSION

The objectives of my PhD research were to compare the objective and subjective severity ratings of psoriasis-associated nail symptoms and the efficacy of biological therapies for moderate-to-severe psoriasis-associated nail symptoms using a network meta-analysis model.

In the first part of our research, we assessed the subjective perception of psoriasis associated nail lesions. Psoriasis often affects the nails, leading to varying degrees of functional impairment in psoriatic patients with nail disease. However, the nail is not only functionally important for the human body, but also serves as a significant esthetic element. Although changes in the nail can have a variety of esthetic consequences, to our knowledge our study is the first to systematically investigate the esthetic perception of nail disease in psoriasis. Given the close micro-anatomical relationship between the nail and the articular structures, the appearance of psoriatic nail symptoms may be used to infer possible underlying inflammation of articular components.

Our results suggest that the severity of nail symptoms (based on the NAPSI score) correlated well with subjective scores overall. In particular, nails with low (0-2) and high (6-8) NAPSI scores had relatively evenly low and high subjective scores. This is not surprising, as these nails either show very little or very extensive clinical symptoms eliciting consistent emotions from observers. On the other hand, the esthetic perception of the nails with moderate NAPSI scores was quite heterogeneous. Presumably these differences are due to the inherent nature of NAPSI. Our results show that objective severity does not reliably reflect the esthetic consequences of nail psoriasis for nails with moderate NAPSI scores.

Respondents' age showed a strong positive correlation with subjective ratings of nail symptoms in both the psoriasis and general population. In addition to age-specificity, when looking at gender, women scored higher on nails than men, although the difference was not significant. Interestingly, the presence of psoriasis, severe psoriasis, or nail psoriasis did not have a significant effect on the esthetic perception of nails among respondents. Moreover, the presence of medical knowledge had no significant effect on the aesthetic perception of nail symptoms.

Despite significant advances in the treatment of psoriatic skin symptoms, nail symptoms still remain a therapeutic challenge for physicians in clinical practice. When determining treatment, consideration should be given to whether the nail symptoms occur alone or in association with skin or joint involvement that warrant systemic treatment, how many nails are affected, and whether matrix and/or nail bed abnormalities are detected.

Although several systematic reviews and meta-analyses regarding the efficacy of biological therapies for patients with moderate to severe skin psoriasis exist, there is no NMA assessing the therapeutic efficacy of novel anti-psoriatic medications in nail psoriasis. In our systematic review and network meta-analysis we have set out to evaluate and compare registered biological therapies (TNF-inhibitors, IL-17 inhibitors, ustekinumab and IL-23 inhibitors) and novel anti-psoriatic small molecules (tofacitinib and apremilast) for their therapeutic efficacy in nail psoriasis, and to determine which therapeutic agent should be chosen as first-line treatment.

Our network meta-analysis included publications of randomized controlled trials in which the change in severity of psoriatic nail symptoms was followed up by objective parameters (NAPSI). The short-term (10-16 weeks) efficacy of the selected therapeutic agents was analyzed by NAPSI percentage improvement compared with baseline and the percentage of patients achieving at least 50% improvement (NAPSI50). Not surprisingly, all therapeutic agents were found to be more effective than placebo. In terms of percentage improvement in NAPSI, the IL-17 inhibitor ixekizumab (80 mg given every 4 weeks and every 2 weeks) came first, with 75 mg ixekizumab coming second. Surprisingly, the IL-12/23 inhibitor ustekinumab was ranked second to last, ahead of placebo. An interesting result was obtained for the IL-23 inhibitor guselkumab, which performed worse than the TNFα inhibitor adalimumab in terms of efficacy.

When evaluating NAPSI50 network, etanercept (50 mg once weekly and 50 mg twice weekly) came first and second, respectively, and adalimumab 40 mg every 2 weeks came third, but it

should be emphasized that this network included only etanercept, adalimumab, tofacitinib and apremilast - there were no randomized controlled trials with IL-17, IL-12/23, IL-23 inhibitors.

Our results are supported by a network meta-analysis by Reich et al. in 2021. The study evaluated the efficacy of biologic therapies (ixekizumab, brodalumab, adalimumab, guselkumab, ustekinumab and infliximab) for the treatment of moderate-to-severe psoriasis-associated nail symptoms from baseline to 24-26 weeks based on several objective scoring systems (NAPSI, mNAPSI). Of the therapeutic agents analyzed, ixekizumab came out on top in terms of improvement in nail symptoms based on SUCRA [38]. Furthermore, our results are confirmed by another network meta-analysis published in 2021, which investigated the efficacy of biological therapies and small molecule inhibitors in nail psoriasis. Based on 100% improvement in NAPSI from baseline to weeks 10-16 and 24-26, the IL-17 inhibitor ixekizumab and the JAK 1/3 inhibitor tofacitinib performed best [39].

Based on our results, the IL-17 inhibitor ixekizumab is the most effective agent among biological therapies for the short-term treatment of moderate-to-severe psoriasis with nail symptoms. Surprisingly, the IL-12/23 inhibitor ustekinumab and the IL-23 inhibitor guselkumab, although excellent in reducing the severity of cutaneous symptoms, are less effective in treating nail symptoms. All these considerations suggest that in psoriasis with moderate to severe skin symptoms, where the management of coexisting nail symptoms is an important consideration, IL-17 inhibitors and TNF inhibitors are recommended. Tofacitinib, a JAK 1/3 inhibitor, has shown good results in the treatment of psoriatic nail symptoms associated with psoriasis, but the interventional agent has not been marketed as it was less effective in the treatment of cutaneous symptoms.

In conclusion, a holistic approach to the recognition, management and therapeutic treatment of psoriasis-associated nail symptoms in dermatology should be needed. It is not enough to assess the nail symptoms in isolation, but also to assess any underlying organ abnormalities, as well as the patient's psyche and the psychological difficulties arising from the disease.

NEW RESULTS

1. A partial correlation between the objective NAPSI scoring system for psoriasis-associated nail symptoms and subjective perception of nail lesions was demonstrated. For mild and severe nail symptoms, the subjective score for nails was similar to the objective severity score for nails.

However, for moderately severe nails, heterogeneity was observed in the subjective assessment of nails.

2. Evaluating the results of the network meta-analysis, we determined that for the short-term treatment of moderate-to-severe plaque psoriasis-associated nail symptoms, the IL-17 inhibitor ixekizumab is the most likely to be the most effective agent among biological therapies. For psoriasis with moderate-to-severe cutaneous symptoms, where the management of coexisting nail symptoms is a major consideration, the use of IL-17 inhibitors and TNF inhibitors is recommended.

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PUBLICATIONS

Publications related to the thesis:

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