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Research Article

Improvements in Skin and Nail Psoriasis are Positively Correlated across Systemic Psoriasis Therapies

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Abstract

Objective: For clinical scenarios where patients have moderate to severe psoriasis and nail psoriasis, knowing whether skin response is correlated with nail response would provide insight into the relationship between psoriatic skin and nail unit inflammation. The primary objective of this study was to determine if improvement in skin and nail psoriasis across a range of systemic therapies are correlated.

Methods: Relevant publications pertaining to systemic therapies approved in the US for psoriasis were identified via PubMed search. Only studies with placebo controls were included. The paired point estimates of the PASI 75 response treatment effect [i.e., the placebo-adjusted PASI 75 response rate] (independent variable) and mean percentage NAPSI improvement for target fingernail treatment effect [also placebo-adjusted] (dependent variable) were calculated for each therapy. Simple linear regression analysis weighted by the standard errors for the independent and dependent variables was performed.

Results: Ten paired treatment effects for 4 systemic therapies (apremilast, adalimumab, etanercept, and guselkumab) were obtained. Guselkumab and adalimumab were associated with the greatest nail improvement, and guselkumab was associated with the greatest skin response rate. PASI 75 response rate and mean percentage improvement target fingernail NAPSI were positively correlated (p=0.03), with an R2 value of 0.48.

Conclusions: There is significant positive correlation across different therapies between the magnitude of improvement in psoriatic skin and nail disease among patients with moderate-severe psoriasis and clinically significant nail disease.

Keywords: Moderate-Severe Psoriasis; Nail Psoriasis; Dual Outcomes; Simple Linear Regression

Introduction

Meta-analyses of systemic therapies for moderate to severe psoriasis and for nail psoriasis help clinicians and patients determine the relative efficacy of therapies for these respective conditions [1-4]. Armstrong, et al., and Leonardi, et al., skin psoriasis meta-analyses pooled trials of moderate-severe psoriasis patients with and without clinically significant nail disease. Huang, et al., meta-analysis pooled trials of patients with nail disease, regardless of the presence or severity of skin psoriasis or psoriatic arthritis. Reich, et al., used the outcome of complete resolution of nail psoriasis at Week 24-26 (not controlled for placebo) for their meta-analysis restricted to trials of biologics in patients with moderate-severe psoriasis and clinically significant nail disease [4]. A previous analysis for 10 systemic therapies for psoriasis found that changes in NAPSI or target NAPSI was positively correlated with changes in PASI and duration of treatment, but this study also included trials in which subjects without moderate to severe psoriasis were enrolled and assessed nail outcomes using disparate measures [5].

None of these analyses provide precise placebo-controlled data on the relative efficacy of different systemic therapies among

patients with both moderate to severe psoriasis and clinically significant nail psoriasis, which is a common clinical scenario. An examination of the relationship between simultaneous improvements in skin and nail psoriasis, here termed "dual outcomes", was therefore performed.

Methods

To evaluate the quantitative relationship between improvement in skin and nail psoriasis for treatment pairs (active vs. placebo) across a set of systemic therapies approved for the treatment of moderate to severe psoriasis, relevant publications were first identified using the PubMed search terms nail [tiab], Clinical Trial [ptyp], psoriasis [mh] and the generic name of systemic therapies approved in the US for treatment of psoriasis. In evaluating the endpoints used in these trials, most trials were noted to report Week 16 results, PASI 75 response rate was universally utilized for moderate to severe psoriasis, and mean percentage NAPSI improvement relative to baseline for the target fingernail (i.e., the fingernail with the highest baseline NAPSI score) was the endpoint most utilized for nail psoriasis. Consequently, only publications which reported both endpoints for week 16 were included. Next, those publications in which skin and nail outcomes were reported for the subset of subjects with moderate-severe psoriasis and clinically significant nail disease at baseline were selected [6-10]. The rationale for requiring both manifestations in the same population was to eliminate the possibility of confounding arising from systematic differences in trial conduct, baseline demographics, and clinical characteristics between subjects enrolled in nail psoriasis trials without moderate to severe psoriasis and those enrolled in skin psoriasis trials who lacked clinically significant nail disease.

For each trial, the point estimates of the PASI 75 treatment effect (i.e., PASI 75 response rate for active therapy, adjusted for placebo effect) and mean percentage target fingernail NAPSI improvement treatment effect (similarly adjusted) (i.e., dual outcomes) were abstracted, calculated and plotted on a two-dimensional graph. NAPSI treatment effect was arbitrarily identified as the dependent variable in this plot. Simple linear regression analysis weighted by the standard errors of the independent and dependent variables using R version 4.0.2 was performed. Standard deviations for the point estimates were either supplied in the original trial reports or were calculated from the binomial distribution of the PASI 75 treatment effect. (Standard deviation for the mean percentage NAPSI improvement was not provided with ESTEEM 1 study results, so the mean of the standard deviations for the other treatment pairs was used). The distributions of the percentage NAPSI improvement treatment effect were assumed to be normal. The 95% confidence region boundaries were calculated under the assumption that the errors in these 2 parameters had a bivariate normal distribution with no correlation, and that the total weighted distance to the boundaries is less than what would occur 95% of the time for a chi-squared distribution with 2 degrees of freedom.

Results

A total of 10 placebo-controlled dual outcomes, including dual outcomes from different dosing regimens of the same therapy, were identified from 6 publications (Table 1). A line of best fit and ovals around the treatment effect point estimates representing the 95% confidence regions were generated (Fig. 1).

The regression model estimated 0.27 as the correlation coefficient ($p=0.03$, $R2=0.48$), indicating that PASI 75 treatment effect and mean percentage improvement in target fingernail NAPSI were significantly positively correlated, with a 10-percentage point increase in PASI 75 treatment effect predicting a 2.7 percentage point increase in mean percentage target fingernail NAPSI.

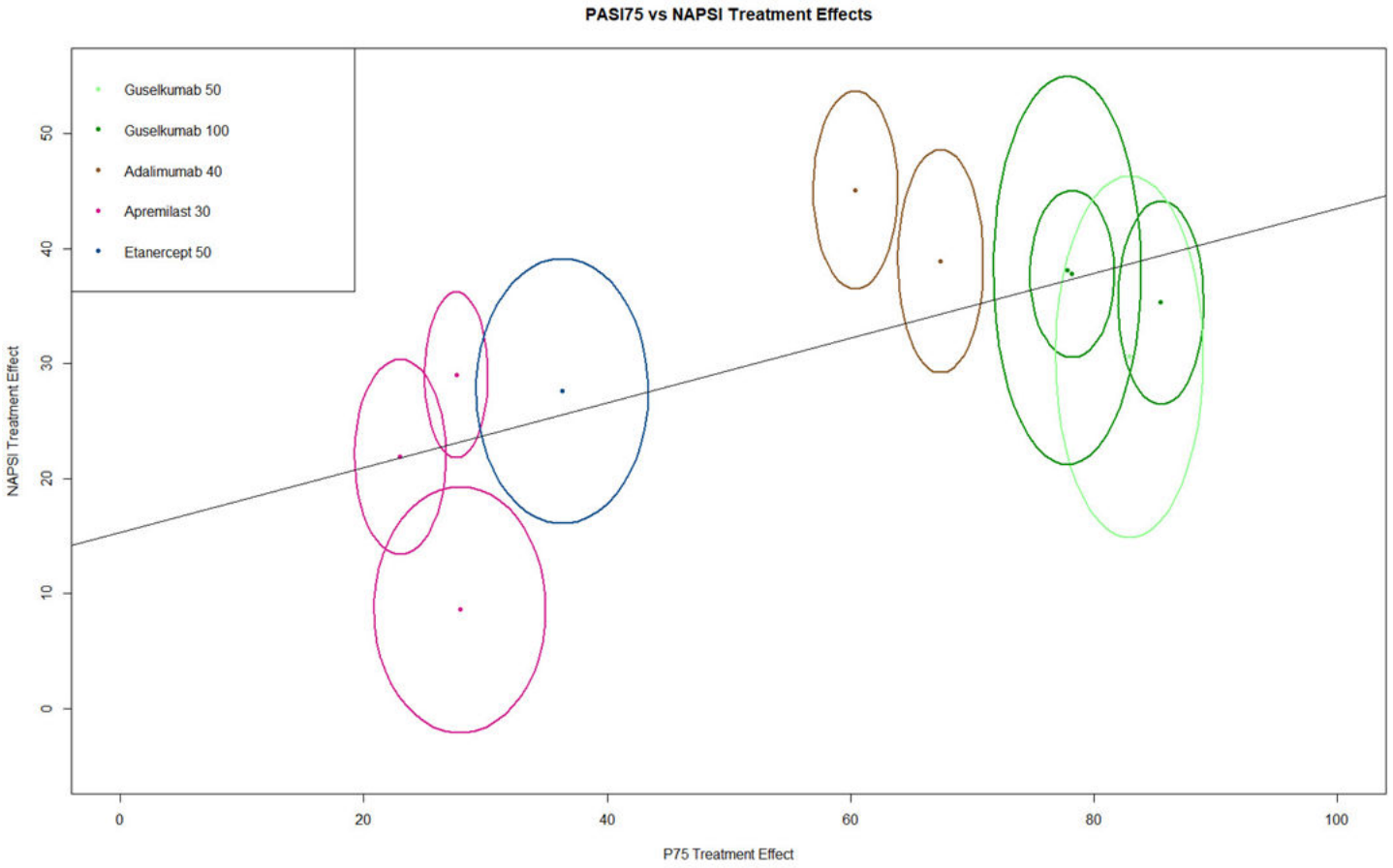

Figure 1: [PASI 75 Treatment Effect vs. Mean Percentage Target Fingernail NAPSI Improvement, with Line of Best Fit.] P75: PASI 75; Guselkumab 100: Guselkumab 100 mg q8 week; Guselkumab 50: Guselkumab 50 mg q8 week; Adalimumab 40: Adalimumab 40 mg every other week; Apremilast 30: Apremilast 30 mg bid; Etanercept 50: Etanercept 50 mg biw; Loading doses are described in the cited publications in Table 1. The equation for the weighted simple linear regression model: NAPSI Treatment Effect = 17.49 + 0.27 * (PASI75 Treatment Effect).

Drug/Dose	PASI 75 Response	Mean % improvement target fingernail NAPSI	Reference	
Guselkumab 50mg q8 wk	82.9	30.6	Ohtsuki et al., 2018	
Guselkumab 100mg q8 wk	77.8	38.1	Ohtsuki et al., 2018	
Guselkumab 100mg q8 wk	85.5	35.3	Blauvelt et al., 2017	
Adalimumab 40 mg eow	67.4	38.9	Blauvelt et al., 2017	
Guselkumab 100mg q8 wk	78.2	37.8	Reich et al., 2017	
Adalimumab 40 mg eow	60.4	45.1	Reich et al., 2017	
Apremilast 30 mg bid	27.6	29.0	Papp et al., 2015	
Apremilast 30 mg bid	23.0	21.9	Paul et al., 2015	
Apremilast 30 mg bid	27.9	8.6	Reich et al., 2017	
Etanercept 50 mg qw	36.3	27.6	Reich et al., 2017	
Loading doses are provided in the references.				

Table 1: [Placebo-adjusted Week 16 PASI and NAPSI data for systemic treatments for psoriasis]. q8 wk: every 8 weeks; eow: every other week.

Discussion

The magnitude of skin improvement was a significant independent variable predictive of nail improvement in moderate or severe psoriasis patients with clinically significant nail involvement. Among the four types of systemic therapy considered, guselkumab provided the greatest efficacy for skin and nail disease. The analysis does not suggest that apremilast is especially effective for nail disease (out of proportion to its effect on skin psoriasis), despite a previous report recommending apremilast specifically for treatment of nail psoriasis [11]. No inferences are possible about the relative efficacy of these four therapies compared with therapies for which other nail outcomes were assessed (e.g., mean percentage all fingernail NAPSI improvement, because these nail efficacy measures are not equivalent [12,13].

The 95% confidence regions depicted in Fig. 1 are likely conservative estimates of the region size, given that the shape of these regions assumes no correlation between the standard errors for PASI 75 response rate treatment effect and mean percentage NAPSI improvement treatment effect. If there is a positive correlation, the axes for the ovals representing the 95% confidence regions would be rotated clockwise, with the axis associated with PASI 75 treatment effect lengthened and the axis associated with mean percentage target fingernail NAPSI improvement treatment effect shortened, thereby resulting in a reduced 95% confidence region.

Rusk and Fleischer previously analyzed the quantitative relationship between skin and nail improvement, and they also concluded that greater improvement in skin severity significantly predicts greater improvement in nail severity ($R2 = 0.52$, $p = 0.001$). Rusk and Fleischer's conclusions differ from the present analysis, for several reasons: (1) their analysis used mean percentage change in PASI, not PASI 75 response rate, as the independent variable; (2) their analysis pooled mean percentage target fingernail NAPSI improvement, percentage mean improvement in all fingernail NAPSI, and mean percentage improvement in all fingernail NAPSI in the same analysis, even though these outcomes are not equivalent and (3) their analysis did not adjust for the placebo response in nail and skin measurements. PASI 75 response rates, but not mean percentage change in PASI, were reported by Blauvelt, et al., and Reich, et al. Had our analysis used mean percentage change in PASI instead of PASI 75 response rate as the independent variable, a total of 4 studies (instead of 6) comprising 6 dual outcomes (instead of 10) would have been amenable to our analysis. The reduction in number of dual outcomes analyzed would have reduced the power of our analysis and increased uncertainty in the estimates of the correlation coefficient and adjusted variance. In both analyses, approximately 50% of the variance in nail outcomes across different therapies is due to differences in the mechanism of action of the different systemic therapies, systematic errors in measuring skin or nail treatment effect, or differences across treatment pairs in baseline demographics or clinical characteristics.

Our analysis has numerous limitations. Several approved systemic therapies have no available mean percentage target fingernail NAPSI improvement results. No adjustment was performed for any differences in baseline characteristics across studies. Long-term skin and nail outcomes differ from 16-week outcomes, but as the placebo-controlled period cannot practically extend beyond 16 weeks, the present methodology could not be applied to assess the relative efficacy of these therapies long-term.

Conflict of Interest

The authors have no conflict of interest to declare.

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