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Improvement of 11 patients with nail psoriasis with apremilast: Results of an investigator-initiated open-label study

To the Editor: Among patients with psoriasis, 80% to 90% are estimated to have nail psoriasis during their lifetimes.[1] Apremilast is an oral phosphodiesterase 4 inhibitor approved for treatment of moderate to severe plaque psoriasis and psoriatic arthritis.[2] In the study to Evaluate Safety and Effectiveness of Oral Apremilast (CC-10004) in Patients With Moderate to Severe Plaque Psoriasis (ESTEEM) 1 and ESTEEM 2 trials, Nail Psoriasis Severity Index (NAPSI) scores were examined as secondary end points after apremilast treatment (30 mg twice daily), and NAPSI decreased by 43.6% and 60.0%, respectively, at week 32.[2]

An investigator-initiated, open-label, single-arm study was conducted to evaluate efficacy and safety of treating nail psoriasis using apremilast (30 mg twice daily) for 52 weeks. Eleven otherwise healthy white adults (6 men; mean age, 47.7 years) with psoriasis (mean Psoriasis Area and Severity Index, 4.5) demonstrating nail involvement (≥1 fingernail with a modified NAPSI [mNAPSI][3] ≥5 and Nail Pain Visual Analog Scale ≥4) were recruited. The mNAPSI is a validated tool with high inter-rater reliability for assessing nail psoriatic involvement.[4,5] Those on phototherapy as well as other systemic or topical therapies were excluded from this study.

The primary end point was the mean percentage change of mNAPSI at week 36 compared with baseline for all nails. The mNAPSI[3] scores range from 0 (no nail disease) to 130 (complete nail involvement in all 10 nails). Six completed the study to week 36, and a per-protocol analysis showed a reduction of mNAPSI by 64.1% (95% confidence interval, 46.5%-81.7%) from 33.8 to 12.3. Sustained reductions of oil spot and onycholysis were visible as early as week 8 (Fig 1). Analysis using a paired *t*-test at a 2-sided significance level of 5%, showed there was a minimum of 90% power to detect a paired mean difference of 21.5% assuming a SD of 10.89% (equivalent to effect size of 1.973; actual power of 96.71%).

For secondary end points, a modified intention-to-treat analysis was performed with inclusion of patients who received at least 1 dose of apremilast and had at least 1 postbaseline mNAPSI assessment. Missing data were handled using the last observation carried forward method. The mean percentage change in mNAPSI of the target nail (nail with highest baseline mNAPSI) at weeks 12, 24, 36, 48, and 52 compared with baseline decreased significantly at all time points (Fig 2). Proportions of patients achieving an mNAPSI ≥75% reduction over baseline mNAPSI (mNAPSI 75) response, were calculated (Table I). Six patients discontinued the study by week 52. Reasons for discontinuation and reported adverse effects are listed in Table I.

Adalimumab is currently the only treatment with United States Food and Drug Administration-approved indication for nail psoriasis. However, it is immunosuppressive, and alternatives are needed for patients with existing risk factors for life-threatening infections. Patients treated with 52 weeks of apremilast, an oral drug without notable immunosuppressive effects, demonstrated significant improvement in nail psoriasis, measured by mNAPSI of all nails and of the target nail. Improvement was seen with apremilast as early as week 12.

This study's limitations include its small number of patients and high rate of patient dropout. A large randomized clinical trial will be ideal for further investigation. Gastrointestinal adverse events were common, as expected, and should be discussed with patients.

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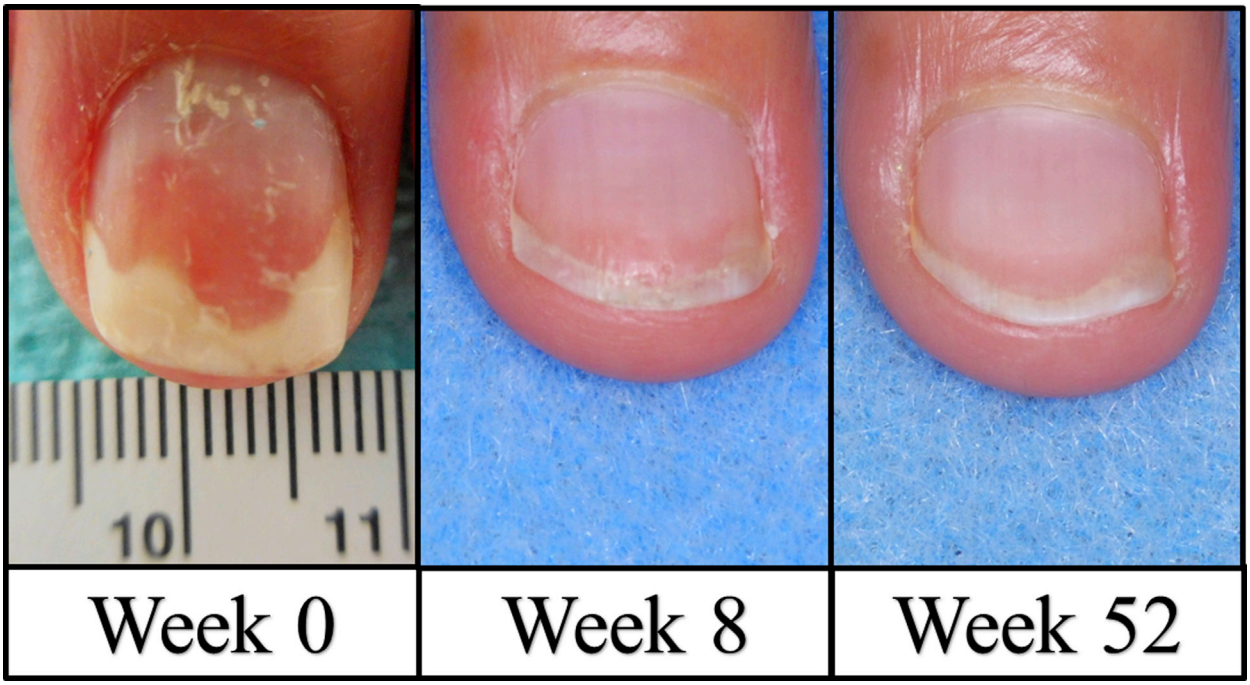
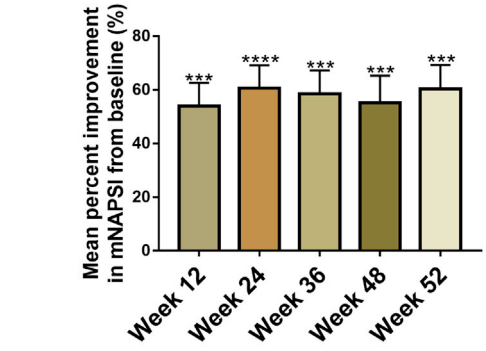


Fig 1. Target nail at week 0, 8 and 52.



Means ± SEM. Analyzed with paired two-tailed *t*-test. Statistically significant differences considered when $p < 0.05$, and were denoted as follows for student's *t*-test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$).

Fig 2. Mean percentage improvement in modified Nail Psoriasis Severity Index (*mNAPSI*) of the target nail compared with baseline.

Conflicts of interest: Dr Elewski is an investigator for AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol-Myers Squibb, Amgen (previously Celgene), Incyte, LEO Pharma, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron, Sun, Valeant (Ortho Dermatology), and Vanda, and is a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Amgen (previously Celgene), LEO Pharma, Lilly, Menlo, Novartis, Pfizer, Sun, Valeant (Ortho Dermatology), and Verrica. Drs Oak and Ho-Pham have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by The University of Alabama at Birmingham Institutional Review Board.

Table I. Modified Nail Psoriasis Severity Index ≥75% reduction over baseline (*mNAPSI 75*), reported adverse events, and reasons for discontinuation

Variable	Proportions of patients, n/N (%)
mNAPSI 75	
Week 12	3/11 (27.2)
Week 36	4/11 (36.4)
Week 52	5/11 (45.5)
Adverse events	
Drug related	
Nausea	5/11 (45.5)
Abdominal pain	2/11 (18.2)
Increased bowel movement	2/11 (18.2)
Possibly related	
Upper respiratory infections	2/11 (18.2)
Headache	1/11 (9.1)
Not related	
Acute stroke	1/11 (9.1)
Reason for discontinuation	
Gastrointestinal adverse events	3/6 (50.0)
Lack of significant body psoriasis improvement	2/6 (33.3)
Acute stroke and acute left eye vision loss (event not related to the study)	1/6 (16.7)

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Outcomes in patients with extramammary Paget disease with brain metastasis: A retrospective analysis

To the Editor: Invasive extramammary Paget disease (EMPD) is an aggressive skin adenocarcinoma that metastasizes to regional lymph nodes (LNs), leading to subsequent distant LN, lung, liver, or bone metastasis. However, the prognosis of brain metastasis of EMPD remains elusive because of the paucity of reports.[1-5] Recently, we examined 8 cases of brain metastasis during the follow-up of patients with advanced EMPD. Here, we retrospectively analyzed the impact of brain metastasis on the prognosis of distant metastatic EMPD.

This study included 35 patients with distant metastatic EMPD who were treated at our department between April 2011 and March 2020; their clinical records were retrospectively reviewed. Overall survival (OS) and local control rates of brain metastasis were evaluated from the first day the indicated metastases were detected. This study was approved by the Ethics Committee of Keio University School of Medicine, and the protocol conformed to the ethical guidelines of the Declaration of Helsinki.

At study baseline, 31 of 35 (88.5%) patients had distant LN metastasis, and the remaining 4 (11.5%) had lung, liver, or bone metastasis (excluding the brain; hereafter referred to as *visceral metastasis*) (Table I). Among 31 patients with distant LN metastasis, 6 and 11 patients developed brain and visceral metastasis, respectively. Among 4 patients with visceral metastasis, 2 patients developed brain metastasis. Collectively, 8 (22.9%) and 15 (42.9%) of 35 patients with EMPD with distant metastasis developed brain and visceral metastases, respectively. All 8 patients

Table I. Characteristics of the study patients

Characteristics	All patients (N = 35)		Distant LN metastasis (n = 31)		Brain metastasis (n = 8)		Visceral metastasis* (n = 15)	
Sex, n								
Male	25		21		7		13	
Female	10		10		1		2	
Age, y								
Median (range)	68.0 (48-83)		68.0 (48-83)		66.5 (53-70)		67.0 (53-78)	
Metastatic sites, n	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	**Baseline**	**Final**
Distant LN only	31	15	31	15	0	0	0	0
Brain only	0	0	0	0	0	0	0	0
Visceral only	4	2	0	0	0	0	4	2
Distant LN + brain	0	5	0	5	0	5	0	0
Distant LN + visceral	0	10	0	10	0	0	0	10
Brain + visceral	0	2	0	0	0	2	0	2
Distant LN + brain + visceral	0	1	0	1	0	1	0	1
Follow-up, mo, median (range)	20.7 (0.8-64.4)		24.4 (0.8-64.4)		12.1 (3.7-18.6)		10.7 (0.8-24.2)	
OS, mo, median	NR		NR		NR		11.9	
1-year survival rate, %	88.2		93.5		83.3		46.2	
P value (vs distant LN metastasis)	—		—		.64		.0003	
P value (vs brain metastasis)	—		.64		—		.07	

LN, Lymph node; *NR*, not reached; *OS*, overall survival.
*Liver, lung, or bone metastases are referred to as *visceral metastases*.