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ORIGINAL ARTICLE

Toenail Psoriasis during Ustekinumab Therapy: Results and Limitations

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Background: Nail psoriasis is a common clinically significant symptom of psoriasis. However, few studies have focused on the characteristics and course of toenail psoriasis. **Objective:** To investigate the treatment response of toenail psoriasis during a 52-week period of ustekinumab use. **Methods:** Patients were evaluated using the Nail Psoriasis Severity Index (NAPSI) at every injection visit. NAPSI score changes throughout the treatment were analyzed. The treatment response in each toenail and each NAPSI characteristic was also analyzed. **Results:** A total of 22 patients with chronic plaque psoriasis with concomitant toenail psoriasis were examined. Several characteristics such as ridging or onychomycosis that mimic psoriasis or hinder the evaluation were identified. NAPSI significantly improved during the treatment ($p < 0.05$). The big and second toes were significantly improved after 52 weeks of ustekinumab treatment ($p < 0.05$). Pitting and oil-drop discoloration were the only two characteristics that showed significant changes post-treatment ($p < 0.05$). **Conclusion:** Ustekinumab proved to be efficacious in treating toenail psoriasis. Because of the factors that hinder the NAPSI scoring, only NAPSI scores of the first and second toes can be used. **(Ann Dermatol 33(2) 131~137, 2021)**

-Keywords-
Nail psoriasis, Nail Psoriasis Severity Index, Psoriasis, Toenail, Ustekinumab

INTRODUCTION

Nail psoriasis is a common characteristic affecting nearly half of patients with psoriasis[1]. As an inflammatory disorder of the nail matrix and bed, nail psoriasis is characterized by various symptoms, such as pitting, onycholysis, and leukonychia. These symptoms not only cause aesthetic problems but also extremely deteriorate the quality of life of the affected patients[2]. Some studies have showed that psoriatic patients with nail involvement have a higher Dermatology Life Quality Index (DLQI) than those without[2-6]. Based on these facts, specific scoring methods used for nail psoriasis have been developed, including Nail Psoriasis Severity Index (NAPSI)[7] and Nail Psoriasis Quality of Life Scale (NPQ10)[8], to evaluate psoriasis severity and patients' quality of life, respectively. Moreover, nail psoriasis indicates the possibility of concomitant psoriatic arthritis[9] as it is one of the diagnostic criteria of the disease[10]. In one study, nail psoriasis was considered as the strongest predictor of concomitant psoriatic arthritis in patients with psoriasis[11].

Despite the constant interest in nail psoriasis because of these reasons, its treatment was generally unsuccessful. Compared to plaque type psoriasis, nail psoriasis improves more slowly with a different pattern of treatment response[12]. As newly developed biological drugs are being investigated, notable advancement in the treatment of nail psoriasis is in progress[13-17]. However, toenail psoriasis was not investigated in many of the studies[15,17,18]. Although the toenails are not usually investigated for convenience or other circumstances, toenail psoriasis has distinctive characteristics not detected in fingernail psoriasis. For exam-

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ple, a study reported that subungual hyperkeratosis and crumbling were prevalent in toenail psoriasis but not in fingernail psoriasis in Italian patients[19].
Several studies discussed the treatment response to ustekinumab in nail psoriasis, but mostly limited to the fingernail involvement[15,20,21]. Although some studies suggested the efficacy of ustekinumab in fingernail psoriasis, some limitations still exist as regards the generalization of results with toenail psoriasis because its characteristics were different with that of fingernail psoriasis. In this study, the efficacy of ustekinumab treatment for toenail psoriasis was investigated, and factors that improved and did not improve toenail psoriasis were identified.

MATERIALS AND METHODS

Patients

This study was approved by the institutional review board (B-1401/234-101). Informed consent was obtained from all study participants. Also, We received the patient's consent form about publishing all photographic materials. We prospectively enrolled patients with chronic plaque psoriasis with toenail involvement who met the following criteria: adults with moderate-to-severe chronic plaque psoriasis (baseline body surface area of $\geq$10% and psoriasis area and severity index [PASI] of $\geq$10) who underwent both systemic therapy (cyclosporine or methotrexate) and phototherapy for $>$6 months. Key exclusion criteria included serious infection including active tuberculosis and previous exposures to ustekinumab. Ustekinumab (45 mg) was administered to eligible patients for a total of 52 weeks at week 0, week 4, and every 12 weeks thereafter.

Study assessment

The 1.5× magnified photographs of all toenails of study participants were taken at every visit. A single investigator evaluated every toenail according to the NAPSI from pretreatment to 52 weeks. NAPSI assessment has already been described elsewhere[7]. The investigator also evaluated each component of the NAPSI assessment: 8 parameters constituting the NAPSI (i.e., pitting, leukonychia, red spots in the lunula, nail plate crumbling, onycholysis, splinter hemorrhages, oil-drop discoloration, and subungual hyperkeratosis). Moreover, each photograph of individual nail was divided into four quadrants[22]. A score was assigned for each parameter depending on how many quadrants were involved: 0 for none; 1, if one quadrant expressed the parameter; 2, if two quadrants expressed the parameter; and so on. As there are ten toenails in a participant, each score for one parameter ranges from 0 to 40.

Statistical analyses

To assess the improvement of toenail psoriasis, changes in NAPSI with time were evaluated using a repeated measures analysis of variance (ANOVA) model. To examine the response of individual NAPSI component, the Wilcoxon signed-rank test was applied to the baseline score of each parameter at baseline and after 52 weeks. To evaluate NAPSI changes in each toenail, baseline and week 52 NAPSI of each toenail were compared using the Wilcoxon signed-rank test. All analyses were performed using the SPSS Statistics 21.0 software package (IBM Corp., Armonk, NY, USA), and $p<0.05$ was considered significant.

RESULTS

Study population

Among 31 patients with chronic plaque psoriasis who were treated with ustekinumab for 52 weeks, 22 who had toenail psoriasis were included. Their mean age at baseline was 48.72 years (range, 28~84 years), consisting of 14 male (63.64%) and 8 female (36.36%). The mean disease duration of psoriasis was 18.68±10.06 years. All patients received both systemic medical treatment (either cyclosporine or methotrexate) and phototherapy (narrow-band ultraviolet B) prior to ustekinumab treatment. Baseline PASI was 19.29±4.92 in average. Eleven (50.0%) of the included patients also had fingernail psoriasis. The baseline mean toenail NAPSI was 17.23±11.61, whereas the total NAPSI was 20.13±13.11 (Table 1). NAPSI characteristics occurring at baseline in individual toes are shown in

Table 1. Clinical characteristics of the study population (n=22)

Variable	Value
Age (yr)	48.72±11.56
Sex	
Male	14 (63.64)
Female	8 (36.36)
Duration of psoriasis (yr)	18.68±10.06
Previous treatments	
Topical agents	22 (100)
Phototherapy	22 (100)
Systemic agents (cyclosporine or methotrexate)	22 (100)
Biologic agents other than ustekinumab	2 (9.09)
Baseline PASI	19.29±4.92
Baseline NAPSI	20.13±13.11
Fingernail NAPSI	2.91±4.74
Toenail NAPSI	17.23±11.61

Values are presented as mean±standard deviation or number (%).
PASI: Psoriasis Area and Severity Index, NAPSI: Nail Psoriasis Severity Index.

Table 2. Appearance of Nail Psoriasis Severity Index (NAPSI) characteristics and Beau's lines in individual toes at baseline (n=44)

Variable	Number of toes with the characteristics				
	1st toe	2nd toe	3rd toe	4th toe	5th toe
Nail matrix characteristics					
Pitting	10 (22.7)	8 (18.2)	3 (6.8)	2 (4.5)	0 (0)
Leukonychia	13 (29.5)	17 (38.6)	19 (43.2)	19 (43.2)	6 (13.6)
Red spots in the lunula	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)
Nail plate crumbling	5 (11.4)	4 (9.1)	2 (4.5)	4 (9.1)	12 (27.3)
Beau's line	5 (11.4)	2 (4.5)	0 (0)	0 (0)	0 (0)
Nail bed characteristics					
Onycholysis	6 (13.6)	2 (4.5)	4 (9.1)	0 (0)	0 (0)
Splinter hemorrhages	1 (2.3)	4 (9.1)	3 (6.8)	1 (2.3)	1 (2.3)
Oil-drop discoloration	12 (27.3)	12 (27.3)	5 (11.4)	4 (9.1)	1 (2.3)
Nail bed hyperkeratosis	4 (9.1)	2 (4.5)	3 (6.8)	5 (11.4)	16 (36.4)

Values are presented as number (%).

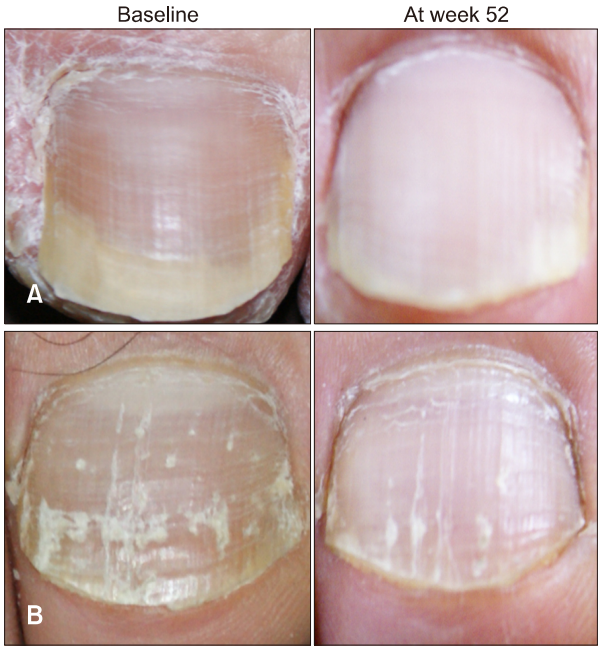

Fig. 1. Representative images of psoriatic nails at baseline and after 52 weeks. (A) An example of psoriatic nail with Nail Psoriasis Severity Index (NAPSI) improvement after ustekinumab treatment. (B) An example of psoriatic nail without significant NAPSI score change in spite of clinical improvement.

Table 2, with leukonychia as the most common in all but fifth toe, which more commonly presented subungual hyperkeratosis.

NAPSI evaluation of the study population

All the 10 toenails of 22 patients were evaluated six times at weeks 0, 4, 16, 28, 40, and 52. Assessment was objectively executed using digital photographs, but several factors were found to interfere with the NAPSI assessment

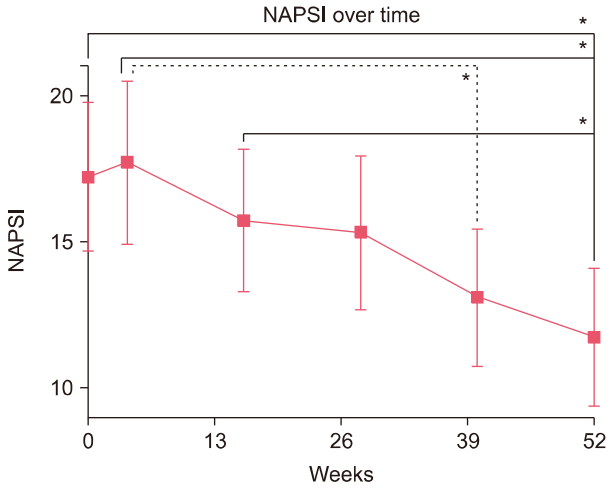

Fig. 2. Changes in toenail Nail Psoriasis Severity Index (NAPSI) scores throughout 52 weeks (range, 0~80) (*$p<0.05$).

in 15 patients (Supplementary Fig. 1). Age-related nail changes such as nail plate ridging or dystrophy would cause some confusion to nail psoriasis evaluation apprentices. Other distinct comorbidities like onychomycosis and subungual hemorrhage were also found in some cases. These nail characteristics were excluded in the NAPSI assessment because they were not caused by nail psoriasis.

Toenail NAPSI score throughout the ustekinumab treatment

During the ustekinumab treatment, the NAPSI score significantly improved when analyzed with repeated measures ANOVA method (Fig. 1, 2). Especially, NAPSI at week 52 significantly improved as compared to the scores at weeks 4, 8, and 20. NAPSI at week 40 was significantly smaller than that at week 8.

The improvement of individual toes were also analyzed. Although the big and second toes displayed substantial differences between weeks 0 and 52, other toes did not show significant changes after 52 weeks (Fig. 3).

When analyzing post-treatment changes of the four matrix components of NAPSI, only pitting showed statistically significant improvement (Fig. 4). Similarly, oil-drop discoloration was the only characteristic of the bed component of NAPSI that displayed significant changes after the ustekinumab treatment.

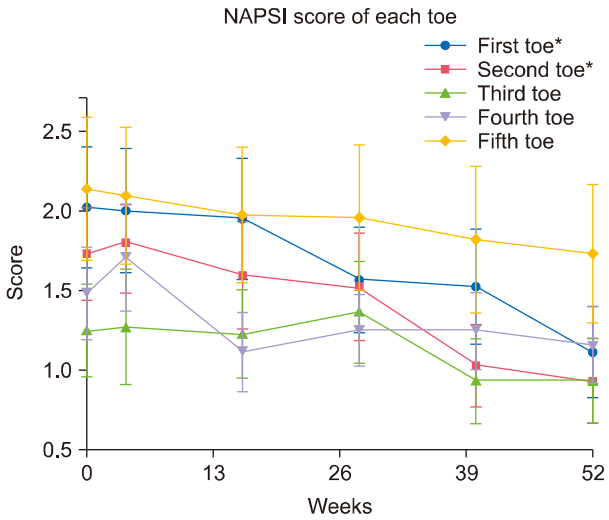

Fig. 3. Changes in toenail Nail Psoriasis Severity Index (NAPSI) scores of each toe throughout 52 weeks (range, 0～8) (*$p<0.05$).

DISCUSSION

Nail psoriasis is one of the most representative symptoms of psoriasis, but tends to be neglected in certain clinical circumstances[23]. Studies or clinical practices are relatively focused on fingernail psoriasis; however, providing sufficient attention to toenail psoriasis is difficult in clinical settings. Furthermore, the prevalence of toenail psoriasis is never lower than that of fingernail psoriasis[19]. Although toenail psoriasis also has a substantial disease burden, our knowledge of its treatment and course is insufficient. Some treatments for psoriasis occasionally succeed in the clearance of fingernail psoriasis but fail to achieve a sufficient response in toenail involvement[24].

Unlike fingernails, toenails are associated with more severe age-related changes due to repeated trauma because of lifelong walking process with continuous contact with the shoes[25]. Therefore, onychodystrophy of the toenail is one of the common symptoms in elderly people[26]. Onychodystrophy due to the aging process can be misunderstood as a manifestation of nail psoriasis such as onycholysis or subungual hyperkeratosis and in severe cases can also interrupt the meticulous evaluation of the presence of subtle changes due to psoriasis in the affected toenail. In this study, 17 patients had onychodystrophy. Moreover, as some aspects of nail psoriasis are attributed to Koebner's phenomenon, repeated trauma acts as a bidirectional factor by not only inducing age-related nail changes but also causing nail psoriasis[27].

In addition, leukonychia occurs as an age-related change of the nail, and splinter hemorrhage is one of the common symptoms of nail aging[26]. These symptoms are included in

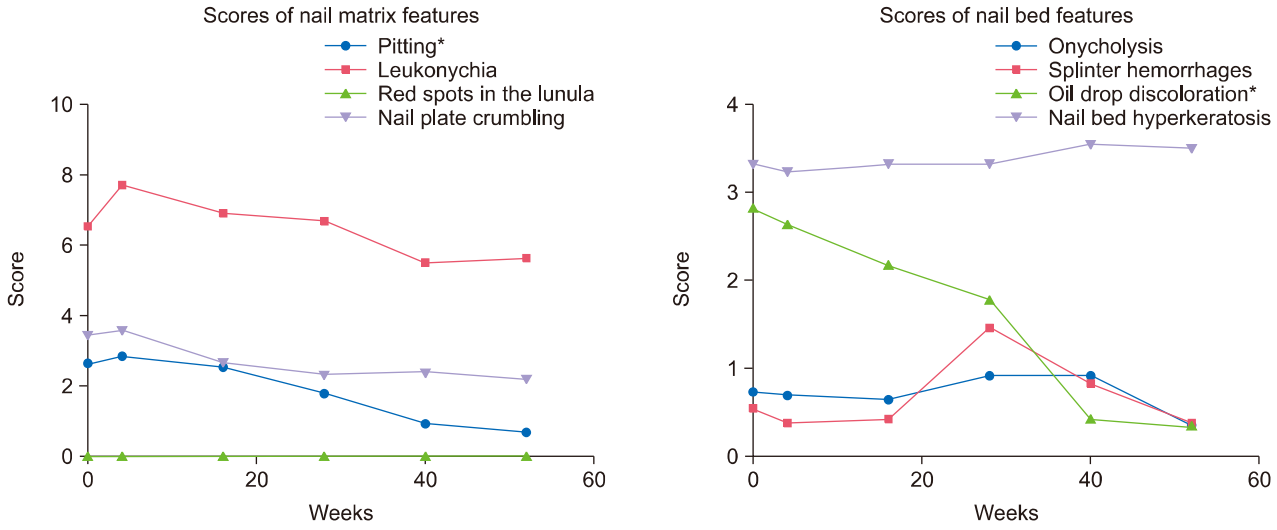

Fig. 4. Changes in toenail Nail Psoriasis Severity Index (NAPSI) scores according to each characteristic throughout 52 weeks (range, 0～40) (*$p<0.05$).

the NAPSI score because differentiating whether the symptom is due to psoriasis or aging is difficult; hence, it is doubtful whether the score really reflects the severity of nail psoriasis. The high frequency of leukonychia occurrence in this study could be attributed to this uncertainty. In addition, NAPSI can be scored even if only one of the bed or matrix characteristics is present; therefore, it may not improve when psoriasis-specific characteristics such as pitting disappear while other symptoms such as leukonychia remain. Age-related changes were commonly detected in this study because all patients aged >40 years, except for two. This circumstance made the study reflect not an ideal nail psoriasis setting but a realistic clinical setting.

Besides, onychomycosis is more common in toenails than in fingernails and is one of the frequently associated comorbidities; therefore, its importance in toenail studies can be emphasized. One study suggested that nearly one fifth of patients with psoriasis suffer from onychomycosis[28]. However, concomitant onychomycosis might hinder the evaluation process of nail psoriasis. Two patients in this study suffered from toenail onychomycosis; therefore, evaluating their NAPSI scores was difficult.

Due to these reasons, NAPSI showed somewhat critical limitations in the evaluation of toenail psoriasis. Moreover, only one Greek open-label study has evaluated both finger and toenail psoriasis in the setting of ustekinumab treatment[14]. To our knowledge, no randomized clinical trials for psoriasis evaluated all the toenails throughout the treatment. Researchers either excluded the toenails[17,29] or only selected the most severe ones[18]. Although NAPSI is currently recognized as a validated tool to evaluate the treatment response of fingernail psoriasis in biological therapy using NAPSI50 (50% improvement in NAPSI score), evidence showing that it is also applicable to toenail psoriasis is limited.

Nevertheless, NAPSI tended to improve throughout the period of ustekinumab injection. In a previous study, ustekinumab was reported to be efficacious in treating toenail psoriasis despite its slow response[24]. However, when individual toenails were analyzed, only the first and second toes were significantly improved. Therefore, this finding cannot be interpreted as the selective efficacy of ustekinumab on the first and second toes. Rather, it is plausible to suppose that the third to fifth toes failed to show NAPSI improvement because factors other than pure psoriatic changes were reflected in the evaluation, which cannot be reversed by ustekinumab. In other words, the third to fifth toes had characteristics that seriously hindered the severity evaluation during the ustekinumab treatment.

Interestingly, pitting and oil-drop discoloration were the only two characteristics that significantly improved throughout the treatment period. Pitting is manifested by abnormality of the proximal nail matrix, whereas oil-drop discoloration is characterized by nail bed inflammation[30]. This shows that ustekinumab is effective in all nail parts from the proximal nail matrix to nail bed. Other characteristics did not show clinical significant changes, which might be due to the fact that subungual hyperkeratosis, onycholysis, and leukonychia can be induced by other factors like aging or trauma, resulting in biased NAPSI scores. Hence, the use of all the eight parameters might hinder the clinically appropriate assessment of toenail psoriasis.

This is the first study that focused on the treatment course of toenail psoriasis. Although fingernail and toenail psoriasis have many similar characteristics, obvious differences were identified. The difference between finger and toenail psoriasis is easily noticeable but is often neglected as fingernails are solely evaluated in most clinical trials. Nonetheless, toenail psoriasis also has a large impact on the quality of life; therefore, its exact assessment and treatment are crucial. Ustekinumab showed its efficacy on toenail psoriasis involving the big and second toes. However, the three lateral toenails could not show their treatment response using the NAPSI score because of their characteristics and NAPSI limitations. Therefore, researchers should recognize that the current evaluation methods cannot fully reflect the course of nail psoriasis during the biological treatment and develop a more practical approach that can represent the actual clinical impacts.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-33-131-s001.pdf.

CONFLICTS OF INTEREST

Dr. Youn has served as an adviser, received speaker honoraria, and participated in clinical trials for AbbVie, CKD-pharma, Elli-Lilly, Janssen, and Novartis. He participated in a clinical trial for Kyowa-Kirin.

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DATA SHARING STATEMENT

Research data are not shared.

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