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REFERENCES

1. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. *Cancer*. 1998;83:1128-1135.
2. Shain AH, Garrido M, Botton T, et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. *Nat Genet*. 2015;47:1194-1199.
3. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521-2532.
4. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(1):34.
5. Eroglu Z, Zaretsky JM, Hu-Lieskovan S, et al. High response rate to PD-1 blockade in desmoplastic melanomas. *Nature*. 2018;553(7688):347-350.

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Optimal concentration range of ustekinumab in patients with plaque-type psoriasis

To the Editor: Ustekinumab has a better efficacy and safety profile than earlier anti–tumor necrosis factor biologics. Some biologics elicit an unwanted immune response in the patient by the production of antidrug antibodies, leading to reduced drug levels, loss of clinical response, and adverse events.[1] Monitoring of ustekinumab levels and antibodies to ustekinumab (ATUs) may be useful for future clinical practice to complement clinical assessment and optimize patient treatment.

The aims of this study were to analyze the association between serum trough levels of ustekinumab and treatment response in patients with psoriasis at 52 weeks and to establish an optimal concentration range of ustekinumab levels. Patients were treated with 45 mg of ustekinumab initially and 4 weeks later, followed by 45 mg every 12 weeks.

We recruited 37 patients with moderate-to-severe psoriasis treated with ustekinumab in an observational, cross-sectional, prospective, single-center study (Table I). Blood samples collected within 72 hours before administration of ustekinumab were analyzed for levels of ustekinumab and ATUs by enzyme-linked immunosorbent assays with Promonitor-UTK and Promonitor-ANTI-UTK tests, respectively (Progenika, Spain).[2]

Table I. Baseline demographics and clinical characteristics for the total population of patients with psoriasis (N = 37)

Variable	Value
Demographics	
Median age, y (IQR)	48.0 (39.0-57.5)
Age at diagnosis, y	23.0 (14.0-39.0)
Age at initial treatment, y	48.0 (38.0-45.5)
Women, (%)	17 (46)
Men, (%)	20 (54)
Disease status	
Mean duration of disease, y (IQR)	19.0 (11.0-35.5)
Mean baseline PASI (IQR)	13.0 (9.4-16.4)
Medication, n (%)	
Ustekinumab-naive group	15 (40.5)
Maintenance group	22 (59.5)
Prior biologic use, n (%)	25 (67.6)
1 biologic	8 (21.6)
2 biologics	10 (27.0)
3 biologics	7 (18.9)
Adalimumab	16 (43.2)
Etanercept	29 (51.3)
Efalizumab	13 (35.1)
Concomitant medications, n (%)	5 (13.5)
Methotrexate	2 (5.4)
Leflunomide	1 (2.7)
Cyclosporine A	2 (5.4)

The mean duration of exposure ustekinumab in the maintenance group before recruitment was 30.6 months.
IQR, Interquartile range; *PASI*, Psoriasis Area and Severity Index.

Disease activity was assessed according to the Psoriasis Area and Severity Index (PASI) and clinical improvement (ΔPASI), as indicated by the proportion of patients achieving a 75% reduction in PASI score or the proportion of patients achieving a 90% in PASI score relative to baseline. The Spearman correlation and Mann-Whitney U test were used to determine the association between ustekinumab and PASI score and that between ustekinumab and clinical response, respectively. Significance was set at P less than .05.

A significant inverse correlation between ustekinumab levels and PASI score at week 52 ($r = -0.39$; $P < .05$) was found. The median concentration of ustekinumab was significantly higher ($P < .05$) in good responders (ΔPASI > 90%) (median concentration 0.47 μg/mL [interquartile range (IQR), 0.31-0.70]) and moderate responders (75% < ΔPASI < 90%) (median concentration, 0.32 μg/mL [IQR, 55 0.15-0.53]) than in nonresponders (ΔPASI < 75%) (median concentration, <0.131 μg/mL [IQR, <0.13 to 0.32]).

Two patients (5.4%) were positive for ATUs, which is in agreement with other cohort studies and clinical trials (5.2%-7.0%)[3-5] and had no

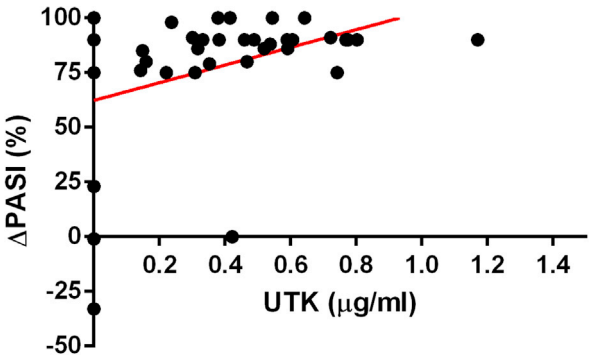

Fig 1. Scatter plot to represent trough levels of ustekinumab (UTK) relative to the change in clinical improvement according to the Psoriasis Area and Severity Index relative to baseline (ΔPASI). Concentrations higher than 0.42 μg/mL have no additional clinical benefit relative to PASI.

detectable level of ustekinumab, as opposed to patients without ATUs (median concentration, <0.13 μg/mL [IQR, 0-0] vs 0.42 μg/mL [IQR, 0.22-0.59] [$P < .05$]) and higher PASI scores (17 [IQR, 10-24] vs 1 [IQR, 0-2] [$P < .05$]) as opposed to patients without ATUs. It must be noted that 13.5% of the patients were undergoing concomitant immunosuppression, and the relationship between low or negative ustekinumab levels, ATU formation, and clinical response is still controversial.[3-5]

The therapeutic ranges of ustekinumab concentration, as calculated from a concentration effect curve of ustekinumab trough levels relative to ΔPASI, are 0.14 to 0.37 μg/mL and 0.37 to 0.42 μg/mL for moderate and good responders, respectively. In addition, our study shows that concentrations higher than 0.42 μg/mL have no additional clinical benefit relative to PASI score (Fig 1). We observed overtreated (ustekinumab concentration, 0.42-1.17 μg/mL) patients (n = 17 [46%]) who theoretically could have had their dose tapered by increasing the time between injections, leading to ustekinumab trough concentrations within the therapeutic range without losing clinical efficacy and saving costs. Another potential use of therapeutic drug monitoring would be to test reactively if patients do not respond to ustekinumab, as was recently recommended for anti–tumor necrosis factor drugs in inflammatory bowel disease.

The number of ATU-positive patients detected in our study is too small to determine a correlation between ATU formation and clinical efficacy, and future studies are needed to determine the optimal management approach to patients who develop ATUs, including possibly increasing the dose of ustekinumab or adding concomitant immunosuppression with a drug such as methotrexate. Despite the limitations of our study, we have presented novel therapeutic ranges of ustekinumab concentration, which may be a valuable tool to improve the management of patients with psoriasis.

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Reprints not available from the authors.

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REFERENCES

1. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. *Ann Rheum Dis*. 2013;72:1947-1955.
2. Ruiz-Arguello B, del Agua AR, Torres N, et al. Comparison study of two commercially available methods for the determination of infliximab, adalimumab, etanercept and anti-drug antibody levels. *Clin Chem Lab Med*. 2013;51:e287-e289.3.

3. Chiu HY, Chu TW, Cheng YP, et al. The association between clinical response to ustekinumab and immunogenicity to ustekinumab and prior adalimumab. *PLoS One*. 2015;10:e0142930.
4. Menting SP, van den Reek JM, Baerveldt EM, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. *Br J Dermatol*. 2015;173:855-857.
5. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675-1684.

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Building a scale for measuring burden of hand eczema: BoHEM

To the Editor: Chronic hand eczema (CHE) results in persistent symptoms that interfere with daily activities, social functioning, and workability.

We failed to find in the literature any specific tool that aimed to assess the burden experienced by patients with CHE. Such a tool would be valuable both for patients and for clinicians who manage patients with CHE daily. Indeed recently, the concept of burden has been given a central role in evaluating patient care.[1] The self-administered Burden of Hand Eczema (BoHEM) questionnaire was developed by using a standard methodology that included 3 distinct phases: conception, development, and validation.[2] Each phase followed a strict methodologic process involving a multidisciplinary team of dermatologists, patients, and experts in patient-reported outcomes. The original BoHEM questionnaire was developed in French. A linguistic and cross-cultural validation following a previously validated methodology[3] was applied to generate an American English–language version.

The initial conceptual phase involved 15 patients who shared their complaints, perceptions, and experiences in relation to CHE, after which 15 items were retained and used to form the conceptual questionnaire (2 questions were removed because they were not related to a particular factor). Principal component factor exploratory analysis was performed to test the questionnaire's robustness. Through the use of standardized regression analysis, 3 dimensions were highlighted (Table I): daily life (8 questions), perceived appearance to others, (5 questions), and relationships (2 questions). The unidimensionality of the BoHEM questionnaire was confirmed by higher-order factor analysis. The practical model fit indices were acceptable, with a comparative fit index of 0.9531 and a non-normed fit index of 0.9783. The model appeared well adjusted and well fitted, offering the possibility of grouping the 3 dimensions into 1 overall score. With regard to

Table I. Loading of questions on the factors after rotation

Item	Factor 1	Factor 2	Factor 3
I have difficulty performing everyday activities.	**0.65**	0.27	0.05
My professional activities are impacted.	**0.62**	0.38	0.05
I have difficulty grooming (styling hair, washing, shaving).	**0.69**	0.17	0.21
I have had problems at work due to my chronic hand eczema.	**0.65**	0.25	0.08
Daily care for my chronic hand eczema is immensely tiring.	**0.76**	0.04	0.27
It seems to me that my chronic hand eczema is costing me more and more.	**0.70**	0.17	0.22
My chronic hand eczema affects my quality of sleep negatively.	**0.69**	0.23	0.21
I believe that my life would have been different without chronic hand eczema.	**0.61**	0.25	0.28
When I show my hands, the looks from other people embarrass me.	0.32	*0.70*	0.22
I hesitate to shake hands when meeting someone.	0.35	*0.56*	0.15
I tend to keep my hands in my pockets.	0.15	*0.80*	0.15
I don't know where to put my hands anymore when at work.	0.17	*0.82*	0.17
Interacting with others is difficult.	0.41	*0.50*	0.46
I have a troubled emotional life.	0.28	*0.26*	<u>0.84</u>
The appearance of my hands (redness, dryness) affects my sex life.	0.18	0.17	<u>0.86</u>

Loadings (correlation coefficients between questions and factors) are computed to facilitate the interpretability of the factors. A loading greater than 0.5 indicates that the couple question and factor are strongly related to each other. A question that does not display a loading greater than 0.5 is not particularly related to any of the selected factors. The questions in this table are reordered to first show those corresponding to factor 1 (*boldface*), then to factor 2 (*italic*), and lastly to factor 3 (*underlined*). We can now interpret factors by looking at the common theme among questions that belong to the same factor. The total score is obtained by summing the scores for each of the 15 items as follows: never or not applicable is scored as 0; rarely is scored as 1, sometimes is scored as 2, often is scored as 3, very often is scored as 4, and constantly is scored as 5, resulting in a maximum of score of 75 and a minimum score of 0. The higher the score, the greater the importance of the burden of the disease.