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Clinically meaningful change in itch intensity scores: An evaluation in patients with chronic kidney disease–associated pruritus

To the Editor: Clinical trials to assess the antipruritic effect of a treatment commonly use a numerical rating scale (NRS) ranging from 0 (no itching) to 10 (worst imaginable itching) to evaluate the worst itch intensity. However, for the drug effect to be clinically relevant, the magnitude of the reduction in the NRS scores must represent a meaningful improvement to the patients. Clinically meaningful changes with respect to NRS scores have been characterized in dermatologic conditions,[1-4] but to our knowledge, the threshold for such changes among patients with systemic chronic kidney disease–associated pruritus (CKD-aP) has not been established.

To address this knowledge gap, we conducted a secondary analysis of data pooled across treatment groups from a phase 2, multicenter, double-blind, randomized, placebo-controlled study (NCT02858726) to determine the magnitude of change required for a meaningful reduction in itch intensity on the Worst Itching Intensity-NRS

Table I. Thresholds for clinically meaningful change for Worst Itching Intensity Numerical Rating Scale (*WI-NRS*) using primary and secondary anchor-based methods*

Criteria	WI-NRS change score (week 8 − baseline), mean	Change from baseline, mean, %	Effect size (Cohen *d*)
Primary anchor			
PGI-C minimally improved	−2.26	−33.56	1.29
PGI-C minimally and much improved	−3.02	−42.99	1.65
PGI-C much improved	−3.41	−47.81	1.83
Secondary anchors			
PGI-S improved 1 point	−2.49	−37.10	1.40
PGI-S improved at least 1 point	−3.45	−49.61	1.75
5-D Itch Direction (Itch)			
A little better	−1.94	−26.37	1.19
A little better or much better	−3.32	−49.61	1.80
5-D Itch Degree (Itch Intensity)			
Improved 1 point	−3.02	−45.23	1.82
Skindex-10 (item 1) Itch	−2.65	−39.05	1.47
Bothersome improved 2 points			
Mean (secondary anchors)	−2.81	−41.16	

PGI-C, Patient Global Impression of Change; *PGI-S*, Patient Global Impression of Severity.
*Anchor-based methods were linked to patients' reports of perception of change in WI-NRS at week 8 and were selected a priori to most closely relate to the concept measured by the WI-NRS. The PGI-C was the primary anchor variable because it is commonly used to evaluate meaningful change, including within populations with pruritus, and is recommended by the United States Food and Drug Administration. "Minimally improved," "minimally and much improved," and "much improved" anchor categories were used to represent minimal to larger improvements. The use of these anchors was justified by the absence of approved therapies for moderate to severe chronic kidney disease–associated pruritus (CKD-aP). Secondary anchors included (1) a 1-point and at least 1-point categorical severity change on the PGI-S, which corresponded to a shift in itch severity category (eg, from severe to moderate). The clinical significance of single-category shifts for CKD-aP is reinforced by data indicating that greater itch severity is linked to higher mortality; (2) the 5-D direction and degree questions asking patients whether itching got better or worse on a scale of 1 (completely resolved) to 5 (getting worse) within the past 2 to 4 weeks and to rate the intensity of their itching on a scale of 1 (not present) to 5 (unbearable), respectively; and (3) the Skindex-10 item 1 asking how often patients were bothered by itching on a scale of 0 (never bothered) to 6 (always bothered) within the past week.

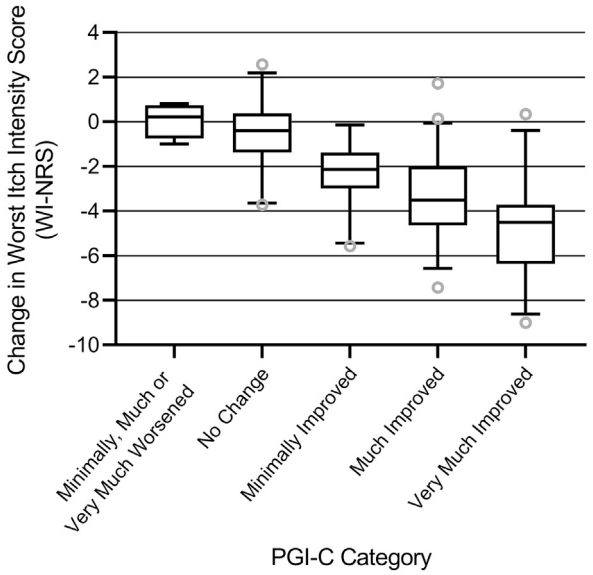

Fig 1. Proportional reductions in Worst Itching Intensity Numerical Rating Scale (*WI-NRS*) point to the level of change perceived by patients on the Patient Global Impression of Change (*PGI-C*). Box plot shows the change in WI-NRS from baseline to week 8 by PGI-C category. The *center line* inside the box represents the median, the *hinges* are the 25th and 75th percentiles, the *whiskers* bound the central 95% of the distribution, and the *circles* beyond the whiskers are outliers. The entire study population was included (n = 174) whether patients received placebo or difelikefalin, with the number ranging from 24 to 49 patients per PGI-C category, except for the categories of "very much worse," "much worse," or "minimally worse," which were combined due to the small sample size (n = 6).

(WI-NRS) (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/yjntdkbp9r.1) in hemodialysis patients with moderate to severe pruritus.

The study was approved by the Quorum Review Institutional Review Board before commencement and was conducted in accordance with the principles of Good Clinical Practice, as described in International Council for Harmonisation Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. Patients provided written, informed consent before any study-related assessments were performed.

This study demonstrated the antipruritic effects of the selective κ-opioid receptor agonist, difelikefalin, with a significant reduction of itch intensity and an improvement of itch-related quality of life (QoL) over placebo.[5] Itch intensity and QoL scores were collected over an 8-week treatment period.[5] The Patient Global Impression of Change (PGI-C), with 7 categories ranging from "very much improved" to "very much worse," Patient Global Impression of Worst Itch Severity (PGI-S), with values from 0 (none) to 4 (very severe), and the Skindex-10 and 5-D itch QoL questionnaires were selected as anchor variables in the present analysis (Supplemental Figs 2-5).

The threshold for meaningful reduction of WI-NRS was estimated using anchor- and distribution-based methods consistent with United States Food and Drug Administration guidance, as described in Table I and Supplemental Table I.

The study included 174 hemodialysis patients, who were predominantly male (60%) and African American (59%), with a median age of 59 years (range, 26-84 years) and history of chronic itching for 4.4 years.

Distribution-based estimates, considered to provide lower boundaries of meaningful change thresholds, ranged from −0.67 to −1.78 points relative to a baseline WI-NRS mean of 6.8 (Supplemental Tables I and II).

In the primary anchor analysis, mean changes in WI-NRS ranged from −2.26 to −3.41 points with large effect sizes (Cohen $d > 1.0$) associated with a priori definitions of a clinically important improvement measured by the PGI-C. This analysis was supported by the analysis of multiple secondary anchors (Table I, Fig 1). The PGI-C was identified as a primary anchor because it specifically asks patients about the improvement of their condition, taking into consideration treatment effect and patient expectation.

These analyses demonstrated that a reduction of ≥3 points on the WI-NRS marks an appropriate threshold for defining a clinically meaningful change in pruritus in patients with CKD-aP.

CKD-aP significantly impacts the patient's QoL, is associated with a poor prognosis, and represents a significant unmet need due to lack of treatment options. The present evidence should facilitate the development of treatments for CKD-aP that could ultimately affect patient care and clinical practice.

Margaret Vernon, PhD,[a] *Sonja Ständer, MD,*[b] *Catherine Munera, PhD,*[c] *Robert H. Spencer, PhD,*[c] *and Frédérique Menzaghi, PhD*[c]

From Evidera, Bethesda, Maryland[a]*; the Center for Chronic Pruritus, Department of Dermatology, University Hospital Münster, Münster, Germany*[b]*; and Cara Therapeutics, Stamford, Connecticut.*[c]

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IRB approval status: Reviewed and approved by the Quorum Review Institutional Review Board.

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Correspondence to: Frédérique Menzaghi, PhD, Cara Therapeutics, Inc, 4 Stamford Plaza, 107 Elm Street, 9th Floor, Stamford, CT 06902

E-mail: fmenzaghi@caratherapeutics.com

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Surgical management and practices in pregnancy and lactation: A survey of United States dermatologic surgeons

To the Editor: Treatment of skin cancers in pregnant and lactating women poses a challenge for dermatologic surgeons because the welfare of both mother and fetus must be considered. A standardized approached is especially important because melanoma is a significant cause of cancer-related deaths in women of reproductive age. While guidelines advocate for the immediate surgical management of skin cancers in pregnancy, whether this is applied in practice is unclear.[1,2] To address this knowledge gap, we surveyed members of the American College of Mohs Surgery (ACMS) to describe current practice patterns in the management of malignant lesions in pregnant and lactating women.

Table I. Management of nonmelanoma skin cancer during pregnancy and lactation

Nonmelanoma skin cancer	Treatment rate, %	RR vs 1st trimester	*P* value*
Basal cell carcinoma (n = 117)			
Any form of treatment(s)†			
Timing			
1st trimester	61.5		
2nd trimester	77.8	1.26	.07
3rd trimester	82.1	1.33	<.001
Lactation	98.3	1.60	<.001
Surgical excision			
Timing			
1st trimester	45.3		
2nd trimester	68.4	1.51	<.001
3rd trimester	75.2	1.66	<.001
Lactation	97.4	2.15	<.001
Squamous cell carcinoma (n = 121)			
Any form of treatment(s)			
Timing			
1st trimester	76.9		
2nd trimester	89.2	1.16	.01
3rd trimester	93.3	1.22	<.001
Lactation	99.2	1.29	<.001
Surgical excision			
Timing			
1st trimester	67.0		
2nd trimester	84.3	1.26	.035
3rd trimester	89.3	1.33	.001
Lactation	99.2	1.48	<.001

RR, Relative ratio.
*The *P* value was determined using χ^2 and Fisher exact tests.
†Treatments surveyed: surgical excision, electrodesiccation and curettage, cryotherapy, and topical chemotherapy.

The survey was completed by 123 ACMS members; of whom, 80% of respondents altered practice based on pregnancy and lactation status, and 65.9% did not use epinephrine-containing anesthetics in pregnant vs 26.0% in lactating women ($P < .001$). In addition, 35.8% avoided prophylactic antibiotics during pregnancy. No difference was found in the choice of antiseptic agents, suture strength, or duration of suture placement.

Respondents were significantly less likely to treat basal cell carcinoma, squamous cell carcinoma,