Clinically Important Difference for the FACIT-Fatigue Scale in Paroxysmal Nocturnal Hemoglobinuria: A Derivation From International PNH Registry Patient Data

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BACKGROUND

- Fatigue is a common symptom associated with paroxysmal nocturnal hemoglobinuria (PNH) and is frequently severe[1-3]
- The Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue) is an instrument validated in patients with PNH and has been used extensively in clinical trials and in the International PNH Registry[4,5]
  - FACIT-Fatigue consists of 13 items each scored from 0–4, yielding a maximum possible score of 52 points, with higher scores indicative of less fatigue[5]
- Several studies have demonstrated that the C5 inhibitor eculizumab, the first therapeutic agent approved for PNH, significantly alleviates fatigue as indicated by improved FACIT-Fatigue scores[6,7]
- A disease-specific clinically important difference (CID) for FACIT-Fatigue has not yet been estimated for patients with PNH, and studies have therefore generally used the CID estimated for other disease states
  - The CID of ≥3 points estimated for patients with cancer is generally used in the studies of patients with PNH[8]
  - Important differences in populations with other immune-mediated diseases are estimated to range from approximately 3–5 points[9-11]
  - A PNH-specific CID for FACIT-Fatigue would be informative in interpreting changes in impact of fatigue and could serve as a more robust criterion for evaluating treatment efficacy and benefit
- The International PNH Registry is a worldwide observational study collecting safety, effectiveness, and quality-of-life data from patients with a confirmed PNH diagnosis or detectable PNH clone, irrespective of treatment. It is the largest existing database of patients with PNH and provides an extensive profile of PNH disease course and outcomes

OBJECTIVES

- To determine the FACIT-Fatigue CID for patients with PNH using distribution- and anchor-based approaches and real-world data from the International PNH Registry

METHODS

Patients

- Adults enrolled in the PNH Registry with a valid patient ID as of January 2021 and who
  - Had nonmissing data for date of birth, sex, enrollment date, and treatment status
  - Had nonmissing FACIT-Fatigue scores and ≥1 nonmissing clinical anchor at baseline
  - Initiated eculizumab within 28 days of enrollment and had not received prior treatment with any non-eculizumab complement inhibitor

Analysis

- FACIT-Fatigue score is collected on the Patient Questionnaire case report form and was derived from 13 fatigue-related questions with 5 ordinal responses (“not at all,” “a little bit,” “somewhat,” “quite a bit,” and “very much”)
  - Score is a sum of 13 item scores (range, 0–52)
  - Score is scaled by multiplying sum by 13 and then dividing by the number of nonmissing questions (minimum of 7 questions must be answered)
- FACIT-Fatigue scores were assessed at baseline and at follow-up visits at 6, 12, 24, and 36 months (±3 months)
  - Baseline was defined as the date of eculizumab initiation
- Two distribution-based[12,13] CID estimates were calculated using the following:
  - 0.5× standard deviation (SD)
  - Standard error of measurement (SEM)
    - The SEM was calculated as SD× sqrt(1–α), where α represents the internal consistency measurement Cronbach’s α
    - Cronbach’s α was calculated from the 13 FACIT-Fatigue items
- Anchor-based estimates considered 2 continuous patient-reported outcome variables
  - European Organisation for Research and Treatment of Cancer (EORTC) Global Health Status Quality of Life (QoL) summary score (quartiles; higher scores indicate better QoL), and
  - EORTC Global Health Status Fatigue Subscale score (quartiles; lower scores indicate less fatigue)
- The baseline FACIT-Fatigue score was calculated for each predefined categorization of the anchors; the mean of differences in FACIT-Fatigue between adjacent categories was calculated and referenced as the anchor-based CID
- Changes in high disease activity (HDA) shift (“yes” to “no” from baseline to each follow-up visit) were then assessed by FACIT-Fatigue score change (≤1 CID, no change, or ≥1 CID estimated from the distribution-based methods)
  - HDA was defined as lactate dehydrogenase ratio ≥1.5×upper limit of normal and ≥1 of the following: history of a major adverse vascular event (including a thrombotic event); anemia; or physician-reported abdominal pain, dyspnea, dysphagia, fatigue, hemoglobinuria, or erectile dysfunction

RESULTS

Baseline Demographics and Disease Characteristics

- 423 patients were included in the analysis (**Table 1**)
  - The study population was similar in terms of demographics to the overall registry population
  - The majority of patients were white or of Caucasian descent (84%); 3% were of Hispanic or Latino ethnicity
- At baseline, 93% of patients had physician documentation of fatigue in their medical history (mean FACIT-Fatigue score, 29.4)

Table 1. Patient Demographics and Baseline Disease Characteristics

	Patients (N=423)
Sex, n (%)	
Female	226 (53)
Male	197 (47)
Race, n (%)	
White or Caucasian descent	355 (84)
Asian	51 (12)
Black or African descent	9 (2)
Other (unlisted, multiple races, Aboriginal)	8 (2)
Age at PNH start,* y	
Mean±SD	39.0±17.5
Median (Q1, Q3)	35.0 (23.2, 51.6)
Mean±SD baseline hemoglobin,† g/dL	9.7±2.09
Mean baseline LDH ratio×ULN,‡ n (%)	
<1.5	40 (11)
≥1.5	324 (89)
Percent GPI-deficient granulocytes,¶ n (%)	
<10%	5 (2)
≥10%–<50%	35 (11)
≥50%	282 (88)
Physician-documented fatigue,§ n (%)	
Yes	386 (93)
No	31 (7)

GPI, glycosylphosphatidylinositol; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; ULN, upper limit of normal. *PNH start date is defined as the earliest date among the following; PNH diagnosis, date of first PNH symptoms, and/or date of reported granulocyte clone lab test. †Baseline hemoglobin, n=370. ‡Baseline LDH, n=364. ¶GPI-deficient granulocytes, n=322. §Physician-documented fatigue, n=417.

Clinically Important Differences

- Distribution-based CIDs were in the range of 5–7 when using SEM and 0.5×SD, respectively (**Table 2**)
  - Internal consistency was high, with Cronbach’s α=0.87, supporting use of SEM-based values

Table 2. Important Difference of FACIT-Fatigue Score at Baseline

				Important Difference	
	Mean FACIT-Fatigue Score	Cronbach’s α (r)	SD	½ SD	SEM
Total Population (N=423)	29.4	0.873	12.9	6.5	4.6

SD, standard deviation; SEM, standard error of measurement.

- For anchor-based measurements, the CIDs were in the range of 8–10 using the EORTC QoL and EORTC fatigue subscale scores, respectively (**Table 3**)

Table 3. Important Difference of FACIT-Fatigue by EORTC QoL Score and EORTC Fatigue Subscale

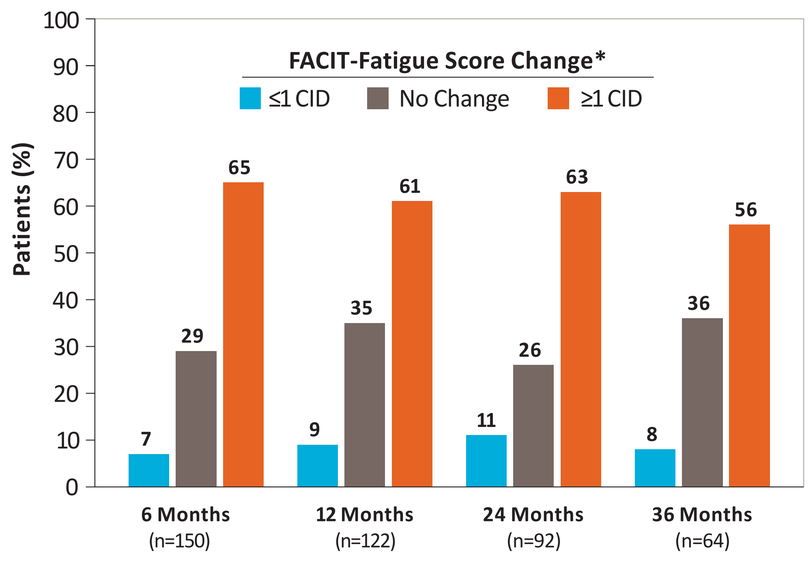
	EORTC QoL Score				
	Q1	Q2	Q3	Q4	Difference
Mean FACIT-Fatigue Score*	15.7	25.5	31.1	40.9	8.4
	EORTC Fatigue Subscale				
	Q1	Q2	Q3	Q4	Difference
Mean FACIT-Fatigue Score*	44.8	36.0	24.4	16.3	-9.5

EORTC, European Organisation for the Research and Treatment of Cancer; QoL, quality of life.
*Higher scores indicate more fatigue.

Outcomes by CID in FACIT-Fatigue

- The percentage of patients who changed from having HDA at baseline to no HDA at eculizumab-treated follow-up visits increased over time
  - Using the SEM as the referent CID, the majority of these patients experienced ≥1 CID in FACIT-Fatigue that was sustained through 36 months (**Figure 1**)
  - Results were similar when 0.5×SD was used (data not shown)

Figure 1. Change in Percentage of Patients With HDA at Baseline to No HDA During Follow-up by FACIT-Fatigue Score Change



CID, clinically important difference; HDA, high disease activity (defined as lactate dehydrogenase ≥1.5 × upper limit of normal and at least 1 PNH symptom); PNH, paroxysmal nocturnal hemoglobinuria; SEM, standard error of measurement.

*CID reflects the SEM-derived value of 5 points.

SUMMARY AND CONCLUSIONS

- This finding, obtained from a real-world data set with a large number of patients, helps establish an important metric for assessment of the meaningful treatment response in patients with PNH
- Collectively, these results support the use of 5 points as the CID for FACIT-Fatigue in individual patients with PNH, which is close to the range of CIDs reported in other diseases (3–5 points)
  - This CID is markedly smaller than the group average FACIT-Fatigue improvement of 10 points achieved with long-term eculizumab treatment in the pivotal blinded phase 3 TRIUMPH study[14]
- Limitations include that the analysis was based on an observational data set and not all patients had available data for every outcome assessed
- Distribution-based approaches to determine the CID rely on statistical data, whereas anchor-based approaches determine CID by comparison to an external standard
  - The anchor-based approach provides clinically meaningful differences in scores, but these are not necessarily the minimally meaningful differences

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DISCLOSURES

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