Relationship between hemoglobin and quality of life in non-transfusion-dependent patients with myelofibrosis treated with luspatercept

PS1841

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Objectives

- This post hoc analysis of the phase 2 MF-001 trial evaluated whether changes in Hb levels, defined as an increase of ≥1.5 g/dL from baseline over 84 consecutive days or achieving a target level of ≥10 g/dL after starting treatment, were associated with improvements in anemia-related QoL in NTD MF patients treated with luspatercept.

Conclusions

- This analysis of the phase 2 MF-001 trial demonstrated a significant and clinically meaningful relationship between Hb outcomes and anemia-related QoL improvement in NTD patients with MF treated with luspatercept.
- Achieving a Hb level of ≥10 g/dL or an increase from baseline of ≥1.5 g/dL was significantly associated with a meaningful improvement in patient-reported anemia and fatigue symptoms.
- Most patients with Hb response and evaluable QoL also experienced an improvement in anemia-related QoL.
- These findings highlight the value of luspatercept in providing QoL benefits among NTD patients with MF whose Hb levels improved during treatment.

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Introduction

- Anemia is a common complication in myelofibrosis (MF) and is associated with fatigue and reduced quality of life (QoL).
- The phase 2 ACE-536-MF-001 (MF-001) trial showed that luspatercept, an erythroid maturation agent, improved hemoglobin (Hb) levels in non-transfusion-dependent (NTD) patients with MF.[1]
- Over the entire treatment period, 7 (19.4%) NTD patients maintained a consistent Hb increase from baseline ≥1.5 g/dL over any consecutive 84-day period without a red blood cell (RBC) transfusion (primary endpoint), and 13 (36.1%) achieved a mean Hb increase from baseline ≥1.5 g/dL over a consecutive 84-day period without an RBC transfusion (secondary endpoint).
- While luspatercept significantly improved Hb levels, the relationship between Hb levels and anemia-related QoL remains unclear in NTD patients with MF.

Methods

Data source

- Data collected from cohorts 1 and 3A in the phase 2 MF-001 trial of luspatercept were pooled in the analysis.[1]
- Cohorts 1 and 3A included patients who met both criteria:
  - Anemic: Requiring a Hb level of ≤9.5 g/dL recorded on ≥3 different days, including the day of first dosing, in the 84 days before the first luspatercept dose
  - NTD: No RBC transfusions in the 84 days before the first luspatercept dose
- Both cohorts received 1.0 mg/kg luspatercept on day 1 of each 3-week cycle, with dose titrations up to a maximum of 1.75 mg/kg.
- Cohort 3A included patients who had been on a stable dose of ruxolitinib for at least 112 days before enrollment; they continued to receive ruxolitinib throughout the study.
- Hb levels were assessed at baseline, each 3-week treatment cycle, and the day-169 assessment for clinical benefit.

QoL instruments and assessment schedule

- The Functional Assessment of Cancer Therapy – Anemia (FACT-An) questionnaire was administered every other treatment cycle (every 6 weeks) to assess patients' fatigue-related symptoms.[2]
- The primary subscales for this analysis included the FACT-An Fatigue Subscale (FS) and the Anemia Subscale (AnS).
  - The FS includes 13 items assessing fatigue and has a scale range of 0 (worst) to 52 (best).
  - The AnS includes the FS items plus an additional 7 items addressing anemia concerns unrelated to fatigue and has a scale range of 0 (worst) to 80 (best).
- For all analyses, thresholds for meaningful improvements were used to evaluate whether changes in QoL were meaningful.[3]
  - Meaningful change in FS score was defined as a ≥3-point increase (improvement) or decrease (worsening) in the FS score.
  - Meaningful change in AnS score was defined as a ≥4-point increase (improvement) or decrease (worsening).

Statistical analysis: Relationship between Hb level and QoL

- Linear mixed-effects regression models with random intercept and slope were estimated to quantify the relationship between change from baseline in FACT-An subscales (dependent variable) and Hb (time-varying independent variable).
- Two models were fitted varying the parameterization of Hb: change from baseline (≥1.5 g/dL vs. <1.5 g/dL) over 84 days and absolute post-baseline Hb target (≥10 g/dL vs. <10 g/dL) without an RBC transfusion.
- Baseline covariates (age, FACT-An subscale score, and sex) and visit (discrete) were included in all models.
- Local and central Hb levels assessed within 3 days of a FACT-An assessment were included in the models.
- Each model included data from baseline through cycle 31 or end of treatment.

Statistical analysis: Association of QoL improvement with clinical response

- Swimmer plots were generated for patients who achieved a clinical response over the entire treatment period (mean Hb increase from baseline ≥1.5 g/dL over a consecutive 84-day period without an RBC transfusion), indicating time periods for clinical response and meaningful QoL improvement.
- Patients were excluded if they had missing baseline QoL scores, baseline scores too high to show meaningful improvement, or baseline scores better than general population norms (i.e., 40.1 for FS and 62.1 for AnS).[4]

Results

Baseline demographics and disease characteristics

- Thirty-six patients were included in the NTD cohorts, with a median age of 68.5 years and median baseline Hb values of 8.6 g/dL (**Table 1**).
- Most patients had primary MF (58.3%) and an Intermediate-risk DIPSS score of 2 or 3 (83.3%).
- The mean baseline FS and AnS scores were 37.3 and 58.3, below the population norms of 40.1 and 62.1, respectively.

Table 1. Baseline demographics and disease characteristics

Characteristic	NTD patients (cohort 1, cohort 3A)
N	36
Age, year, median (min, max)	68.5 (50, 89)
Male n, (%)	20 (55.6)
Race n, (%)	
White	26 (72.2)
Asian	5 (13.9)
Black or African American	1 (2.8)
Other	1 (2.8)
Not collected or reported	3 (8.3)
MF subtype, primary (%)	21 (58.3)
DIPSS score	
Intermediate-risk 1	5 (13.9)
Intermediate-risk 2	27 (75.0)
High-risk	3 (8.3)
Unknown	1 (2.8)
Baseline Hb levels (g/dL), median (min, max)	8.6 (6.6, 9.7)
Baseline FS score, mean (SD)	37.3 (11.2)
Baseline AnS score, mean (SD)	58.3 (13.8)

Abbreviations: AnS, Anemia Subscale; DIPSS, Dynamic International Prognostic Scoring System; FS, Fatigue Subscale; Hb, hemoglobin; MF, myelofibrosis; NTD, non-transfusion dependent; SD, standard deviation

FACT-An completion rate

- At baseline, 35 of 36 (97.2%) patients had non-missing FACT-An scores.
- At day 169, 17 of 27 (63.0%) patients still on treatment had non-missing FACT-An scores.

Relationship between Hb level and QoL

- A change from baseline in Hb of ≥1.5 g/dL was a significant predictor of improvements in both FS and AnS scores (**Table 2**, p <0.01).
- Additionally, achieving a target Hb level of ≥10 g/dL was a significant predictor of improvements in AnS and FS scores (**Table 2**, p <0.05).
- Coefficients indicated that the magnitude of QoL changes associated with each Hb target exceeded meaningful thresholds for improvement.

Table 2. Relationship between Hb targets and change from baseline in QoL

QoL Domain	Definition of Meaningful Improvement	Change from baseline in Hb (≥1.5 vs <1.5 g/dL)		Absolute Hb Level (≥10 vs <10 g/dL)	
		41 *vs* 103 observations†		52 *vs* 92 observations†	
	Change from baseline	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
FS	≥3	**4.32** (2.07, 6.57)	<0.001	**3.09** (0.42, 5.76)	0.024
AnS	≥4	**5.26** (2.30, 8.23)	0.001	**4.55** (1.14, 7.95)	0.009

†Multiple observations per patient. Coefficients exceeding the meaningful threshold are indicated in bold and blue.
Abbreviations: AnS, Anemia Subscale; FS, Fatigue Subscale; Hb, hemoglobin; QoL, quality of life

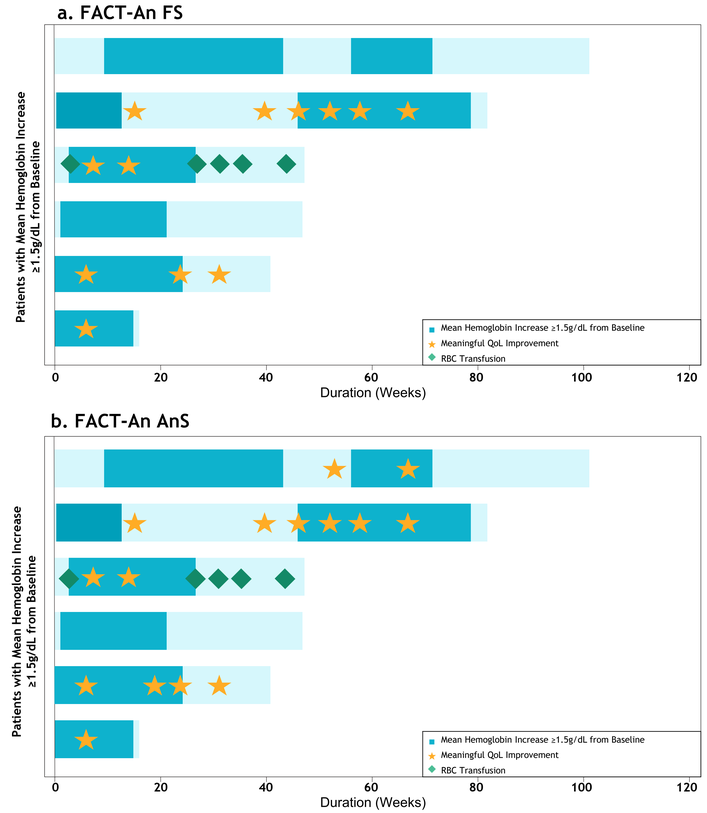
Association between FS improvement and clinical response

- Thirteen of 36 (36.1%) patients achieved a clinical response as defined by a mean increase ≥1.5 g/dL in Hb during a consecutive 84-day period without an RBC transfusion throughout the entire treatment period.
- Of these patients, 7 were not evaluable or were not expected to experience an improvement in FS score due to their baseline score:
  - 1 had a missing baseline score
  - 6 had a baseline score better than the general population norm (40.1) and/or a baseline score too high to experience further improvements (i.e., baseline score >49 [maximum possible score – threshold for meaningful improvement]).
- Among the 6 remaining patients, 4 (66.7%) patients had at least one meaningful improvement in FS overlapping with a clinical response (**Figure 1a**).

Association between AnS improvement and clinical response

- Similar to the FS, of the 13 patients with a clinical response, 7 were not evaluable or were not expected to experience an improvement in AnS score due to their baseline score.
- Among the 6 remaining patients, 5 (83.3%) patients had at least one meaningful improvement in AnS overlapping with a clinical response (**Figure 1b**).

Figure 1. Meaningful improvement in FACT-An during clinical response



Abbreviations: FACT-An AnS, Functional Assessment of Cancer Therapy – Anemia Anemia Subscale; FACT-An FS, Functional Assessment of Cancer Therapy – Anemia Fatigue Subscale; RBC, red blood cell; QoL, quality of life

Limitations

- Limitations of this study include a small sample size and low completion rates related to challenges with implementation of the electronic patient diaries.

References

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