Reduction in HRQOL with increasing VOC frequency among patients with SCD

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Introduction

- Sickle cell disease (SCD) is a single gene disorder marked by a mutation in the beta chain of hemoglobin (Hb) and multicellular adhesion to the endothelium.[1; 2] While the mutation inhibits the Hb function of carrying oxygen to the lungs and body tissues, multicellular adhesion blocks blood flow to tissues and culminates in a painful vaso-occlusive event.[2; 3]
- SCD is most prevalent in Africa where up to 80% of diagnosed children die by the age of five.[4] However, the worldwide childhood incidence of SCD is an estimated 300,000,[5] and the median age of death in North America and Europe is 40-60 years.[6-8]
- The clinical presentation of SCD is highly heterogenous, with some patients constantly ill and others having few signs or symptoms.[1] Symptoms are primarily caused by haemolysis and haematological complications, vaso occlusion, infection, and organ dysfunction.[5]
- Many of the serious complications in SCD are related to recurrent and unpredictable episodes known as vaso-occlusive crises (VOCs).[9] A VOC is associated with severe pain, fatigue, reduced activity, emotional distress, and a high need for emergency treatment and hospitalization.[10]
- Vaso-occlusive crises are the primary cause of SCD hospitalizations, are a primary risk factor for adult mortality,[11; 12] and negatively impact health-related quality of life (HRQoL).[13] However, the long-term impact of VOCs on HRQoL remains unknown.
- More research is needed to understand the long-term impact of VOCs on HRQoL and utility, and whether this impact is greater with higher frequencies of VOCs. Such research will support care providers and decision makers estimating the burden of SCD over time and will inform cost-effectiveness models for newly developed SCD therapies.

Objective

- The aim of this study was to investigate the long-term impact of annualized VOC rate on health-related quality of life (HRQoL) and the associated utility in patients with SCD.

Methods

US38T Registry (CICL670AUS38)

- The US38T registry is a 3-year, prospective, multicenter, observational study that was conducted to collect information on a large prospectively selected cohort of SCD patients.[14-16]
- A total of 498 SCD patients from 54 centers in the United States[9] (US) were enrolled, and data was collected from January 13, 2010 to September 30, 2014.
- The primary objective of the US38T registry was to document clinical outcomes in SCD patients under current treatment practices. **Table 1** reports the inclusion and exclusion criteria for the registry.
- A secondary objective of the registry was to measure HRQoL in patients using the SF-36® Health Survey. Additional secondary objectives have been published.[14-16]

Table 1. LEGACY study inclusion and exclusion criteria[14]

Inclusion Criteria	Exclusion Criteria
Male or female patients with HbSS, HbS/beta-thalassemia, or HbSC	Patients with sickle cell trait (HbAS)
Age ≥ 2 years	Patient or legal guardian unable or unwilling to give consent or pediatric assent where indicated
Informed consent provided by patients or legal guardians, or pediatric assent where indicated	

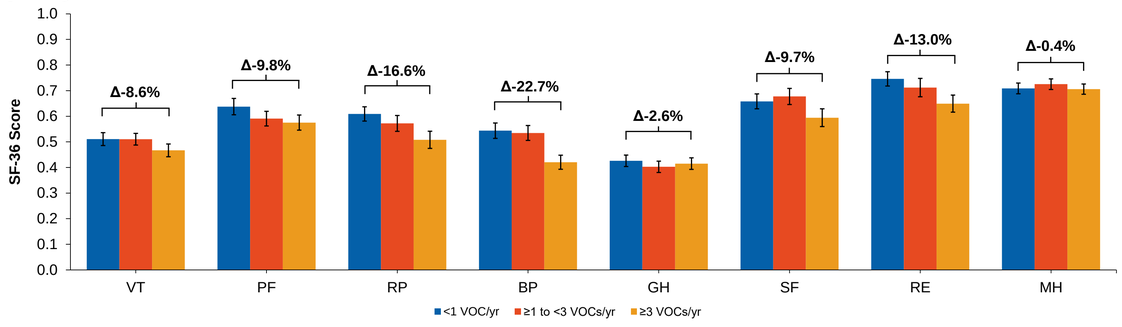
Quality of Life and Vaso-occlusive Crisis Rate

- Patients in the US38T registry completed short-form 36 (SF-36) health survey questionnaires at baseline and follow-up visits every 6 months, for 3 years or until discontinuation.
- For each of the 181 adult patients (≥18 years), the annualized rate of VOC events was calculated from first visit to each subsequent visit with short-form 36 (SF-36) health survey results reported.
  - The definition of a VOC included any pain crisis, acute chest syndrome, or priapism event.
- Patients were categorized as having <1, ≥1 to <3, or ≥3 VOCs/year as per Platt et al. 1991, which showed a significant relationship between pain rate and death when patients were stratified into these groups.[17]
- After grouping patients according to their annualized VOC rates, mean scores for the SF-36 domains, physical component summary (PCS), and mental component summary (MCS) were compared between groups using generalized estimating equations to account for within-patient correlation across visits.
- Using the random effects generalized least squares (GLS) mapping algorithm published by Rowan and colleagues (2009)[18], SF-36 scores were mapped to the EuroQoL five-dimension (EQ-5D) questionnaire in order to derive utility values. Utility values are important in that they allow comparisons of HRQoL across diseases and are needed in addressing cost-effectiveness for SCD therapies.
  - Mean EQ-5D scores were also compared between annualized VOC groups using generalized estimating equations.

Results

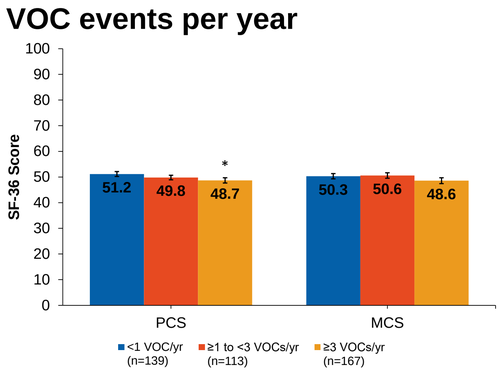
- Across SF-36 domains, a trend of lower scores was observed in patients with ≥3 VOCs/year compared to patients with <1 VOC/year **(Figure 1)**. These differences were largest in the Role Physical, Bodily Pain, and Role Emotional domains where scores were 17%, 23%, and 13% lower in patients with ≥3 VOCs/year compared to patients with <1 VOC/year.
- Compared to patients with <1 VOC/year, patients with ≥3 VOCs/year had lower SF-36 scores by 2.5 points on the PCS and by 1.7 points on the MCS **(Figure 2)**, showing a clinically meaningful difference in physical aspects of HRQoL for these patients (PCS difference of ≥2).[19]
- Stratification by annualized VOC rate (<1, ≥1 to <3, or ≥3 VOCs/year) showed a decreasing trend in mean mapped EQ-5D scores as VOC event rate increased.
  - Patients with ≥3 VOCs/year had, on average, a mapped EQ-5D score 10% lower than patients with <1 VOC/year **(Figure 3)**.
  - EQ-5D scores are consistent with the published literature; Anie et al. 2012 reported utility values for a SCD patient discharged from a VOC hospitalization (0.65) and at 1-week follow-up (0.75).[13] Further comparisons of the EQ-5D scores to the general population and other diseases are shown in **Table 2**.

Figure 1. SF-36 domain scores for patients with <1, ≥1 to <3, or ≥3 VOC events per year



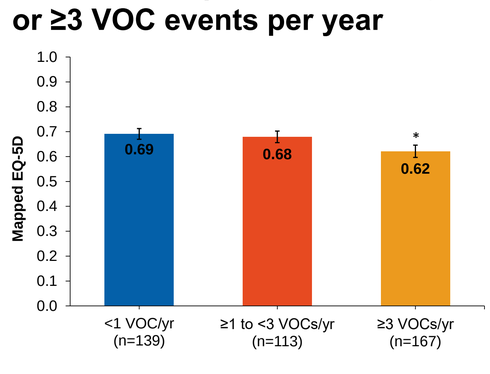
Error bars represent standard errors. Δ% represents the percent difference in domain scores between patients with <1 VOC/year and ≥3 VOCs/year; negative signs indicate lower scores for the ≥3 VOCs/year group. The number of records used in domain comparison analyses ranged from n=147 to n=153.
Abbreviations: BP = body pain; GH = general health; MH = mental health; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; SF-36 = short-form 36 health survey; VOC = vaso-occlusive crisis; VT = vitality; yr = year.

Figure 2. SF-36 MCS and PCS scores for patients with <1, ≥1 to <3, or ≥3 VOC events per year



* P-value <.05 compared to <1 VOC/year.
Error bars represent standard errors.
Abbreviations: MCS = mental component summary; PCS = physical component summary; SF-36 = short-form 36 health survey; VOC = vaso-occlusive crisis; yr = year.

Figure 3. EQ-5D scores mapped from the SF-36 for patients with <1, ≥1 to <3, or ≥3 VOC events per year



* P-value <.05 compared to <1 VOC/year.
Error bars represent standard error.
Abbreviations: EQ-5D = EuroQoL Five-Dimensional questionnaire; SF-36 = Short Form 36 health survey; VOC = vaso-occlusive crisis; yr = year.

Table 2. Summary of mapped EQ-5D values for SCD patients with <1, ≥1 to <3, or ≥3 VOC events per year and comparison to utility values in the published literature

	Utility Value
LEGACY Analysis Results	
SCD patients with <1 VOC per year	0.69
SCD patients with ≥1 to <3 VOCs per year	0.68
SCD patients with ≥3 VOCs per year	0.62
Reference Utility Values	
Healthy 25-34-year-old (UK)	0.930[20]
SCD patient at hospital admission for a VOC	0.35[13]
SCD patient discharged from a VOC hospitalization	0.65[13]
SCD patient at 1-week follow-up from discharge after a VOC hospitalization	0.75[13]
Severe COPD	0.72[21]
Cystic fibrosis with moderate lung disease	0.749[22]
Severe haemophilia	0.66[23]
Severe thalassemia patients without cardiac complications	0.61[24]

Abbreviations: COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQoL Five-Dimensional questionnaire; SCD = sickle cell disease; VOC = vaso-occlusive crisis.

Conclusions

- This analysis shows the long-term impact of VOC rate on HRQoL and utility. Patients with SCD who had a higher number of VOCs were found to have a worse HRQoL than patients with no VOCs. Decrements in physical aspects of HRQoL were particularly of clinical importance.[19]
- Additional research is required to understand the drivers of the difference in HRQoL.

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