

M. Soriano¹, C. Sangarapillai¹, W. Hann², K. Wiczorek¹, J. Bestwick², R. Nzouakou³, B. Kaya³, F. Barroso³, S. Bennett³, C. Walls⁴, A. Chawla⁴, S. Kommera⁴, C. Puri-Sharma⁴, P. Telfer¹ /

1 Centre of Genomics and Child Health, Queen Mary University of London | 2 Wolfson Institute of Preventive Medicine, Queen Mary University of London | 3 Haematology, Barts Health NHS Trust, London, United Kingdom | 4 bluebird bio, Massachusetts, United States

INTRODUCTION

- Hydroxyurea (HU) and chronic transfusion therapy (CTT) are the only disease modifying therapies (DMTs) currently available in the UK for patients with sickle cell disease (SCD) and haematopoietic stem cell transplant (HSCT) is only available to a small number of patients with an HLA matched sibling donor.
- New therapies are under investigation; however, uncertainty remains regarding the degree to which morbidity and mortality could be improved and how to evaluate the health economic potential of these therapies.
- Long-term follow up studies demonstrating the range of complications and morbidity and mortality under current standard of care are needed.
- The East London Newborn Cohort Study aims to study long-term outcomes of patients with SCD in the UK.

OBJECTIVE

To assess the effect of current DMTs on acute complications in patients with SCD in the East London Newborn Cohort Study over the years 2015-2018.

INCLUSION AND EXCLUSION CRITERIA

- Birth in the London boroughs of Hackney and Tower Hamlets
- Diagnosis of *HbSS*, *HbS/Beta⁰-thalassaemia* and *HbS/Beta⁺-thalassaemia* via newborn screening between 1983-2015
- Patients who were followed-up in Royal London Hospital during the study period 2015-2018
- Patients who died or had HSCT before or during (2 patients died and 1 patient received HSCT) the study period were excluded.

METHODS

- Patients were categorised according to treatment received during follow-up (HU, CTT or no treatment), where duration was at least 6 consecutive months.
- Patients who switched treatment were allocated according to the longest duration of therapy in follow-up.
- Data on all acute complications requiring hospital treatment (in-patient, emergency department (ED), clinical decision unit (CDU)) were collected.
- Chi-squared test was used for comparison of categorical variables and Kruskal-Wallis test for continuous variables.
- p-values ≤ 0.05 were considered statistically significant.
- Severe vaso-occlusive events (sVOEs) are defined as events requiring admission to the hospital, CDU or ED for the following: Acute chest syndrome, acute hepatic/splenic sequestration, acute ischaemic stroke, acute painful crisis, dactylitis and priapism.
- Non-sickle related acute episodes are complications requiring hospital admission with no known relation to SCD (e.g. Acute febrile episode, gastroenteritis and urinary tract infection).
- To give context to results of gene therapy trials, a sub-cohort of patients who would potentially meet inclusion criteria similar to these trials was analysed (i.e. ≥ 4 sVOEs from 2015 and 2016, age ≥ 12 on the index date of 01/01/2017).

RESULTS

- The East London Newborn Cohort Study consists of 410 patients of which 172 (42.0%) met inclusion criteria.
- N=161 (93.6%) patients had the *HbSS* genotype; N=89 (51.7%) were female.
- N=92 (53.5%) patients were managed in paediatrics services, and N=80 (46.5%) in adult services.
- Median age at study entry was 11.6 years (range 0.2 to 31.4 years).
- Median age was significantly different across treatment groups; patients receiving HU tended to be younger, while patients receiving CTT tended to be older.
- According to our institutional standard of care, 47 (27.3%) patients received HU, 53 (30.8%) CTT and 72 (41.9%) did not receive any treatment during the study period.
- 83.0% of patients on HU, 60.4% of patients on CTT and 56.9% of patients receiving No Therapy had at least 1 sVOE during the study period; patients on HU had the highest rate of sVOEs.

Table 1: Acute complications including severe vaso-occlusive events (sVOEs) during follow-up period 2015-2018

	Disease Modifying Therapy			p-value
	HU (N = 47)	CTT (N = 53)	No Therapy (N = 72)	
Demographics				
Total patient-years of follow-up	188	212	288	-
Age at study entry : median (range)	8.5 (0.2 - 24.1)	14.4 (1.7 - 31.4)	10.1 (0.2 - 27.4)	< 0.001 ^b
Complications				
All sVOEs[†]				
Patients with ≥ 1 episode	39 (83.0%)	32 (60.4%)	41 (56.9%)	0.010 ^a
Number of episodes	378	261	184	
Episodes per patient-year Median (range)	0.75 (0 - 39.5)	0.25 (0 - 13.50)	0.25 (0 - 8.75)	0.002 ^b
Acute painful crisis				
Patients with ≥ 1 episode	39 (83.0%)	31 (58.5%)	38 (52.8%)	0.003 ^a
Number of episodes	353	231	165	
Episodes per patient-year Median (range)	0.50 (0 - 39.5)	0.25 (0 - 13.50)	0.25 (0 - 7.50)	0.002 ^b
Acute Chest Syndrome				
Patients with ≥ 1 episode	10 (21.3%)	11 (20.8%)	8 (11.1%)	0.232 ^a
Number of episodes	18	14	15	
Episodes per patient-year Median (range)	0 (0 - 1)	0 (0 - 0.75)	0 (0 - 1.25)	0.245 ^b
All non-sickle related acute episodes[‡]				
Patients with ≥ 1 episode	22 (46.8%)	21 (39.6%)	28 (38.9%)	0.663 ^a
Number of episodes	52	42	66	
Episodes per patient-year Median (range)	0 (0 - 3.25)	0 (0 - 1.50)	0 (0 - 1.75)	0.713 ^b

^a p-value obtained from the Chi-Squared test.

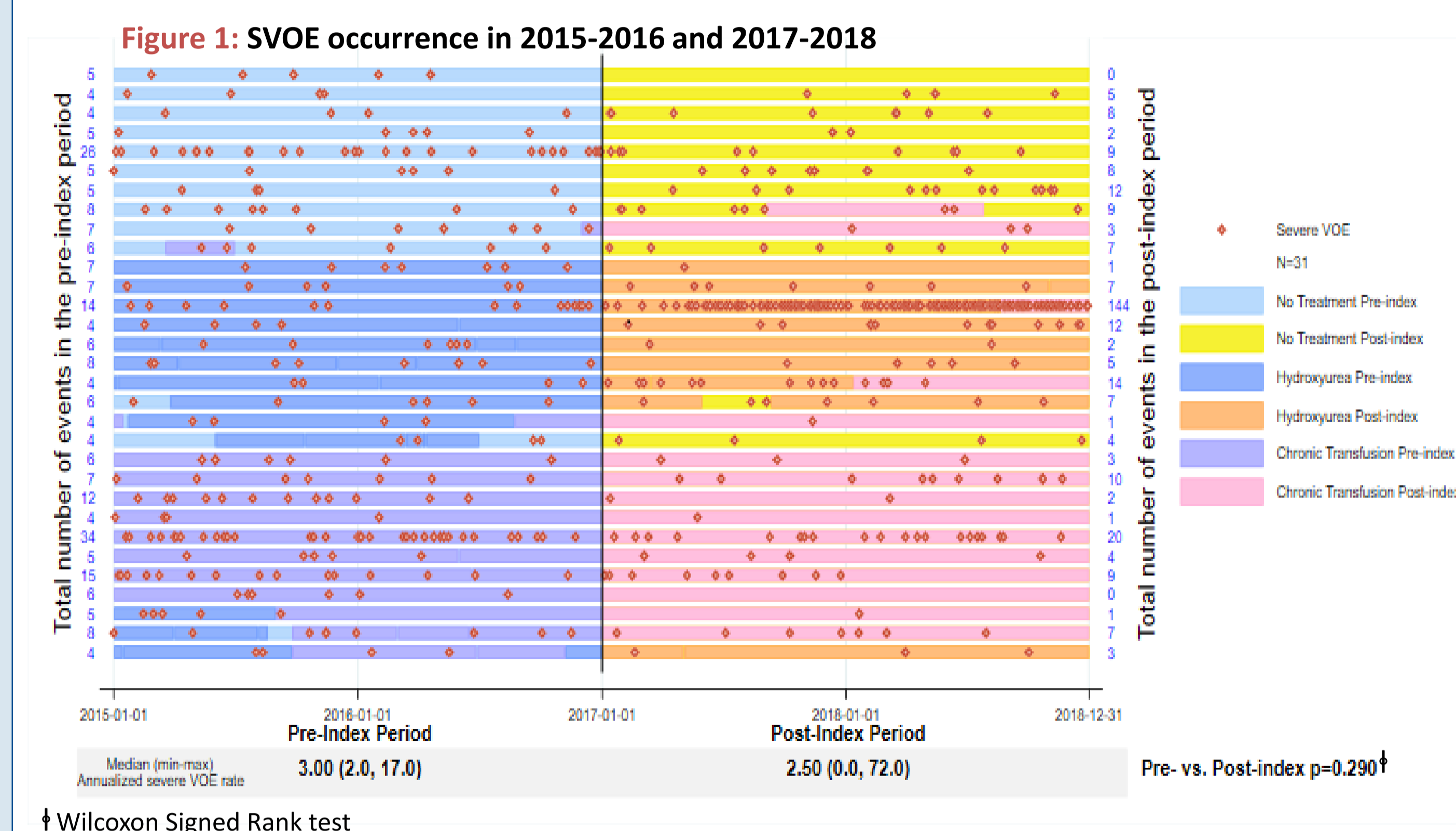
^b p-value obtained from the Kruskal-Wallis test.

[†] Defined as events requiring admission to the hospital, CDU or ED for the following: Acute chest syndrome, acute hepatic/splenic sequestration, acute ischaemic stroke, acute painful crisis, dactylitis and priapism.

[‡] Complications with no known relation to SCD

Sub-cohort analysis using gene therapy trial inclusion criteria

- 31 patients fulfilled the inclusion criteria (age ≥ 12 on 01/01/2017 and ≥ 4 sVOEs from 2015-2016).
- 100.0% of patients in this sub-cohort had the genotype *HbSS*; 51.6% were female.
- 90.3% were followed-up in adult services and 9.7% in paediatric services.
- Median age at study entry was 18.3 years (range 10.5 to 30.9 years), and median age at index date was 20.3 years (range 12.5 to 32.9 years)
- For this sub-cohort analysis, real time patient treatment was captured from medical records.
- There was no statistically significant difference seen in sVOE rates between 2015-2016 and 2017-2018 (see Figure 1 below).



CONCLUSION

- The results confirm that current standard therapies are only partially effective in controlling acute complications of SCD.
- Patients receiving DMTs continue to experience sVOEs.
- Patients who did not receive DMTs during the study period may represent a milder phenotype, but about half continue to experience acute complications.
- In the subset of patients meeting approximate gene therapy trial inclusion criteria, sVOEs persist over the subsequent 2 years despite receiving appropriate standard of care.
- Substantial morbidity remains among SCD patients in the East London Newborn Cohort Study, and a significant unmet need exists for effective disease modifying or curative therapies for patients experiencing sVOEs.

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CONTACT INFORMATION

Muriel Soriano: muriel.soriano@nhs.net