Comorbidities and complications across genotypes in adult patients with pyruvate kinase deficiency: Analysis from the Peak Registry

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BACKGROUND

• Pyruvate kinase (PK) deficiency is a rare, congenital, glycolytic enzymopathy caused by mutations in the PKLR gene, which leads to lifelong hemolytic anemia and may result in complications such as iron overload, pulmonary hypertension, and gallstones.

• PK deficiency has wide genetic heterogeneity, with >300 mutations reported, and previous data suggest that disease complications may be common regardless of genotype.

• To better understand the characteristics and disease burden of patients diagnosed with PK deficiency, this comorbidity substudy of the real-world Peak Registry was performed. (ClinicalTrials.gov identifier: NCT02058490) was initiated in 2014 at 31 sites across 6 countries, and followed patients for 2 years.

• The Peak Registry (NCT03487783) was initiated in 2018 as a global retrospective and prospective observational study of patients diagnosed with PK deficiency to continue and expand on the PK Deficiency NH and the understanding of PK deficiency, with a targeted enrollment of approximately 500 adult and pediatric patients at ~60 sites in up to 20 countries.

OBJECTIVE

• To further characterize comorbidities and complications across genotypes in adult patients with PK deficiency enrolled in the Peak Registry

METHODS

• The Peak Registry is a global retrospective and prospective observational study of adult and pediatric patients diagnosed with PK deficiency (Figure 1)

RESULTS

Baseline characteristics

• As of the 26 June 2021 data cut-off date, 50 (13.7%) adult patients in the registry had complete comorbidity and outcome data (Table 1).

• Of those 50 patients, 57 (33.5%) were classified as M/M, 28 (31.5%) as NM/NM, and 5 (5.0%) as NM/NM.

• The distribution of the 3 classes of genotypes from patients with available data in each Peak Registry enrollment country is shown in Figure 2

Medical history

• Median age (range) of PK deficiency diagnosis was 16.0 years (0–68) for the overall adult population (all genotypes), 21.0 years (0–68) for M/M patients, 12.0 years (0–40) for M/NM patients, and 0.0 years (0–0) for NM/NM patients (Table 1).

• Among the 8 patients with known transfusion status, 28.6% had never been transfused (M/M: 44.4%, M/NM: 26.8%, NM/NM: 0.0%).

• Spleenectomy had been performed in almost half of M/M patients (47.3%), the majority of M/NM patients (67.5%), and all NM/NM patients (100%).

• Adult patients (≥18 years) were eligible for inclusion in this analysis if they had available age at enrolment and complete genotype information as of the data cut-off date of 26 June 2021.

• For this analysis, adults with complete PKLR genotypes data were grouped into 3 cohorts: missense/missense (M/M), missense/non-missense (M/NM), and non-missense/non-missense (NM/NM).

• Key inclusion criteria:
  − Patients of any age with a confirmed diagnosis of PK deficiency who are genetically confirmed
  − Each patient or their parent/guardian must be willing and able to give informed consent; a parent/guardian must be 18 years or older

• Data on demographics, laboratory values, and medical history inclusive of complications and comorbidities at enrolment were summarized descriptively.

• Comorbidities and complications common in patients with PK deficiency were identified in collaboration with Peak Registry Steering Committee members and based on evidence previously reported in the literature.

• Categories of comorbidities and complications with high clinical significance to the PK deficiency population were included in the analyses (supplemental material [QR code]) contains the full breadth of comorbidities and complications

• The most common cardiac complication in the overall adult population was arrhythmias (5.8%) and was observed in 5.5% of M/M patients, 4.4% of M/NM patients, and 0.0% of NM/NM patients (Supplemental Table 2 [QR code]).

• At least 1 thrombembolic event was reported in 7 patients of the 10 patients who experienced thrombembolic events, the timing of the events relative to splenectomy was known for 6 patients, and in all 6 patients the 13 thrombembolic events occurred after splenectomy (Supplemental Table 3 [QR code]).

• Details of the thrombembolic event in a 7 patient were unexpected.

• Of patients with a history of iron overload, 25.0% of M/M patients and 0.0% of NM/NM patients had never been transfused (Table 3)

• Of patients with a history of liver disease, 44.4% of M/M patients and 0.0% of NM/NM patients had never been transfused (Table 3)

• Of patients with a history of history of endocrine disorders, 25.0% of M/M patients and 0.0% of NM/NM patients had never been transfused (Table 3)

• Of patients with a history of complications, 25.0% of M/M patients and 0.0% of NM/NM patients had never been transfused (Table 3)

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• The breadth of complications captured in the real-world setting for this analysis suggests a wide range of clinical phenotypes experienced by patients with each PKLR genotype.

• Centralized classification of genotypes in the Peak Registry allows for consistent interpretation of data in line with previous research and publications in patients with PK deficiency.

Limitations

• The absence of certain complications, such as biliary events and bone complications, in the NM/NM group may reflect the low number of patients with available data in the analysis (n=4), the true prevalence of these complications difficult to assess.

• Although PK deficiency is a rare condition, the number of patients with available data in the analysis (n=4), and the overall prevalence of clinical phenotypes, for many adult patients, recall errors or incomplete medical histories may result in their medical records inadequately reflecting conditions that they may have had as children or young adults; thus, the frequencies reported here could be understated.

• Prevalence rates for comorbidities and complications in this analysis represent only the data collected, so any occult complications that have not yet been diagnosed or have been misdiagnosed, thereby potentially underestimating their true prevalence

CONCLUSIONS

• This analysis reveals that adult patients across PKLR genotypes experienced a wide range of complications and comorbidities across multiple systems.

• In addition to the breadth of comorbidities presented, these data highlight the existence of multiple complications in individual patients with PK deficiency and the need for appropriate monitoring and management of these patients, regardless of genotype.

Figure 1. Peak Registry study design and duration

Figure 2. Genotype distribution by enrollment country

Figure 3. Percentage of patients experiencing complications in each genotype group

Table 2. Baseline hematologic and iron markers

Table 3. Number of patients with a history of iron overload by transfusion status

STRENGTHS AND LIMITATIONS

Strengths

• The Peak Registry is a global study, with patients based at numerous sites around the world, which reduces biases toward genotypes that are more common in certain geographic areas or populations.

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The longitudinal (up to 9 years) design of the Peak Registry will allow for continued monitoring and follow-up of complications and comorbidities in patients with PK deficiency

The results presented are based on data from the Peak Registry patients and should be discussed in the context of their clinical significance.

Acknowledgements: The authors wish to thank the patients and study investigators for taking part in this study. Biologics and orphan drugs from the following manufacturers: Amgen, Alexion, Apellis, bluebird bio, Celgene, Forma Therapeutics, Inc, Janssen, Jazz, Lutetia, Mylan, Nordic, Novartis, Pfizer, Raadix, Roche, Sanofi, Shire, Takeda, and TCRx. Funding: This study was supported by the Peak Registry steering committee, the National Institute for Health Research, and Alexion. The authors declare no conflicts of interest.

Disclosures: The study was funded by Alexion Pharmaceuticals, Inc. There are no relevant data to disclose.