Clinical monitoring practices among adult patients with pyruvate kinase deficiency who have never been transfused

3696

Stefan W Eber, MD[1], Andreas Glenthøj, MD, PhD[2], Bertil Glader, MD, PhD[3], Dagmar Pospisilova, MD, PhD[4], Eduard J van Beers, MD, PhD[5], Rachael F Grace, MD[6], Joan-Lluis Vives Corrons, MD, PhD[7], Hitoshi Kanno, MD, PhD[8], Kevin HM Kuo, MD, MSc[9], Paola Bianchi, PhD[10], Audra Boscoe, PhD[11], Bryan McGee, PharmD, MBA[11], Yan Yan, MS[11], Junlong Li, PhD[11], Janet Ford, MPH, PhD[11], Carl Lander, RN[12]

[1]Special Practice for Pediatric Hematology/Oncology and Children's Hospital, Technical University, Munich, Germany; [2]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [3]Division of Pediatric Hematology/Oncology, Stanford University School of Medicine, Palo Alto, CA, USA; [4]Department of Pediatrics, Palacky University and University Hospital, Olomouc, Czech Republic; [5]Center for Benign Haematology, Thrombosis and Haemostasis, Van Creveldkliniek, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [6]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; [7]Red Blood Cell and Haematopoietic Disorders Research Unit, Institute for Leukaemia Research Josep Carreras, Barcelona, Spain; [8]Department of Transfusion Medicine and Cell Processing, Tokyo Women's Medical University, Tokyo, Japan; [9]Division of Hematology, University of Toronto, Toronto, ON, Canada; [10]Hematology Unit, Pathophysiology of Anemia Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [11]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [12]Thrive with PK Deficiency, MN, USA

BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, congenital, hemolytic anemia caused by a glycolytic defect, characterized by deficient PK enzyme activity in red blood cells (RBCs)[1,2]
- Patients with PK deficiency are at risk of both acute symptoms and long-term complications, including anemia and chronic hemolysis, low bone mineral density, and iron overload[1,2]
- Iron overload may be associated with serious disease complications and can occur in all patients with PK deficiency, including those who have never received a RBC transfusion[2]
- The long-term complications of PK deficiency can negatively affect patient-reported health-related quality of life and may lead to increased risk of early mortality[3–5]
- In 2024, the first international expert guidelines for managing PK deficiency were published and included recommendations for never transfused (NT) patients[2]

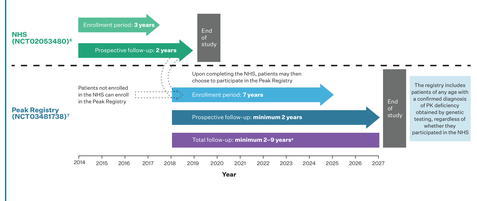
OBJECTIVE

- **To describe (1) reasons provided by clinicians for not transfusing patients with PK deficiency who were never transfused and (2) disease monitoring activities in these patients, using data from 2 real-world studies:the PK deficiency Natural History Study (NHS) and Peak Registry**

METHODS

- The NHS (NCT02053480)[6] and Peak Registry (NCT03481738)[7] were designed as global, longitudinal, observational studies to address the knowledge gaps in PK deficiency and the variability and severity of disease complications
- The registries enrolled patients with PK deficiency (NHS 2014–2017, Peak Registry 2018–ongoing [data cutoff: 15May2023])
  - Study design details are displayed in **Figure 1** and the country study sites are shown in **Supplemental figure 1**
- This descriptive analysis used merged data from both studies and included patients aged ≥18 years (at last documented visit), with a confirmed diagnosis of PK deficiency, who were NT (defined as no lifetime history of blood transfusions before/during study follow-up)
- Details of the inclusion and exclusion criteria and the study population are shown in **Figure 2**

Figure 1. NHS and Peak Registry study design and duration



[a]Participants in the Peak Registry who were originally included in the NHS from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years.
NHS, PK deficiency Natural History Study; PK, pyruvate kinase

Figure 2. Study population

Key inclusion/exclusion criteria

Inclusion
- ≥18 years of age (at last documented visit)
- Confirmed diagnosis of PK deficiency
  - **Peak:** Patients with a confirmed diagnosis of PK deficiency via genetic testing[a]
  - **NHS:** Patients with biochemically or genetically diagnosed PK deficiency OR patients with a hemolytic anemia AND a family member with genetically diagnosed PK deficiency
- **NT:** No lifetime history of blood transfusions before/during study follow-up

Exclusion
- Patients homozygous for p.R479H
- Unknown transfusion status
- Patients whose participation in mitapivat interventional trials overlapped with registry participation[b]

Study population

Overall NT group
- All adult NHS and Peak NT patients
  - **NT 12M+ subgroup:** Patients with ≥12 months of retrospective data
  - **Anemia not very severe/symptomatic (as reason for not transfusing) subgroup:** Documented treatment decision of "Anemia not very severe" OR "Anemia not symptomatic" for not transfusing (either or both reasons could be selected) (Peak Registry only)

[a]Clinical features consistent with PK deficiency together with the presence of 2 or more *PKLR* gene mutations. For novel or indeterminate *PKLR* gene mutations, patients are deemed eligible if, in the opinion of the investigator, the reported *PKLR* gene mutations are sufficient to support a diagnosis of PK deficiency; [b]To prevent confounding factors from interventional trials impacting real-world study data. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

- An analysis of monitoring practices was performed on the following groups of patients:
  - All adult NHS and Peak Registry patients who were NT
    - Subgroup of patients with ≥12 months of retrospective data (to permit adequate time for monitoring in line with guidelines[2])
    - Subgroup of patients with reason for not being transfused reported as "Anemia not very severe/ symptomatic" (clinically relevant indicator for patient management)
- Results were evaluated relative to pertinent recommendations from the PK deficiency international expert guidelines[2]

RESULTS

Patient disposition and characteristics

- A total of 55 adult NT patients were included in the analysis: patients enrolled in NHS only: 10 (18.2%); patients in Peak Registry only: 31 (56.4%); patients in both registries: 14 (25.5%) (**Table 1; Supplemental table 1** [QR code])
  - Median age (min, max) at the last visit was 39 years (18, 81); 24 patients (43.6%) were female
  - 42 patients (76.4%) had ≥12 months of retrospective data
  - Regional variations in the lifetime prevalence of NT patients were observed, with the greatest proportion residing in Southern Europe (24 patients [43.6%])
- *PKLR* genotype distribution was 62% missense/missense (M/M), 34% missense/non-missense (M/NM), and 4% non-missense/non-missense (NM/NM)
- Median (quartile [Q]1, Q3) lab results at last patient visit included hemoglobin 11.4 g/dL (10.3, 12.2), absolute reticulocyte count 207.0 10^9/L (134.3, 300.0), and ferritin 312.0 ng/mL (176.0, 404.0) (**Table 2; Supplemental Table 2** [QR code])
- Overall, 93 adult patients, who did not meet the criteria of never having received a transfusion, were excluded from the analysis (**Supplemental table 3** [QR code])
- Reasons for non-transfusion of patients are shown in **Figure 3**

Table 1. Patient demographics

	NT[a] (N=55)	NT 12M+ subgroup[b] (N=42)	Anemia not very severe/ symptomatic subgroup[c] (N=34)
Age at last documented visit, median (min, max), years	39.0 (18.0, 81.0)	35.0 (18.0, 75.0)	40.0 (20.0, 75.0)
Female, n/N[r] (%)	24/55 (43.6)	19/42 (45.2)	17/34 (50.0)
Race, n/N[r] (%)			
Asian	2/50 (4.0)	2/39 (5.1)	0/30
Black or African American	3/50 (6.0)	2/39 (5.1)	1/30 (3.3)
American Indian or Alaska Native	1/50 (2.0)	0/39	0/30
White	43/50 (86.0)	35/39 (89.7)	29/30 (96.7)
Other	1/50 (2.0)	0/39	0/30
Ethnicity, n/N[r] (%)			
Not Hispanic or Latino	44/49 (89.8)	33/38 (86.8)	24/29 (82.8)
Age at PK deficiency diagnosis, n	54	41	33
Median (min, max), years	21.5 (0.0, 76.0)	22.0 (2.0, 55.0)	28.0 (2.0, 55.0)
Time from symptom onset to diagnosis,[d] n	10	8	8
Median (min, max), months	29.1 (0.0, 252.8)	4.6 (0.0, 219.2)	4.6 (0.0, 252.8)

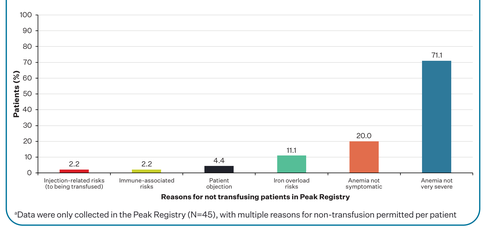
N[r] represents the number of patients with data available. [a]NT = subject has never been transfused up to data cutoff date; [b]NT 12M+ = NT with ≥12 months of retrospective data; [c]Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; [d]Including 2 scenarios: complete date; year and month are available with day as missing. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 2. Laboratory parameters at last documented visit

Laboratory values	NT[a] (N=55)	NT 12M+ subgroup[b] (N=42)	Anemia not very severe/ symptomatic subgroup[c] (N=34)
Hemoglobin, n	47	40	30
Median (Q1, Q3), g/dL	11.4 (10.3, 12.2)	11.3 (10.2, 12.1)	11.3 (10.3, 12.1)
Absolute reticulocyte count, n	32	31	25
Median (Q1, Q3), 10^9/L	207.0 (134.3, 300.0)	210.0 (138.0, 302.9)	204.0 (138.0, 297.0)
Indirect bilirubin, n	38	33	25
Median (Q1, Q3), mg/dL	2.0 (1.1, 3.5)	2.0 (1.1, 3.3)	1.9 (1.2, 3.3)
Lactate dehydrogenase, n	40	37	26
Median (Q1, Q3), U/L	221.0 (165.5, 327.0)	206.0 (165.0, 301.0)	204.0 (164.0, 288.0)
Ferritin, n	39	37	25
Median (Q1, Q3), µg/L	312.0 (176.0, 404.0)	312.0 (179.3, 404.0)	280.5 (176.0, 360.0)
Ferritin in males, n	22	21	12
Median (Q1, Q3), µg/L	318.2 (240.0, 671.0)	317.0 (240.0, 671.0)	298.8 (209.7, 535.0)
Ferritin in females, n	17	16	13
Median (Q1, Q3), µg/L	278.0 (163.0, 362.0)	287.0 (163.5, 383.0)	278.0 (163.0, 360.0)

N[r] represents the number of patients with data available. [a]NT = subject has never been transfused up to data cutoff date; [b]NT 12M+ = NT with ≥12 months of retrospective data; [c]Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase; Q, quartile

Figure 3. Reasons given for non-transfusion[a] (Peak Registry only)



[a]Data were only collected in the Peak Registry (N=45), with multiple reasons for non-transfusion permitted per patient

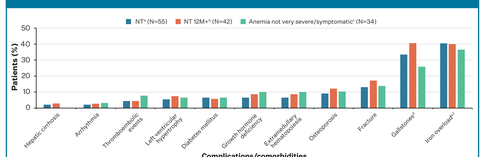
Medical complications

- Among the 42 NT patients with ≥12 months of retrospective data, the most commonly observed complications included iron overload (40.0%) and osteoporosis (12.1%) (**Figure 4**)
  - All complications, except hepatic cirrhosis, were also observed in the subgroup reporting anemia not very severe and/or not symptomatic (**Figure 4**)
- Further data on medical complications are displayed in **Supplemental table 4** (QR code)

Disease management

- Among NT patients, 18.9% had previously undergone splenectomy (**Table 3**)
- Despite never receiving transfusions, the number of interventions received among patients with ≥12 months of retrospective data was high, with 31.7% receiving cholecystectomy and 20.0% receiving splenectomy

Figure 4. PK deficiency-related medical history and medical complications



[a]NT = subject has never been transfused up to data cutoff date; [b]NT 12M+ = NT with ≥12 months of retrospective data; [c]Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; [d]Pooled gallstones and asymptomatic gallstones; [e]Iron overload was defined as: having ever received chelation/phlebotomy for the removal of iron OR had any of the following (for Peak Registry participants): ferritin >1000 ng/mL; liver MRI (including FerriScan®) >3 mg Fe/g dry weight; cardiac T2 MRI ≤20 ms OR had any of the following (for NHS participants): ferritin >1000 ng/mL in the 12 months prior to enrollment; liver MRI (including FerriScan®) >3 mg Fe/g dry weight; cardiac T2 MRI ≤20 ms; [f]Iron overload occurred in 43.3% (13/30) of males and 36.4% (8/22) of females in the NT group. MRI, magnetic resonance imaging; NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 3. Disease management among NT patients with PK deficiency

Intervention, n/N[r] (%)	NT[a] (N=55)	NT 12M+ subgroup[b] (N=42)	Anemia not very severe/ symptomatic subgroup[c] (N=34)
Cholecystectomy	18/54 (33.3)	13/41 (31.7)	11/33 (33.3)
Chelation treatment	14/52 (26.9)	10/40 (25.0)	7/33 (21.2)
Alternative treatments[d,e]	6/24 (25.0)	6/24 (25.0)	4/13 (30.8)
Splenectomy	10/53 (18.9)	8/40 (20.0)	4/32 (12.5)
Phlebotomy treatment	8/53 (15.1)	6/41 (14.6)	4/32 (12.5)
Ever treated with mitapivat[f]	4/55 (7.3)	2/42 (4.8)	3/34 (8.8)
Other treatments			
Folic acid[g]	37/55 (67.3)	31/42 (73.8)	24/34 (70.6)
Anxiolytics and/or antidepressants	9/55 (16.4)	7/42 (16.7)	7/34 (20.6)
Vitamin D and analogs[h]	6/45 (13.3)	4/32 (12.5)	4/34 (11.8)

N[r] represents the number of patients with data available. [a]NT = subject has never been transfused up to data cutoff date; [b]NT 12M+ = NT with ≥12 months of retrospective data; [c]Anemia not very severe/ symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; [d]Alternative, non-traditional, or investigational therapies, stem cell transplant; [e]Data from NHS registry only; [f]Number from clinical trials (n=3); number from commercial use (n=1); [g]Due to a lack of evidence, international expert guidelines for PK deficiency do not include a recommendation on folic acid use; [h]Data available from Peak Registry only. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Monitoring among the 42 patients who were NT with ≥12 months of retrospective data

- Clinical monitoring received during registry participation (and recent pre-baseline history) included lab assessments for hemoglobin (97.6%), reticulocytes (85.7%), and ferritin (95.2%) (**Table 4**)
- Bone health was monitored via 25-hydroxyvitamin D levels (23.8%) and DEXA scan (12.9%[only assessed in the Peak Registry])
- Cardiovascular monitoring occurred in 37.5% and 19.4% of NHS and Peak Registry patients, respectively
- MRI for iron assessment (liver and/or cardiac) was performed for 28.6% of patients (NHS and Peak Registry pooled data)
- Among 5 patients with ongoing chelation therapy (treatment durations ranged from 2.3 to 6.1 years), all had registry documentation of ferritin monitoring, and none had a liver iron concentration evaluation via MRI

Table 4. Disease monitoring among NT patients with PK deficiency (1/2)

Disease monitoring[a] (documented during registry participation)	NT[b] (N=55)	NT 12M+ subgroup[c] (N=42)	Anemia not very severe/ symptomatic subgroup[d] (N=34)
Iron assessment, n/N[r] (%)			
Any of the iron assessments	51/55 (92.7)	40/42 (95.2)	34/34 (100.0)
Iron assessment details,[e] n/N[r] (%)			
Ferritin	48/55 (87.3)	40/42 (95.2)	31/34 (91.2)
MRI for iron assessment	14/55 (25.5)	12/42 (28.6)	10/34 (29.4)
Transferrin saturation[f]	22/45 (48.9)	20/32 (62.5)	21/34 (61.8)
Cardiovascular, n/N[r] (%)			
Echocardiogram[g]	9/24 (37.5)	9/24 (37.5)	6/13 (46.2)
Cardiac assessment (ECG, MUGA, other)[f]	7/43 (16.3)	6/31 (19.4)	6/33 (18.2)
Bone health, n/N[r] (%)			
25-hydroxyvitamin D levels	11/55 (20.0)	10/42 (23.8)	8/34 (23.5)
DEXA scan[f]	4/44 (9.1)	4/31 (12.9)	3/33 (9.1)

N[r] represents the number of patients with data available. [a]Data only available from 1 registry for some monitoring procedures; [b]NT = subject has never been transfused up to data cutoff date; [c]NT 12M+ = NT with ≥12 months of retrospective data; [d]Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; [e]Liver biopsy for iron was performed in 1 patient in the NT 12M+ subgroup from the NHS registry; [f]Data available from Peak Registry only; [g]Data available from NHS registry only. ECG, electrocardiogram; MRI, magnetic resonance imaging; MUGA, multigated acquisition; NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

Table 4. Disease monitoring among NT patients with PK deficiency (2/2)

Disease monitoring[a] (documented during registry participation)	NT[b] (N=55)	NT 12M+ subgroup[c] (N=42)	Anemia not very severe/ symptomatic subgroup[d] (N=34)
Laboratory, n/N[r] (%)			
Hemoglobin	48/55 (87.3)	41/42 (97.6)	31/34 (91.2)
Ferritin	48/55 (87.3)	40/42 (95.2)	31/34 (91.2)
% reticulocyte and/or absolute reticulocyte count	41/55 (74.5)	36/42 (85.7)	29/34 (85.3)
Total, direct, and/or indirect bilirubin	39/55 (70.9)	34/42 (81.0)	26/34 (76.5)
Transferrin saturation[e]	22/45 (48.9)	20/32 (62.5)	21/34 (61.8)
Among those with iron overload, n/N[r] (%)	**N=21**	**N=16**	**N=12**
Endocrinopathy panel: thyroid hormone, sex hormones[f]	6/8 (75.0)	6/8 (75.0)	3/3 (100.0)
Fructosamine[f,g]	0/8	0/8	0/3
Endocrinopathy panel: sex hormones[e]	3/17 (17.6)	3/12 (25.0)	3/12 (25.0)
Among those with ongoing chelation, n/N[r] (%)	**N=7**	**N=5**	**N=4**
Ferritin	6/7 (85.7)	5/5 (100.0)	3/4 (75.0)
Creatinine[f]	3/3 (100.0)	3/3 (100.0)	1/1 (100.0)

N[r] represents the number of patients with data available. [a]Data only available from 1 registry for some monitoring procedures; [b]NT = subject has never been transfused up to data cutoff date; [c]NT 12M+ = NT with ≥12 months of retrospective data; [d]Anemia not very severe/symptomatic = NT with documented rationale of "Anemia not very severe" and/or "Anemia not symptomatic"; only common terms reported in both the Peak Registry and NHS were included; [e]Data available from Peak Registry only; [f]Data available from NHS registry only; [g]Fasting glucose, oral glucose tolerance testing, or fructosamine measurements are recommended as glycated hemoglobin A1C measurements are unreliable in hemolytic anemia. NHS, PK deficiency Natural History Study; NT, never transfused; PK, pyruvate kinase

LIMITATIONS

- Over- or under-reporting of disease monitoring may have occurred in the registries
- Potential for information bias due to inaccurate documentation, or missing data (some outcomes were only collected by 1 of the 2 registries)
- Registry sites tend to be specialty and/or academic centers of excellence; their monitoring/treatment practices may not be representative of the management of patients in community/primary care settings

CONCLUSIONS

- **Our findings show that NT patients with PK deficiency are at risk for complications, such as iron overload, gallstones, osteoporosis, extramedullary hematopoiesis, and pulmonary hypertension, that require monitoring**
  - **The most common response for not transfusing included "Anemia not very severe" followed by "Anemia not symptomatic", yet even this subgroup of patients experienced disease complications**
- **Although patients were NT, other types of disease management procedures, including cholecystectomy, splenectomy, and mitapivat treatment were observed**
- **Observed medical monitoring practices among NT patients fall short of evidence-based recommendations in recently published guidelines, such as annual ferritin monitoring, annual liver iron concentration by MRI among those on chelation or consistent serum ferritin concentrations >500 ng/mL, echocardiography and DEXA scan screening in all patients ≥18 years, and vitamin D monitoring at all ages[2]**
- **Findings emphasize the need for evidence-based disease monitoring to be consistently implemented for all patients with PK deficiency, enabling early detection and management of complications**
- **Given the significant rate of complications in patients with PK deficiency who have never been transfused, treatment to improve anemia and reduce hemolysis should be considered in these patients**

References and supplemental material are available via the QR code

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