Pyruvate Kinase Deficiency Related Abstracts
EHA 2023

Abstract: P1479

Title: COMORBIDITIES AND COMPLICATIONS IN ADULTS WITH PYRUVATE KINASE DEFICIENCY ACCORDING TO HEMOGLOBIN STRATA – A DESCRIPTIVE ANALYSIS FROM THE PEAK REGISTRY

Lead Author: Dagmar Pospisilova

Abstract Type: Poster Presentation

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Pyruvate kinase (PK) deficiency is a rare, congenital hemolytic anemia caused by mutations in the PKLR gene. Hemoglobin (Hb) levels are an important assessment of disease, yet patients

(pts) with less pronounced anemia (Hb >10 g/dL) may still experience complications due to the underlying pathophysiology of PK deficiency.

Aims:

To describe the disease burden of adults with PK deficiency and average Hb >10 g/dL enrolled in the Peak Registry (NCT03481738).

Methods:

The Peak Registry is an ongoing, retrospective, and prospective observational study of pts with PK deficiency, with 243 pts enrolled as of 13May2022. This analysis included adult pts (≥18 years at enrollment) with Hb data available. Hb data were collected within 3 months prior to enrollment and during follow-up. All Hb data collected ≤61 days post-transfusion were considered ineligible. Pts were grouped into 2 cohorts based on mean Hb value across eligible data: >10 g/dL and ≤10 g/dL. Demographics, clinical characteristics, medical history, hemolysis markers, and select medical complications were summarized descriptively for all pts and for each cohort.

Results:

Ninety-five pts were included in the analysis (8 pts were excluded as all their Hb measurements were collected ≤61 days post-transfusion), of whom 48 (51%) had mean Hb >10 g/dL. Age and sex were similar between cohorts (Table). In the Hb >10 g/dL cohort, median (range) % reticulocyte count was 5.7% (2.7–40.9), indirect bilirubin was 1.8 mg/dL (0.7–10.8), and ferritin was 304.0 µg/L (34.5–6208.0). In the Hb ≤10 g/dL cohort, the median (range) values for these markers were 25.3% (4.0–43.0), 2.7 mg/dL (0.8–8.1), and 683.5 µg/L (16.6–7050.0), respectively.

Thirty-five percent of pts in the Hb >10 g/dL cohort and 83% of pts in the Hb ≤10 g/dL cohort had received ≥1 transfusion in their lifetime; 18% and 40% had received regular transfusions (≥6 transfusions in any 12-month period), respectively. Thirty-three percent of pts with Hb >10 g/dL and 62% of pts with Hb ≤10 g/dL had a history of iron overload. Twenty-seven percent of pts with Hb >10 g/dL and 61% of pts with Hb ≤10 g/dL had received chelation therapy in their

lifetime. Thirty-three percent of pts with Hb >10 g/dL had undergone splenectomy, at a median (range) age of 14 years (2–58), compared with 80% of pts with Hb ≤10 g/dL, at a median (range) age of 7 years (2–20).

Bone health complications occurred in 21% of pts with Hb >10 g/dL and 40% of pts with Hb ≤10 g/dL. Notably, both cohorts had high proportions of pts with osteopenia/osteoporosis (Hb >10 g/dL: 19%; Hb ≤10 g/dL: 21%). Cholecystitis was also reported at similar levels in both cohorts (Hb >10 g/dL: 21%; Hb ≤10 g/dL: 28%) and substantial numbers of pts experienced jaundice (Hb >10 g/dL: 23%; Hb ≤10 g/dL: 51%). Other complications included biliary events (Hb >10 g/dL: 33%; Hb ≤10 g/dL: 49%), liver complications (Hb >10 g/dL: 5%; Hb ≤10 g/dL: 19%), thromboembolic events (Hb >10 g/dL: 2%; Hb ≤10 g/dL: 9%), cardiac complications (Hb >10 g/dL: 5%; Hb ≤10 g/dL: 9%), and retinal problems (Hb >10 g/dL: 18%; Hb ≤10 g/dL: 0%).

Summary/Conclusion:

Adults with PK deficiency, including those with less pronounced anemia (Hb >10 g/dL), experienced a wide range of comorbidities and complications. As with pts with lower Hb values, those with Hb >10 g/dL also had hemolysis, transfusion requirements, iron overload, and a need for chelation, as well as serious conditions such as osteoporosis and biliary events. Clinicians should consider that all pts with PK deficiency, regardless of Hb level, require careful monitoring to minimize the risk of long-term complications.

Table. Clinical characteristics, laboratory parameters, and select complications of adult pts with PK deficiency enrolled in the Peak Registry, stratified by average Hb level

	Total	Pt groups by average Hb level	
	All pts N=95	Hb >10 g/dL N=48	Hb ≤10 g/dL N=47
Age, mean (SD), year	35.8 (14.0)	36.7 (14.7)	34.9 (13.2)
Female, n (%)	54 (56.8)	27 (56.3)	27 (57.4)
Clinical characteristics, n/N* (%)			
Ever transfused	50/85 (58.8)	15/43 (34.9)	35/42 (83.3)
Regularly transfused (≥6 transfusions) in any 12-month period	25/88 (28.4)	8/45 (17.8)	17/43 (39.5)
History of iron overload[a]	45/95 (47.4)	16/48 (33.3)	29/47 (61.7)
Ever had chelation therapy	37/85 (43.5)	12/44 (27.3)	25/41 (61.0)
Ever had splenectomy	52/93 (55.9)	16/48 (33.3)	36/45 (80.0)
Hematologic and iron markers			
Indirect bilirubin, median (range), mg/dL	2.4 (0.7–10.8)	1.8 (0.7–10.8)	2.7 (0.8–8.1)
Lactate dehydrogenase, median (range), U/L	198 (119–770)	180 (133–625)	219 (119–770)
Percent reticulocyte count, median (range), %	6.5 (2.7–43.0)	5.7 (2.7–40.9)	25.3 (4.0–43.0)
Ferritin, median (range), µg/L	388.4 (16.6–7050.0)	304.0 (34.5–6208.0)	683.5 (16.6–7050.0)
Select comorbidities/complications[b,c], n/N* (%)			
Bone health complications[d]	26/86 (30.2)	9/43 (20.9)	17/43 (39.5)
Biliary events[e]	35/86 (40.7)	14/43 (32.6)	21/43 (48.8)
Liver complications[f]	10/85 (11.8)	2/43 (4.7)	8/42 (19.0)
Hematologic complications[g] and jaundice	38/84 (45.2)	13/43 (30.2)	25/41 (61.0)
Thromboembolic events[h]	5/92 (5.4)	1/46 (2.2)	4/46 (8.7)
Cardiac complications[i]	6/86 (7.0)	2/43 (4.7)	4/43 (9.3)
Retinal problems[j]	6/60 (10.0)	6/34 (17.6)	0/26 (0.0)

N* represents the number of pts with data available. Range represents the minimum and maximum values within the group.
[a]History of iron overload defined as ever having received: 1) chelation therapy; 2) phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 ng/mL; 4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight; 5) cardiac T2* MRI ≤20 ms; [b]Comorbidities and complications were derived from baseline and/or follow-up data; [c]Not all specific conditions collected under these terms were necessarily observed in the registry; [d]Bone health complications were fracture, osteoporosis, osteopenia, and bone pain; [e]Biliary events were cholecystitis, cholangitis, asymptomatic gallstones, and bile duct stones; [f]Liver complications were non-alcoholic steatohepatitis, non-alcoholic fatty liver, hepatic cirrhosis, and hepatomegaly; [g]Hematologic complications were extramedullary hematopoiesis, positive Coombs direct test, myelodysplastic syndrome, reticulocytopenia, hemolytic crisis, and hemochromatosis; [h]Thromboembolic events were deep vein thrombosis, pulmonary embolism, venous embolism, cerebral venous thrombosis, portal vein thrombosis, ischemic stroke, and other; [i]Cardiac complications were pulmonary hypertension, arrythmia, left ventricular hypertrophy, and congestive cardiac failure; [j]Retinal problems were reported as "Other, please specify" in the case report forms.
Hb, hemoglobin; MRI, magnetic resonance imaging; PK, pyruvate kinase; pt, patient; SD, standard deviation.

Keywords: Pyruvate kinase deficiency, Comorbidities, Hemoglobin, Hemolysis

Abstract: PB2547

Title: ESTIMATING HEALTH-RELATED QUALITY OF LIFE IN ADULT PYRUVATE KINASE DEFICIENCY: A TIME TRADE-OFF UTILITY STUDY

Lead Author: Sara Higa

Abstract Type: Publication Only

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Pyruvate kinase (PK) deficiency is a rare, inherited hemolytic anemia which may lead to serious complications such as iron overload and pulmonary hypertension. Health-Related Quality of Life (HRQoL) utilities are needed to support economic evaluations to assess the value and impact of treatments. However, utilities are typically derived from generic patient-reported outcome (PRO) measures (e.g., EQ-5D) which may be insensitive to unique aspects of PK deficiency that reduce HRQoL. A recently published study showed an average utility of 0.88 (measured 0-1 scale; 0: death, 1: full health) in adult patients with PK deficiency, similar to that of the general population. As patients with PK deficiency are born with the disorder, they may under-report its impact due to adapting to their condition (i.e., habituation). Assessing HRQoL in patients with PK deficiency using the general population's perception of the disease may generate more accurate utilities, as they are not conditioned to habituation.

Aims:

To estimate utilities for health states associated with PK deficiency as evaluated by the general population.

Methods:

To elicit utilities in PK deficiency, vignettes (scenarios characterizing various health states experienced by patients) were developed with input from a literature review, symptoms and impacts from disease-specific PRO data from two phase 3 trials in PK deficiency, and 1:1 online

interviews with two hematologists and three adult patients with PK deficiency. Six vignettes were created to describe health states stratified by transfusion status and hypothetical response to an intervention. Response health states were described as having lower levels of severity and/or frequency of symptoms (e.g., fatigue, shortness of breath, jaundice, and bone pain) and less impact on HRQoL (e.g., physical, work, social, and emotional) compared to non-response health states. The final vignettes were evaluated via online interviews with demographically representative participants from the general public in the UK and France who were recruited online (panels and advertising). Utilities were elicited during these interviews using the time trade-off (TTO) method where participants chose between a shorter life in perfect health or living longer in one of the health states. Utilities were summarised descriptively (mean, SD) and compared between health states using the Wilcoxon test.

Results:

200 participants evaluated the vignettes (52% female; mean age 42.5 years). TTO utilities were similar for the UK and France across all health states. Utilities in the non-response health states ranged from 0.407 to 0.829 and 0.417 to 0.766 in the UK and France, respectively. Overall, mean utility values were significantly higher in response health states ($p<0.001$) compared to non-response [Table 1]).

Summary/Conclusion:

Significantly higher utilities for treatment response health states compared to non-response suggests that participants valued states with less PK deficiency-related symptoms higher than a life with more severe or frequent symptoms that negatively impact daily life. TTO utilities elicited from the general population were descriptively lower than previous estimates from generic instruments in patients with PK deficiency. These results generated from a population not habituated to the condition indicate that symptoms of PK deficiency have a higher impact than patients may perceive and further validate that generic instruments completed by patients who are habituated by the condition may not sufficiently capture HRQoL in PK deficiency.

Keywords: Quality of life, Hemolytic anemia, Clinical outcome, Pyruvate kinase deficiency

Abstract: P1497

Title: MITAPIVAT IMPROVES IRON OVERLOAD IN PATIENTS WITH PYRUVATE KINASE DEFICIENCY WHO ARE REGULARLY TRANSFUSED

Lead Author: Eduard van Beers

Abstract Type: Poster Presentation

Session Title: Iron metabolism, deficiency and overload

Background:

Iron overload is highly prevalent in patients (pts) with pyruvate kinase (PK) deficiency, regardless of transfusion status, and can lead to serious complications including organ damage. Regular transfusions further add to the burden of iron overload, negatively impacting pts' quality of life and healthcare costs. Mitapivat is a first-in-class, oral, allosteric activator of PK, approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency and by the European Medicines Agency for the treatment of PK deficiency in adults. Previously reported data from ACTIVATE (NCT03548220) and its long-term extension (LTE; NCT03853798) showed that mitapivat improved iron overload in adults with PK deficiency who were not regularly transfused.

Aims:

Present long-term data from ACTIVATE-T and its LTE on the impact of continued mitapivat treatment on iron overload, as measured by liver iron concentration (LIC) by magnetic resonance imaging (MRI), in pts with PK deficiency who were regularly transfused and classified as achieving transfusion-reduction response (TRR) or transfusion-free status in ACTIVATE-T.

Methods:

ACTIVATE-T was a phase 3, global, single-arm study of mitapivat in adult pts with PK deficiency who were regularly transfused (≥6 episodes in the previous year). Pts who demonstrated a clinical benefit from mitapivat in the fixed-dose period of ACTIVATE-T, in the opinion of the investigator, were permitted to continue to the LTE. This analysis included pts who achieved a TRR (defined as ≥33% reduction in red blood cell units transfused during the fixed-dose period vs historical control) and pts who achieved transfusion-free status were a subset of the pts who achieved TRR. Change from baseline (BL) in LIC by MRI up to Week (Wk) 136 and changes in chelation therapy were assessed. Data were reported as of 27Mar2022 of the LTE study.

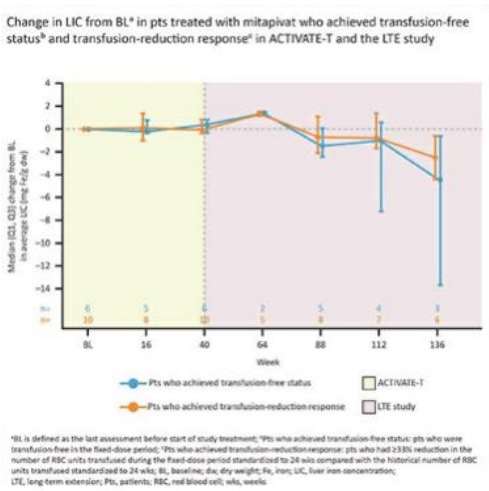
Results:

In ACTIVATE-T, 37% (10/27) of pts achieved a TRR, of which 6 pts achieved transfusion-free status. Clinically meaningful improvements over time in LIC were observed in these pts. Median (Q1, Q3) LIC decreases from BL to Wk 136 of mitapivat treatment were –2.5 (–4.4, –0.6) mg Fe/g dry weight (dw) and –4.4 (–13.7, –0.6) mg Fe/g dw for the pts who achieved TRR and the subset of pts who achieved transfusion-free status, respectively (Figure). Both (2/2) pts who achieved transfusion-free status, and 3 out of 4 pts who achieved TRR, with BL LIC >5 mg Fe/g dw had decreases to <5 mg Fe/g dw after treatment with mitapivat, which occurred between wks 112 and 136. Of the 6 pts who achieved transfusion-free status, 4 were receiving iron chelation at the start of mitapivat treatment. Of these 4 pts, 3 discontinued chelation, and 1 remained at a stable dose without increase. In 2 of the 3 pts who discontinued chelation, LIC continued to improve over time on mitapivat after chelation had been stopped. Furthermore, 2 of the 6 pts who achieved transfusion-free status did not receive chelation therapy and had improved LIC after starting mitapivat.

Summary/Conclusion:

Treatment with mitapivat improved iron overload in adults with PK deficiency who are regularly transfused and may therefore provide additional clinical benefits to those suffering from this condition. Importantly, pts that were chelation naïve as well as pts that discontinued chelation while on mitapivat continued to show meaningful improvements in LIC, suggesting that mitapivat's beneficial effects on iron overload may occur independently

from chelation therapy.



Keywords: Iron overload, Iron chelation, Pyruvate kinase deficiency, Transfusion

Abstract: P1477

Title: MITAPIVAT EFFICACY IN ADULTS WITH PYRUVATE KINASE DEFICIENCY AND BASELINE HEMOGLOBIN LEVELS >10 G/DL

Lead Author: Rachel Grace

Abstract Type: Poster Presentation

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Pyruvate kinase (PK) deficiency is a chronic hereditary disorder characterized by hemolysis, ineffective hematopoiesis, and varying degrees of anemia. Patients (pts) with PK deficiency have a wide range of hemoglobin (Hb) levels, yet those with less pronounced anemia (Hb >10 g/dL) may still experience complications including iron overload, gallbladder disease, and osteopenia. Mitapivat is a first-in-class, oral, allosteric activator of PK approved by the US Food and Drug Administration for the treatment of hemolytic anemia in adults with PK deficiency, and by the European Medicines Agency for the treatment of adults with PK deficiency. In the phase 2, proof-of-concept DRIVE-PK (NCT02476916) study and the global, phase 3, randomized, placebo-controlled ACTIVATE and its long-term extension (LTE) (NCT03548220/NCT03853798) study, mitapivat demonstrated clinically meaningful improvements in Hb level.

Aims:

To evaluate changes in Hb and hemolysis after mitapivat treatment in adult pts with PK deficiency and baseline Hb >10 g/dL who were not regularly transfused and enrolled in the DRIVE-PK and ACTIVATE/LTE studies.

Methods:

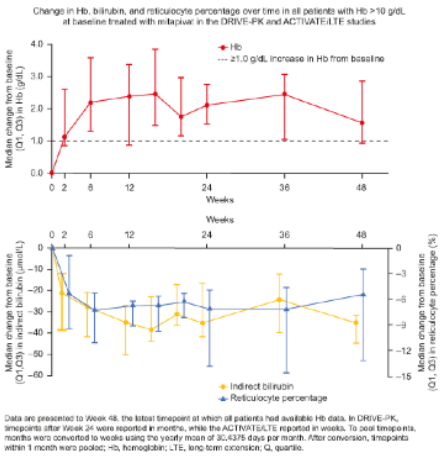
For this analysis, adult (≥18 years) pts with post-screening baseline Hb >10 g/dL who received mitapivat 50 mg twice daily in the DRIVE-PK and ACTIVATE/LTE studies were included (data as of 28Aug2021 and 12Sep2021, respectively). The numeric change in Hb from baseline and the proportion of pts with increases in Hb from baseline of ≥1.0 and ≥1.5 g/dL, were evaluated to Week 48. Hb values within 61 days post-transfusion were excluded. Changes from baseline in markers of hemolysis (indirect bilirubin and reticulocyte percentage) were also measured.

Results:

Six pts from DRIVE-PK had baseline Hb >10 g/dL, ranging from 10.2 to 12.3 g/dL, as did 4 pts from ACTIVATE/LTE (range: 10.1 to 10.2 g/dL). The median change from baseline in Hb concentration at Week 48 (the latest timepoint with Hb assessments available for all pts) was 1.6 g/dL (range: −2.0 to 4.7; Figure). All 10 pts (100%) achieved improvements in Hb ≥1.0 g/dL by 16 weeks. Of these 10 pts, 7 (70%) had early increases in Hb concentration within 6 weeks (all improvements ≥1.5 g/dL). At Week 48, the majority of pts (7/10, 70%) had improvements in Hb ≥1.0 g/dL, with 5/10 (50%) having improvements ≥1.5 g/dL at this same time point. These 5 pts sustained this ≥1.5 g/dL Hb improvement throughout treatment from Weeks 6 to 48. At Week 48, indirect bilirubin levels were reduced from baseline in 9/10 pts (90% [data missing for 1 pt]; median change −35.1 µmol/L, range: –94.1 to −6.9 µmol/L; Figure) and reticulocyte percentage was reduced from baseline in 9/10 pts (90%; median change −5.5%, range: −25.3 to 0.5%; Figure).

Summary/Conclusion:

This analysis shows that mitapivat improved Hb levels in adults with PK deficiency and baseline Hb >10 g/dL who were not regularly transfused, indicating that this group of pts derived therapeutic benefit from this drug. Importantly, these pts also experienced a reduction in markers of hemolysis, indicative of improvements in the underlying pathophysiology of this condition. By improving red blood cell health, mitapivat may ameliorate the development of complications in this subset of pts with PK deficiency.



Keywords: Pyruvate kinase deficiency, Hemoglobin, Anemia

Abstract: P1476

Title: THE CLINICAL CHARACTERISTICS AND OVERALL SURVIVAL OF PATIENTS WITH PYRUVATE KINASE DEFICIENCY IN THE UK: A REAL-WORLD STUDY

Lead Author: Sara Higa

Abstract Type: Poster Presentation

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Pyruvate kinase (PK) deficiency is a rare genetic red blood cell enzyme disorder that leads to lifelong hemolytic anemia. It is associated with multiple complications, such as iron overload and gallstones and may lead to a lower life expectancy. Due to the rarity of PK deficiency and its common misdiagnosis, the understanding of its burden is limited.

Aims:

To evaluate the patient characteristics, burden of selected PK deficiency-related complications, and overall survival (OS) among patients with PK deficiency within primary and secondary care settings in the UK.

Methods:

A retrospective cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) database. Patients were selected for inclusion if they had ≥1 instance of a PK deficiency diagnosis code in CPRD and were matched 1:5 with controls with no PK deficiency or congenital anemia based on birth year, sex, availability of records in the databases, registered general practitioner, and at least one medical record in the same year as the PK deficiency patient's diagnosis. The total study period was

from the earliest data availability from CPRD or HES, until 31st October 2020. Demographics and clinical characteristics (i.e., rates of iron overload, gallstones, or cholecystectomy during the study period) were summarized descriptively. OS gathered from mortality data (CPRD death dates and linked death registration data from the Office for National Statistics) was estimated using the Kaplan-Meier method and compared using the log-rank test.

Results:

89 patients with PK deficiency met the inclusion criteria and were matched with 445 non-PK deficiency controls. For patients with PK deficiency and controls, respectively, mean [SD] age at index was 24.7 [21.4] and 24.5 [21.3] years, and 56% were male for both groups. Median [Q1-Q3] duration of follow-up from earliest medical record and first occurrence of a diagnosis code were 23.6 [21.3 - 23.6] years and 11.7 [6.5 - 17.5] years, respectively for patients with PK deficiency. For controls this was 23.4 [19.3 - 23.6] years from earliest medical record and 11.8 [6.8 - 17.3] years from the medical record dated in the same year as the matched PK deficiency patient's diagnosis. From earliest medical record to end of follow-up, patients with PK deficiency had a numerically higher frequency of iron overload than matched controls (16% vs <1%). Within the same period, 26% of patients with PK deficiency had a record of gallstones and 21% had received a cholecystectomy, whilst this was 2.5% and 1.6% for matched controls, respectively. The OS rate (95% CI) at 15 years post-index for patients with PK deficiency was similar to matched controls (95% [89% - 100%] and 98% [96% - 99%], respectively), but was significantly lower at 30 years post-index (64% [44% - 95%] and 97% [94% - 99%]; p=0.001) (Figure 1).

Summary/Conclusion:

Findings from this study provide insight into the substantial real-world disease burden of PK deficiency in the UK. These patients had increased rates of complications such as iron overload and gallstones and had a higher 30-year mortality than matched controls. As this may consequently increase the need for disease management and healthcare resource use, clinicians should consider early intervention to help mitigate serious medical complications.

Figure 1. Kaplan-Meier analysis of time from PK deficiency diagnosis record to death in patients with PK deficiency diagnosis vs time from medical record dated in the same year as the PK deficiency patient's diagnosis in the matched non-PK deficiency comparison cohort.

Keywords: Hemolytic anemia, Pyruvate kinase deficiency, Real world data, Clinical outcome

Abstract: PB2546

Lead Author: Paolo Bianchi

Title: DIAGNOSTIC POWER OF ERYTHROCYTE AND RETICULOCYTE AUTOMATIC PARAMETERS IN THE SCREENING FOR CONGENITAL HEMOLYTIC ANEMIAS

Abstract Type: Publication Only

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Congenital hemolytic anemias (CHAs) are a group of disorders caused by defects of red cell membrane or metabolism, or by abnormal hemoglobin. Due to their rarity and heterogeneity, diagnosis is often challenging, and requires specific tools not always available outside reference centers; as a consequence, many cases may remain undiagnosed or misdiagnosed. The availability of additional parameters for complete blood count has emerged in recent hematology analyzers; however, a few studies have been conducted on advanced RBC parameters and hemolytic anemias. Diagnostic algorithms for screening of hereditary spherocytosis (HS) have been reported using Sysmex XE and Sysmex XN analyzers.

Aims:

We investigated the use of Sysmex parameters, the percentage of microcytes (MicroR) and hypochromic red blood cells (Hypo-He), as well as the immature fraction of reticulocytes (IRF) in combination with complete blood and reticulocyte count, for screening HS and pyruvate

kinase deficiency (PKD) with the final aim to develop a diagnostic algorithm for differential diagnosis of CHAs.

Methods:

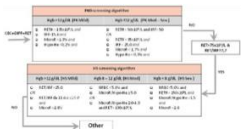
Complete blood count and reticulocytes from 319 patients with a confirmed diagnosis of CHAs were analyzed (In particular, HS: 81; PKD: 18; autoimmune hemolytic anemia: 50; congenital dyserythropoietic anemia: 9 patients; PIEZO1 gene mutations/ stomatocytosis: 9; thalassemia and sickle cell disease: 118 patients; and the other CHAs: 34 patients) on Sysmex XN analyzer. To further increase number of cases, data were merged with that of 94 other CHAs patients, including 61 HS, available from literature and analyzed on the same instruments (F. Mullier et al. 2011; F. Persijn et al. 2012; V. Bobée et al. 2018; Sottiaux et al. 2020). Patients were stratified according to the severity of anemia (Hb <8g/dL; Hb 8-12g/dL and Hb >12g/dL) and ROC curve analysis was performed for each parameter and condition to establish optimal cut-off limits. A control group of 149 patients with hematological disorders of different etiology, and an extended database of 11.194 (blood count results) cases has been used to establish algorithm disease specificity.

Results:

All 142 HS patients had RET>75x10^9/L and RET/IRF>7.7 ("pre-screening" condition) and were characterized by reticulocytosis without an increase in IRF, increased MicroR without significant increase of Hypo-He. Instead, PKD patients showed increased IRF (>25% and >15,6% in non-anemic and anemic, respectively) accompanied by reticulocytosis, MicroR and Hypo-He reduction. Based on ROC curves analysis results, by combining parameters (Hb, RET, IRF, MicroR, Hypo-He) a diagnostic algorithm was developed for screening of HS and PKD showing a sensitivity and specificity of 97.9% and 92.6% for HS and 94.4% and 99.2% for PKD respectively (figure 1). The algorithm showed a superior diagnostic performance when all patients were tested in parallel by using all the previous algorithms reported in literature.

Summary/Conclusion:

The presented algorithm proposes an easy, economic and efficient approach to detect HS and PKD using Sysmex analyzers, definitely contributing to an early diagnosis and a better management of these patients.



Keywords: Automation, Hereditary spherocytosis, Hemolytic anemia, Pyruvate kinase deficiency

Abstract: P1485

Title: PKM AND PKR EXPRESSION DURING HEMATOPOIESIS AND ERYTHROPOIESIS

Lead Author: Erin Tsai

Abstract Type: Poster Presentation

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Dysregulation of hematopoiesis and ineffective erythropoiesis are linked to many complications and comorbidities that are associated with serious disorders, such as thalassemia, myelodysplastic syndrome-associated anemia, sickle cell disease, and pyruvate kinase (PK) deficiency. A key enzyme in the glycolytic pathway, PK is needed for the production of adenosine triphosphate, which is essential for overall red blood cell health. The 4 main tissue- specific PK isoforms are encoded by 2 genes. The PKLR gene encodes the PKL and PKR isoforms through tissue- specific promoters, and the PKM gene encodes the PKM1 and PKM2 isoforms through alternative splicing. mRNA expression varies throughout the stages of normal hematopoiesis and erythropoiesis. In this study, transcriptomes from hematopoietic and erythroid progenitors were evaluated, and mRNA levels of PKL, PKR, PKM1, and PKM2 were measured at different stages of hematopoiesis and erythropoiesis.

Aims:

To understand relative expression and potential roles of PK isoforms during normal hematopoiesis and erythropoiesis.

Methods:

Two RNA-sequencing data sets were obtained from public functional genomics data repositories. (1) PRJEB19300/E-MTAB-5456 (CD34+, lineage-depleted umbilical cord blood from normal/healthy donors): transcriptomes of multipotent long-term hematopoietic stem cells (LT-HSC), multipotent progenitors (MPP), common myeloid progenitors (CMP), and megakaryocyte erythroid progenitors (MEP). (2) PRJNA475757/GSE115678 (in vitro cultured CD34+-derived erythroblasts): transcriptomes of CMP, colony- forming unit – erythroid (CFU-E), proerythroblasts (ProE), basophilic erythroblasts (BasoE), polychromatic erythroblasts (PolyE), orthochromatic erythroblasts (OrthoE), and reticulocytes (Retic). Raw sequencing data were processed using FastQC, Trimmomatic, Spliced Transcripts Alignment to a Reference (STAR), and RNA-Seq by Expectation-Maximization (RSEM). RSEM-normalized data were preprocessed to provide a transcripts-per-million (TPM) matrix. PKL, PKR, PKM1, and PKM2 expression data were visualized using RStudio.

Results:

In the early hematopoietic data set, PKR, PKL, and PKM1 transcripts had low to no detectable expression in any cell type. PKM2 was expressed (minimum, mean, maximum TPM) in LT-HSCs (37.3, 63.4, 120.3), MPPs (0.0, 47.4, 78.5), CMPs (67.3, 86.7, 113.4), and MEPs (45.5, 64.0, 101.3). In the erythroid progenitors' data set, PKM1 transcripts were not detected, and PKL transcripts were detected at extremely low levels. PKR transcripts were detected in CFU-E (11.9, 42.8, 62.6), ProE1 (52.5, 72.8, 84.4), ProE2 (65.8, 75.5, 81.8), and BasoE (5.4, 14.1, 23.5) cell types. PKM2 was detected in CMPs (76.3, 291.4, 489.0), CFU-Es (38.5, 65.3, 86.8), and ProE1 (19.7, 22.1, 25.5). PKM2 and PKR expression during early hematopoiesis and erythropoiesis are illustrated in Figure 1.

Summary/Conclusion:

These analyses showed that transcripts of PKM1 and PKL were present at low-to-undetectable levels in hematopoietic and erythroid progenitors. PKM2 transcripts were present at early stages of hematopoiesis and were the dominant isoform compared with PKR. Importantly, PKM2 and PKR transcripts were both expressed in early erythropoiesis, with the level of PKM2 expression decreasing upon maturation. Similar studies of transcriptomes derived from patients with diseases that feature compromised erythrocyte maturation may inform effective pharmacotherapeutic approaches.

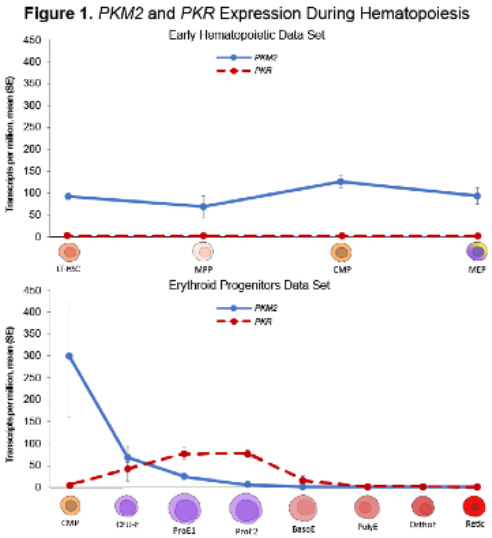


Figure 1. *PKM2* and *PKR* Expression During Hematopoiesis

Keywords: CD34+ cells, Pyruvate kinase, Hematopoiesis, Erythropoieisis

Abstract: P1473

Title: CLINICALLY RELEVANT HEMOGLOBIN RESPONSE IN ADULTS WITH PYRUVATE KINASE DEFICIENCY TREATED WITH MITAPIVAT – A SUB-ANALYSIS OF THE ACTIVATE TRIAL

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Abstract Type: Poster Presentation

Session Title: Enzymopathies, membranopathies and other anemias

Background:

Mitapivat, an oral, allosteric activator of pyruvate kinase (PK), is approved by the US FDA for the treatment of hemolytic anemia in adults with PK deficiency and by the EMA for the treatment of PK deficiency in adults. In the ACTIVATE trial (NCT03548220), mitapivat demonstrated improvements in hemoglobin (Hb) in patients (pts) who were not regularly transfused. 16/40 (40%) pts receiving mitapivat met the primary endpoint of Hb response (≥1.5 g/dL increase from baseline [BL] sustained at ≥2 scheduled assessments at weeks [wks] 16, 20, and 24 in the fixed-dose period) compared with 0 for placebo (PBO). Understanding Hb response using a clinically applicable definition of ≥1.0 g/dL improvement after mitapivat treatment may provide additional benefits.

Aims:

This analysis examined Hb, hemolysis, and disease-specific patient-reported outcome (PRO) responses to mitapivat during ACTIVATE and/or the long-term extension (LTE) (NCT03853798) in pts who had a ≥1.0 g/dL Hb increase.

Methods:

In the global, phase 3, randomized, PBO-controlled ACTIVATE trial, 80 pts were randomized 1:1 to receive mitapivat or PBO for a 12-wk dose-optimization period (5/20/50 mg twice daily), followed by a 12-wk fixed-dose period. This analysis included pts treated with mitapivat in ACTIVATE who continued into the LTE and had a clinically relevant Hb response defined as ≥1.0 g/dL increase from BL for at least 2 timepoints after the start of the fixed-dose period. Hemolysis was evaluated through bilirubin and reticulocyte analyses. Quality of life was evaluated by using the PRO measures, PK deficiency diary (PKDD) and PK deficiency impact assessment (PKDIA); for both, a lower score represents lower disease burden. The minimal clinically important change (MCIC) is defined as a reduction of 4.2 and 5.5 in PKDD and PKDIA scores, respectively.

Results:

25/40 (62.5%) pts originally randomized to mitapivat in ACTIVATE/LTE met the criteria for having a clinically relevant Hb response (≥1.0 g/dL) which occurred as early as 20 wks and as late as 108 wks. Median (Q1, Q3) Hb improvement from BL to Wk 108 was 2.6 g/dL (1.17, 3.27; n=19) (Figure). This group included a subset of 9 pts who did not meet original protocol endpoint (≥1.5 g/dL increase in Hb). For this subset, median (Q1, Q3) Hb improvement from BL at Wk 108 was 1.07 g/dL (0.69,1.92; n=8). 19/25 pts meeting the criteria for clinically relevant Hb response had a ≥1.5 g/dL Hb increase on ≥2 timepoints after the start of the fixed-dose period, of which 16 achieved this by Wk 24; 3 pts achieved ≥1.5 g/dL Hb improvement after Wk 24 (up to Wk 120). Median (Q1, Q3) change from BL to Wk 108 in bilirubin was -30.1 µmol/L (-55.15, -19.20; n=17) and in reticulocyte % was -8.3% (-19.2%, -2.8%; n=18). Improvements in hemolysis markers were similar in the subset of 9 who did not meet original protocol endpoint. At Wk 108, mean (95% CI) changes from BL in PKDD and PKDIA scores were -7.2 (-11.1, -3.2; n=15) and -7.3 (-10.8, -3.8; n=17), respectively (Figure). For the subset of 9 pts, mean (95% CI) changes from BL in PKDD and PKDIA scores were -6.1 (-14.6, 2.3; n=4) and -6.2 (-15.5, 3.2; n=6), respectively.

Summary/Conclusion:

This analysis shows that a majority of pts treated with mitapivat in ACTIVATE/LTE (62.5%) achieved a clinically relevant Hb response, defined as a Hb increase of ≥1.0 g/dL, along with improvements in hemolysis and PROs,

indicating beneficial effects to pts with PK deficiency. Further, some Hb responses ≥1.0 g/dL occurred after 6 months, indicating that certain pts may reach this threshold with continued treatment regardless of initial Hb response.

Keywords: Hemolysis, Pyruvate kinase deficiency, Hemolytic anemia, Hemoglobin