Case report

Mitapivat therapy in a patient with nonsense homozygous mutation of the Pyruvate Kinase L/R gene: a case report

Sara Ceglie[1,2], Caterina G. Valentini[1], Claudio Pellegrino[1,2], Giuseppina Massini[1], Luciana Teofili[1,2]

[1]*Dipartimento Scienze di Laboratorio ed Ematologiche, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy;*
[2]*Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy;*

INTRODUCTION

Pyruvate kinase (PK) deficiency leads to chronic hereditary non-spherocytic hemolytic anemia, with long-term complications such as iron overload, liver cirrhosis, endocrinopathies, osteoporosis, and pulmonary hypertension[1-3].

This condition is caused by germline mutations in the PKLR gene, which encodes for the erythrocyte-specific (PKR) and liver-specific (PKL) isoforms of the PK enzyme[4]. In glycolysis, PK catalyzes the transfer of a phosphate group from phosphoenolpyruvate to ADP, producing pyruvate and ATP[5]. Reduced PK activity depletes ATP in red blood cells, increasing hemolysis susceptibility[3].

Over 300 pathogenic mutations in PKLR have been identified, mainly missense substitutions affecting enzyme stability or function[6]. PK deficiency follows an autosomal recessive inheritance pattern, often with compound heterozygosity for two different mutations, whereas the homozygous inheritance of two missense (e.g., p.R479H and p.R510Q) or non-missense variants has also been described[6].

The wide molecular heterogeneity of PK deficiency translates into a variety of clinical presentations, ranging from compensated anemia to life-threatening forms requiring continuous transfusion support[6]. Until recently, clinical management of PK deficiency has been limited to supportive therapies, such as red blood cell (RBC) transfusions (either occasional or at regular intervals), vitamin supplementation, splenectomy, and treatment of complications, such as iron overload and decreased bone mineral density[7].

Mitapivat is a first-in-class oral allosteric activator of PKR, shown to activate both mutant and wild-type variants of the enzyme in vitro. The phase II DRIVE-PK study revealed that mitapivat's effectiveness varies by genetic defect. Patients with at least one missense mutation tend to respond better than those with two non-missense mutations[8], likely due to higher baseline PK levels. The subsequent European marketing authorization for mitapivat (Pyrukynd®, Agios Pharmaceuticals,Cambridge, MA, USA) was based on two phase-III trials, ACTIVATE and ACTIVATE-T. In ACTIVATE, mitapivat significantly increased hemoglobin (Hb), reduced hemolysis, and improved patient-reported outcomes in non-regularly transfused adults with PK deficiency[9]. Moreover, in the ACTIVATE-T trial, significantly reduced the transfusion burden of patients regularly transfused[10]. Of note, both ACTIVATE-T and ACTIVATE trials were restricted to patients carrying at least one missense mutation. Therefore, much less data are available on the mitapivat efficacy in patients carrying two non-missense mutations. Here we report the beneficial effect of mitapivat in a patient with the PKLR gene's homozygous c.1528C>T mutation, causing abnormal p.R510X splicing and a truncated enzyme lacking 63 C-terminal residues[11,12].

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Correspondence: Sara Ceglie
e-mail: sara.ceglie@guest.policlinicogemelli.it

CASE REPORT

A 20-year-old Latin-American male presented at our center in September 2022, having received regular RBC transfusions since childhood in Venezuela due to chronic hemolytic anemia of unknown origin. At age 12, he underwent splenectomy, which improved his anemia and reduced transfusion needs. Three years later, he moved to Italy and began regular follow-ups at a pediatric hematology center, where next-generation sequencing confirmed a homozygous mutation in the PKLR gene, with PK activity levels at 5-6 UI/gHb (normal values 11.6-16.1 UI/gHb)[12]. By the time he came to our observation, he required one RBC transfusion approximately every two months and was on daily low-dose aspirin and 5 mg folic acid. His hemoglobin was 9 g/dL and total and indirect bilirubin were 9.1 mg/dL and 8.3 mg/dL, respectively, while ferritin was 1,650 ng/mL with 83% transferrin saturation. Iron chelation with deferasirox was initiated, and an abdominal CT scan ruled out the presence of accessory spleens. Given his chronic transfusion needs and lack of other treatment options, we commenced a trial of mitapivat therapy. Mitapivat was kindly provided by Agios Pharmaceuticals under the Global Management Access Program and administered after the approval of the regional Ethics Committee (CET Lazio Area 3, prot. N 163/23). Drug administration was started at the recommended dose of 5 mg bid and progressively increased until the maximum dose of 50 mg bid over a 2-month period. **Figure 1** illustrates bilirubin levels, hemoglobin concentration, and transfusion needs recorded over the 12 months before and during mitapivat treatment. During the treatment, we observed a significant decrease in the bilirubin levels (from 6.7±1.3 mg/dL to 5.5±0.8 mg/dL, mean values ± SD before and during mitapivat, respectively; p=0.002 at the Mann-Whitney U test). Moreover, transfusion needs reduced from 9 to 5 RBC units before and during mitapivat therapy, respectively, with nearly unchanged mean Hb values (8.8±0.4 g/dL and 9.1±0.4 g/dL, respectively, p=0.07) (**Figure 1**). Liver and renal function parameters remained within normal ranges for the whole period of observation and no relevant side effects were reported. The patient experienced only a slight, not disabling daytime sleepiness, mainly related to initial insomnia, as already reported in previous clinical trials[9,10]. This side effect completely resolved after the first 2 months of treatment. Of notice, the patient reported a subjective improvement of general conditions at every outpatient visit. In particular, during the treatment period, the progressive relief of symptoms related to anemia had a positive impact on physical daily activities and school performances.

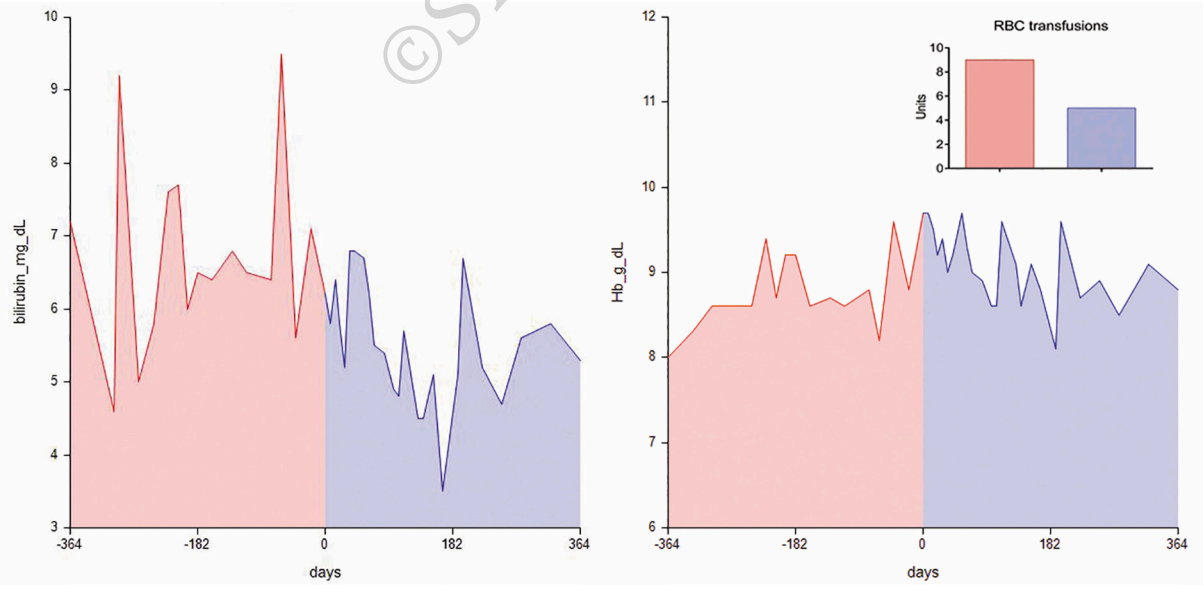

Figure 1 - Area under the curve of total bilirubin and hemoglobin values in the 1-year period before (red area) and during (blue area) mitapivat therapy
Transfusion needs in the two periods are shown in the upper graph.

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DISCUSSION

This case report provides insights into mitapivat therapy for pyruvate kinase deficiency. Previous data suggest that only patients with at least one missense mutation respond to mitapivat[10], as seen in the DRIVE-PK trial, where hemoglobin response was unmet in those without missense mutations[13]. Our patient, homozygous for a nonsense mutation, exhibited very low baseline PK activity. Despite an initial response to splenectomy, his anemia worsened over time, significantly affecting his quality of life. Interestingly, after starting mitapivat, he showed clinical improvement, including a 44.4% reduction in transfusion requirements (5 *vs* 9 units), lower hemolysis rate and better quality of life outcomes. Notwithstanding the underlying genetic defect and though hemoglobin levels remained stable, the reduction in transfusions and improved quality of life align with the 2024 guidelines for continued therapy in PK deficiency[14]. We can speculate that in this case, the low PK enzyme activity was indeed enough to sustain a response to mitapivat. This data prompts us to continue mitapivat treatment.

Our experience supports further investigation on mitapivat therapy in patients carrying non-sense mutations, even considering the favorable safety profile of the drug and the lack of alternative options.

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AUTHOR CONTRIBUTIONS

SC and LT designed the work and analyzed data, SC, CP, GM and CGV treated the patient, SC and LT wrote the paper and all co-Authors reviewed critically the manuscript and gave their final approval.

The Authors declare no conflicts of interest.

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