A Systematic Review of Efficacy and Safety of Mitapivat to Treat Hemolytic Anemia in Pyruvate Kinase Deficiency

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Veeranki P, Rayapureddy G, Kummari P, Mir J, Manne M, Chidirala S, Hyderboini R, Rajput A, Kohli IS, Goyal R, ***Aggarwal A****, Tanushree C*

IQVIA, India

Background and objectives

- Pyruvate kinase deficiency (PKD) is caused by mutations in the PKLR gene encoding the red blood cell PK enzyme (PKR) leading to defective glycolysis and hemolytic anemia[1].
- Mitapivat is a first-in-class, allosteric activator of PKR.
- We aimed to evaluate efficacy and safety of Mitapivat in adult patients with PKD.

Methodology

- A literature search was conducted in Embase®, MEDLINE® and Cochrane databases via Ovid to identify English language articles published from database inception to 17 June 2022 using “pyruvate kinase”, “PK deficiency”, “mitapivat”, “PYRUKYND”, “AG-348” terms.
- All the identified studies were screened based on the title/abstracts and followed by full-text screening against the eligibility criteria (Table 1) and data extraction by two reviewers and any disagreements were resolved by consensus.
- The quality assessment of included randomized study was conducted by using Cochrane risk of bias assessment tool (ROB2).

Table 1: Study eligibility criteria

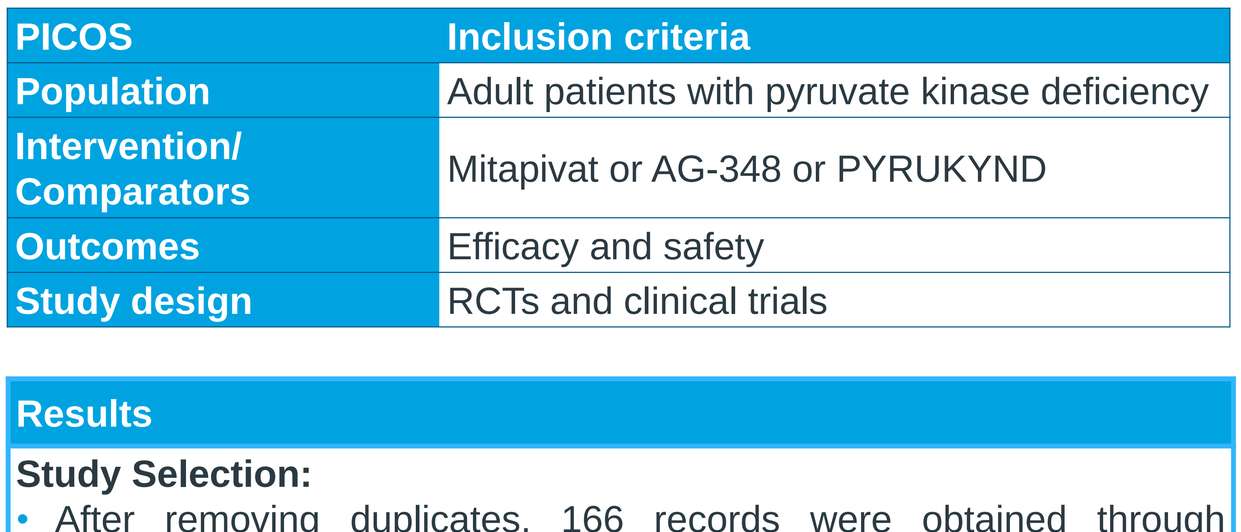
PICOS	Inclusion criteria
Population	Adult patients with pyruvate kinase deficiency
Intervention/ Comparators	Mitapivat or AG-348 or PYRUKYND
Outcomes	Efficacy and safety
Study design	RCTs and clinical trials

Results

Study Selection:

- After removing duplicates, 166 records were obtained through databases and additional searches.
- A total of two trials with three publications including (n= 107) adult patients with pyruvate kinase deficiency were included, of which 1 trial was double-blind, phase III clinical trial (ACTIVATE trial) and another trial was single arm phase III trial (ACTIVATE-T) **(Figure 1)**.

Figure 1: PRISMA chart of included studies



Note: * Two studies (3 publications) included for review

Results

ACTIVATE trial (NCT03548220)[2]:

- The Mitapivat receiving patients (40%) achieved a significantly higher sustained hemoglobin (Hb) response compared with placebo group (0%).
- The LSM difference between the Mitapivat and placebo showed statistical results for the mean change from baseline of Hb-concentration 1.8 g/dL (95%CI 1.2 to 2.4; p<0.0001), indirect bilirubin -26.26 µmol/L (95% CI -37.82 to -14.70; p<0.0001), reticulocyte percentage (%) -0.1011 (95%CI -0.1391 to -0.0632; p<0.0001), lactate-dehydrogenase -70.81 U/L (95%CI -115.88 to -25.74; p=0.0027), haptoglobin 0.158 g/L (95%CI 0.043 to 0.273; p=0.0079).
- In the long-term extension (LTE) study, patients who received placebo in the ACTIVATE study were assigned to Mitapivat and 35% (6/17) of patients achieved Hb responses[1].
- No treatment-emergent adverse events (TEAEs) led to discontinuation.

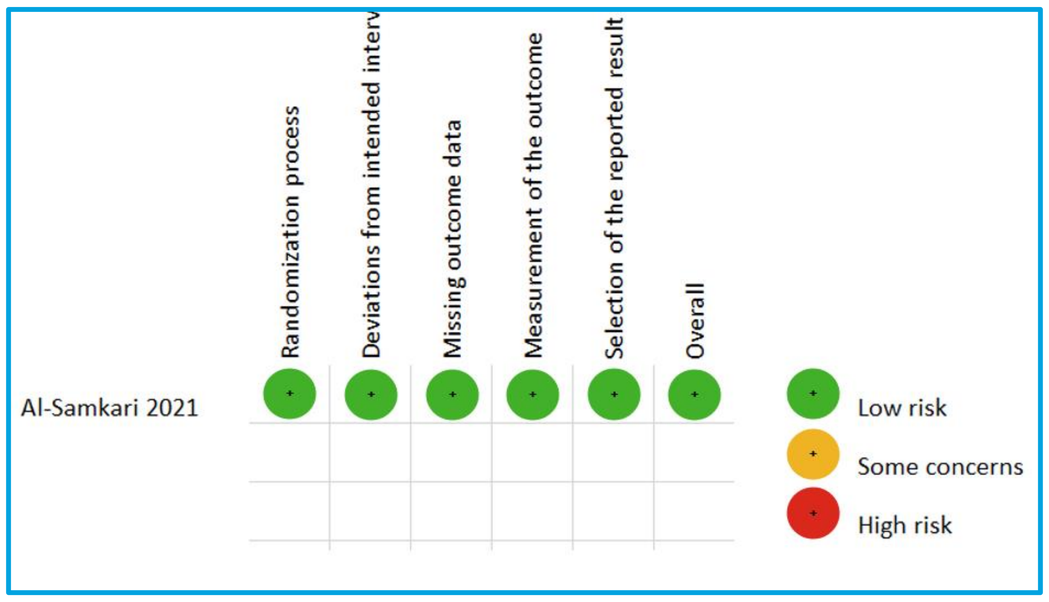
ACTIVATE-T trial (NCT03559699)[3] :

- Patients with regular transfusion status reported a ≥33% reduction in transfusion burden in 37% (10/27) of patients receiving Mitapivat and 22% (6/22) of patients were transfusion free.
- 30% (8/27) of patients had grade ≥3 treatment-emergent adverse events.
- No treatment-emergent adverse events (TEAEs) led to discontinuation.

Quality Assessment:

- The overall methodological quality of the included randomized trial (Al-Samkari 2021)[2] showed low risk of bias according to the Cochrane risk of bias assessment tool (ROB2) **(Figure 2)**.

Figure 2: Quality Assessment



Conclusions

- Data from ACTIVATE, ACTIVATE-T, and the LTE study demonstrated that Mitapivat improved Hb level and reduced transfusion burden in patients with PKD
- Mitapivat has the potential to become the first approved therapy in PK deficiency with beneficial effect on iron overload

References:

1.Grace RF, Glenthoej A, Barcellini W, Verhovsek M, Rothman JA, Morado M, Layton DM, Andres O, Galactéros F, Van Beers EJ, Onodera K. Durability of Hemoglobin Response and Reduction in Transfusion Burden Is Maintained over Time in Patients with Pyruvate Kinase Deficiency Treated with Mitapivat in a Long-Term Extension Study. Blood. 2021 Nov 23;138:848.

2.Al-Samkari H, Galacteros F, Glenthoj A, Rothman JA, Andres O, Grace RF, Morado AM, Layton DM, Onodera K, Verhovsek M, Barcellini W, Judge MP, Beynon V, Xu E, ACTIVATE: A phase 3, randomized, multicenter, double-blind, placebo-controlled study of mitapivat in adults with Pyruvate kinase deficiency who are not regularly transfused. Oncol Res Treat 2021;44(suppl 4):1–329

3.Glenthoj A, Van Beers E.J, Al-Samkari H, Viprakasit V, Kuo K.H.M, Galacteros F, Chonat S, Porter J, Gheuens S, Beynon V, Xu E, Hawkins P, Zagadailov E, Oluyadi A, Barcellini W. Activate-T: A phase 3, open-label, multicenter study of mitapivat in adults with pyruvate kinase deficiency who are regularly transfused. HemaSphere 2021;5:S2