

NEW APPROVED DRUG FOR THE TREATMENT OF ADULTS WITH POLYCYTHEMIA VERA

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INTRODUCTION

Polycythemia vera (PV), a myeloproliferative neoplasm (MPN), is a disease where there is an increased red cell mass. The pathology lies in the clonal proliferation in the erythroid lineage, granulocytic and megakaryocytic. Genetic mutation is seen in JAK2 phenotype where 95% of patients have V617F mutation.^[1-3] The presenting symptoms range from pruritis, fatigue, headaches and progression of the disease leads to thrombosis, hemorrhage and acute myeloid leukemia. Blood counts present as increased erythrocytosis and increased hematocrit and hemoglobin concentrations. The mainstay of treatment for patients of all ages is phlebotomy and cytoreductive therapy which aims to bring down hematocrit value below 45%. The main drawback of these two therapies is failure to achieve the required hematocrit value and as such many patients suffer from iron deficiency anemia.^[4-6] Rusfertide is a new drug whose novel mechanism of action is to mimic the action of endogenous hepcidin to control erythropoiesis and decreased hematocrit value below 45% in patients with Polycythemia Vera (PV).

Hepcidin and Regulation of Iron homeostasis

Erythropoiesis is initiated with the availability of iron which is in turn dependent on hepcidin, the main regulator of systemic iron homeostasis. Hepcidin is a 25-amino-acid peptide hormone synthesized mainly in the liver acting as a negative regulator of iron acquisition and recycling. It has been shown that increased hepcidin reduces availability of iron and less synthesis of hepcidin will increase availability of iron. Hepcidin binds to Ferroportin an iron exporter on enterocytes, macrophages and hepatocytes. The mechanism involves the internalization and degradation of 'ferroportin', thereby reducing the iron absorption from the intestine and iron release from the storage site. In Polycythemia vera, hepcidin levels are found to be low despite adequate iron stores leading to increased iron availability and uncontrolled erythropoiesis.^[7-9]

HAMP gene and signaling pathways involved in regulating hepcidin synthesis

HAMP, is the hepcidin-coding gene and mature hepcidin is produced via cleavage of the pre-propeptide. HAMP gene is involved in transcriptional regulation which includes bone morphogenetic protein responsive elements (BMPREs), a STAT3-responsive element (STAT3RE), and upstream promoter elements, such as C/EBP and CRE. These responsive elements are again regulated by BMP–Smad and STAT3. Hepcidin synthesis begins when multiple BMP - SMAD connects with bone morphogenetic protein receptors (BMPRs) and induce the phosphorylation of intracellular Smad. The ultimate signaling pathway involves the formation of a complex of Phosphorylated Smad1/5/8 and Smad4 which is transferred to the nucleus of HAMP gene through BMPREs where HAMP gene transcription takes place. It is important to understand that abnormal expression of these proteins which are cofactors of HAMP synthesis are the main cause of defective hepcidin synthesis.^[10–15] (Fig 1)

HAMP gene and signaling pathways involved in regulating hepcidin synthesis

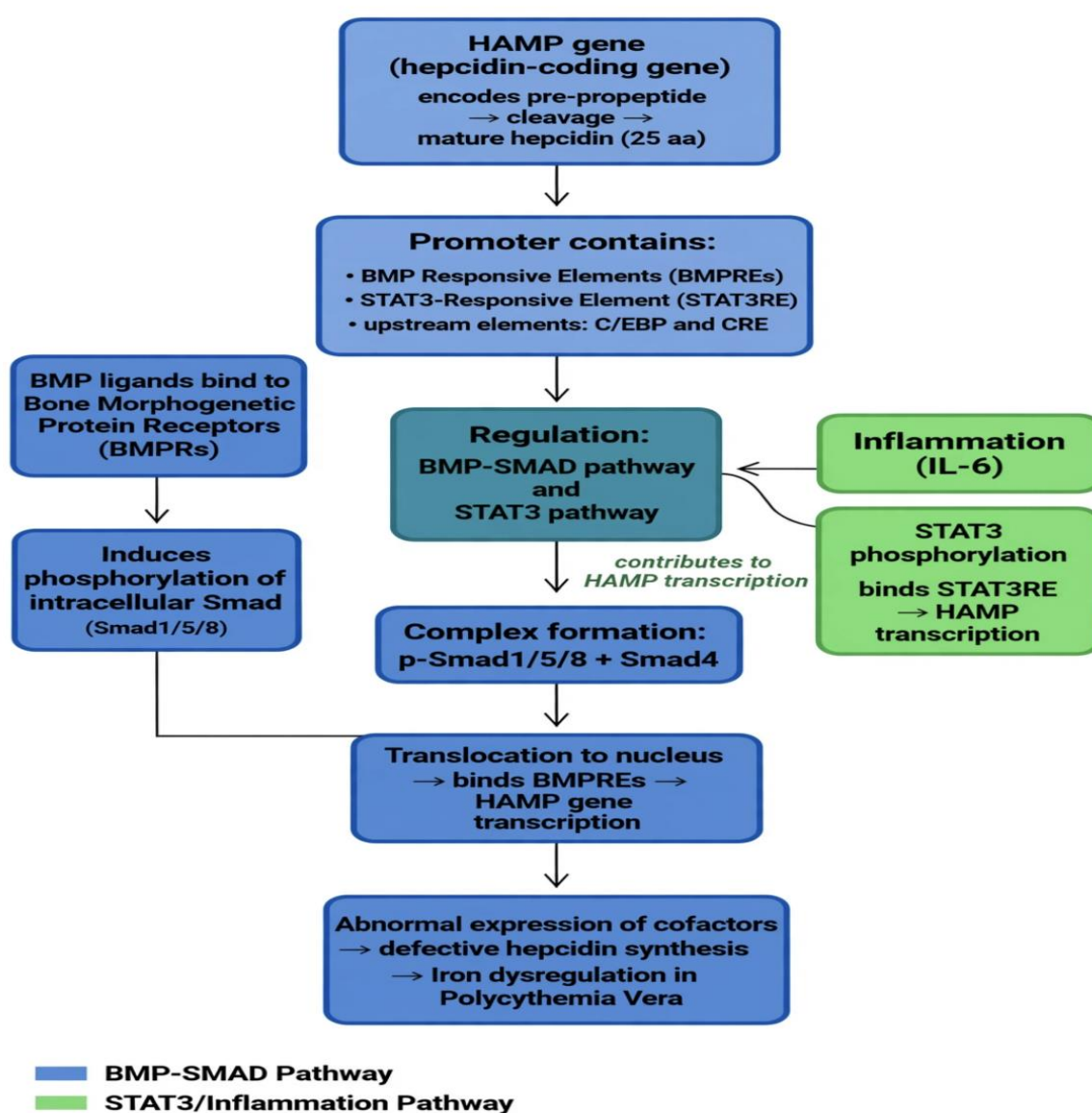


Fig. 1

Mechanism of Action of Rusfertide (Hepcidin Mimetic) in Polycythemia Vera

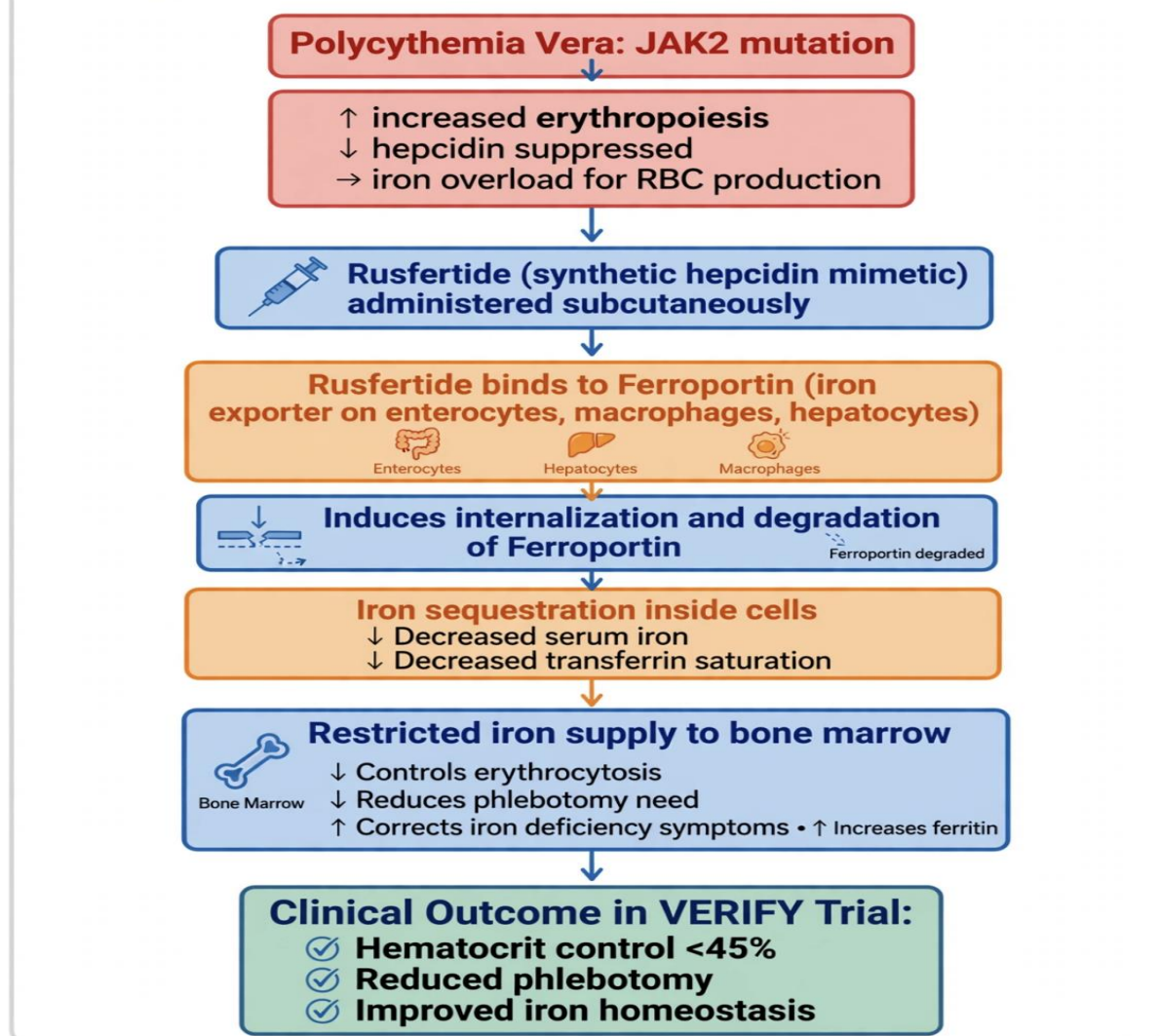


Fig. 2

Drawbacks of present treatment guidelines of Polycythemia vera.

The treatment guidelines for Polycythemia vera recommend maintaining hematocrit below 45% to minimize thromboembolic and cardiovascular risk. Despite phlebotomy and cytoreductive therapy with hydroxyurea and ruxolitinib, many patients fail to achieve durable hematocrit control and suffer from iron deficiency-related symptoms. Treatment of Polycythemia vera is started with phlebotomy and low dose (100mg) of Aspirin which has frequently resulted in low reduction of hematocrit values with risk of thromboembolic complications. High-risk patients above 60 years with a previous history of thrombosis are treated with cytoreductive agents namely: Hydroxyurea and interferon alpha and sometimes addition of ruxolitinib. These drugs have shown to produce adverse reactions like gastric complications, blood dyscrasias, mucositis, leg ulcers, skin cancers, dermatitis, and occasional flu-like symptoms leading to treatment failure. While these phlebotomies may help the overproduction of red blood cells in these patients, they do not address the iron deficiency and consequent fatigue, brain fog, and other disabling symptoms that affect

patient's daily lives. Moreover, in Polycythemia vera, endogenous hepcidin levels are inappropriately low relative to iron stores. Hepcidin mimetic drugs would help restore this negative regulation.

Pharmacology of Rusfertide

Chemically Rusfertide is a cyclic peptide $C_{114}H_{181}N_{27}O_{28}S_2$ available as an acetate salt which is off white in colour and hygroscopic in nature. Rusfertide binds to Ferroportin thereby, restricting iron supply to the bone marrow resulting in lower hematocrit levels. "VERIFY" phase 3 clinical trial shows a reduction in serum iron and an increase in the serum ferritin concentrations indicating restoration of iron homeostasis. The efficacy of Rusfertide was based on the proportion of patients achieving a response between week 20 – week 32 (absence of phlebotomy). Phlebotomy eligibility being defined as a confirmed hematocrit greater than 45%. [Fig.2]

Pharmacokinetics

Rusfertide is administered subcutaneously once weekly with a bioavailability of 50% with a peak concentration at 24 hours. It is highly protein bound to plasma proteins and apparent volume of 38L. It is metabolized by trypsin-like proteases to active metabolites of lower potencies and excreted mainly in the urine in trace amounts.

Safety profile of Rusfertide

The safety profile of Rusfertide was evaluated in the VERIFY trial, randomized, double-blind, placebo-controlled phase III study of 293 adults with Polycythemia vera who required frequent phlebotomies followed for a period of 52 weeks. The most common adverse reactions were injection site reactions (56%) and anemia (16%), thrombocytosis (8%) and dyspnea (6%).

CONCLUSION

Rusfertide is a novel synthetic hepcidin mimetic which has recently been approved by FDA in August 2026 for the treatment of Erythrocytosis in Adults with Polycythemia Vera. By targeting the hepcidin pathway it represents a new shift from cytoreductive phlebotomy to iron-restrictive disease control. Clinical evidence from the VERIFY trial shows durable hematocrit control, lessening of phlebotomy in majority of patients with improvement in fatigue and iron deficiency symptoms. It offers a promising therapeutic option for patients who are not able to tolerate cytoreductive therapies or require frequent phlebotomies. However, the post marketing surveillance needs to be adhered to strictly in order to monitor safety profile of Rusfertide in the near future.

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