Rusfertide and hepcidin mimetics: a different way to control erythrocytosis

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Managing erythrocytosis, particularly in conditions like polycythemia vera, has long relied on phlebotomy to reduce red blood cell mass and mitigate thrombotic risk. This approach, while effective in reducing haematocrit, often comes with its own set of challenges, including iron deficiency symptoms and the burden of frequent clinic visits. The field has sought therapies that could offer more precise and less burdensome control over red cell production.

Emerging strategies, specifically those involving rusfertide and hepcidin mimetics, represent a significant departure from this established paradigm. These agents aim to modulate iron metabolism directly, offering a different way to control erythrocytosis by limiting iron availability for erythropoiesis.

KEY TAKEAWAYS

- The Pivot: Novel agents like rusfertide and hepcidin mimetics offer a mechanism-based approach to erythrocytosis by modulating iron metabolism, rather than simply removing red cells.
- The Data: While specific trial data is not provided, the underlying principle involves increasing hepcidin activity to restrict iron supply for red blood cell production.
- The Action: Clinicians should be aware of these emerging therapeutic classes as they represent a potential shift in how chronic erythrocytosis, particularly in myeloproliferative neoplasms, might be managed in the future.

Erythrocytosis, the elevation of red blood cell mass, is a hallmark of several haematological disorders, most notably polycythemia vera (PV). In PV, a myeloproliferative neoplasm, uncontrolled proliferation of myeloid stem cells leads to an overproduction of red blood cells, often accompanied by increased white blood cells and platelets. This heightened red cell mass significantly increases blood viscosity and the risk of thrombotic events, which are the primary cause of morbidity and mortality in these patients. Current management strategies for PV primarily focus on reducing the haematocrit to target levels, typically below 45%, to minimise these risks. The cornerstone of this management has been therapeutic phlebotomy, a procedure that directly removes red blood cells from circulation. While effective in achieving haematocrit control, phlebotomy can induce iron deficiency, leading to symptoms such as fatigue, restless legs syndrome, and impaired cognitive function, which can significantly impact a patient's quality of life. For patients who cannot tolerate phlebotomy or require more aggressive control, cytoreductive agents like hydroxyurea are employed, but these also carry their own side effect profiles and long-term considerations.

The unmet need in erythrocytosis management extends beyond simply controlling haematocrit. There is a clear demand

for therapies that can maintain haematocrit within target ranges without inducing symptomatic iron deficiency, reduce the frequency of phlebotomy, and ideally, address the underlying pathological drivers of erythrocytosis. This is where agents like rusfertide and hepcidin mimetics enter the discussion, representing a mechanistic shift in how we might approach these conditions. These therapies do not directly target the clonal proliferation of myeloid cells, but rather modulate the body's iron homeostasis, thereby indirectly limiting red blood cell production. Understanding the intricate regulation of iron is key to appreciating the potential of these new drug classes.

The Iron-Hepcidin Axis and Erythropoiesis

Iron is an essential component of haemoglobin, and its availability is a rate-limiting factor for erythropoiesis. The body meticulously regulates iron absorption, recycling, and utilisation through a complex system centred on hepcidin, a small peptide hormone primarily produced by the liver. Hepcidin acts as the master regulator of systemic iron homeostasis. It controls the entry of iron into the plasma from dietary absorption in the duodenum, from macrophage recycling of senescent red blood cells, and from hepatic stores. Hepcidin achieves this by binding to ferroportin, the only known cellular iron exporter, leading to its internalisation and degradation. This action effectively traps iron within cells, reducing its availability for erythropoiesis.

In conditions of chronic inflammation or iron overload, hepcidin levels typically rise, restricting iron supply. Conversely, in iron deficiency or states of increased erythropoietic demand, hepcidin levels fall, allowing more iron to enter circulation. In polycythemia vera, despite the increased red cell production, hepcidin levels are often inappropriately low or normal, failing to adequately restrict iron supply to the hyperactive erythroid precursors. This dysregulation contributes to the persistent erythrocytosis. The concept behind rusfertide and hepcidin mimetics is to restore or enhance hepcidin's iron-restrictive function, thereby starving the hyperproliferative erythroid lineage of the iron it needs to produce excessive red blood cells. This approach aims to achieve haematocrit control by reducing the raw materials for erythropoiesis, rather than by removing the finished product.

Rusfertide's Mechanism of Action

Rusfertide is a hepcidin mimetic, specifically a hepcidin agonist. It is designed to mimic the action of endogenous hepcidin, binding to ferroportin and promoting its degradation. By doing so, rusfertide effectively reduces the amount of iron released into the bloodstream from enterocytes, macrophages, and hepatocytes. This reduction in circulating iron, particularly transferrin-bound iron, limits the iron available for erythroid precursors in the bone marrow. The consequence is a decrease in red blood cell production, leading to a reduction in haematocrit. This mechanism is distinct from traditional cytoreductive agents, which directly suppress bone marrow proliferation, and from phlebotomy, which removes mature red cells. Rusfertide offers a more targeted approach to iron metabolism, aiming to achieve haematocrit control while potentially mitigating the symptomatic iron deficiency often associated with frequent phlebotomy. The goal is to maintain iron stores within cells, preventing systemic iron overload, but restricting its mobilisation for erythropoiesis. This control over iron availability could allow for sustained haematocrit reduction without the debilitating fatigue and other symptoms that often accompany chronic phlebotomy-induced iron deficiency. For clinicians managing patients with PV, particularly those struggling with phlebotomy burden or iron deficiency symptoms, this mechanism offers a compelling alternative. The role of iron status in erythrocytosis is increasingly recognised as central to patient symptoms and disease progression.

The Broader Class of Hepcidin Mimetics

Beyond rusfertide, the concept of targeting the hepcidin-ferroportin axis has spurred the development of other hepcidin mimetics. These agents broadly fall into two categories: those that directly mimic hepcidin's structure and function, and those that modulate hepcidin production or signalling pathways. The overarching goal remains the same: to increase functional hepcidin activity and thereby reduce systemic iron availability for erythropoiesis. This class of drugs represents a significant area of research in haematology, not only for polycythemia vera but potentially for other conditions characterised by iron overload or dysregulated erythropoiesis. The specificity of these agents for iron metabolism offers a potential advantage in terms of side effect profiles compared to broader cytoreductive therapies. The precision of this approach means that while iron is sequestered, it is not necessarily depleted from the body, which could prevent the profound iron deficiency symptoms seen with phlebotomy. This is a critical distinction, as patients with PV often experience a paradoxical combination of high red cell mass and functional iron deficiency due to the high demand for iron by the hyperproliferative marrow. By controlling iron mobilisation rather than total body iron, these mimetics aim to strike a balance.

Clinical Considerations and Future Directions

The introduction of hepcidin mimetics into the therapeutic armamentarium for erythrocytosis would necessitate a careful re-evaluation of current management algorithms. While phlebotomy and cytoreductive agents have established roles, a therapy that can reduce phlebotomy burden and improve iron-related symptoms would be highly valued. The long-term safety and efficacy of these agents, particularly regarding potential off-target effects of chronic hepcidin agonism, will be critical areas of investigation. For instance, the impact on iron-dependent processes outside of erythropoiesis, or the potential for iron accumulation in specific organs, would need thorough assessment. The optimal patient population for these therapies also requires definition. Will they be reserved for patients intolerant to or refractory to existing treatments, or will they find a place earlier in the treatment pathway? These are questions that future clinical trials will need to address. The development of these agents also highlights the growing understanding of the molecular pathogenesis of myeloproliferative neoplasms and the potential for targeted therapies that exploit specific biological pathways. This move towards precision medicine in haematology is consistent with trends across other therapeutic areas, offering hope for more effective and better-tolerated treatments. The understanding of inflammation in haematological disorders, for example, has also led to novel therapeutic targets.

The open-label nature of some early studies is an obvious caveat, as is the relatively small patient numbers often seen in initial investigations of rare diseases. The true impact on long-term thrombotic risk, the ultimate clinical endpoint in PV, will require larger, adequately powered studies with extended follow-up. Whether these agents can truly replace or significantly reduce the need for cytoreductive therapy in high-risk patients remains an open question. The current standard of care, as outlined in major guidelines, relies on risk stratification to guide treatment intensity, and any new therapy would need to demonstrate its place within this framework. The potential for these drugs to improve quality of life by reducing phlebotomy frequency and alleviating iron deficiency symptoms is a significant draw. But, clinicians will need clear data on hard clinical outcomes before widespread adoption. The integration of these novel agents into clinical practice will also require careful monitoring of iron parameters and haematological responses, potentially necessitating new guidelines for patient management. The principles of tight control are applicable across many chronic conditions, and erythrocytosis is no exception.

CLINICAL IMPLICATIONS

The emergence of rusfertide and other hepcidin mimetics represents a genuine shift in how we might approach erythrocytosis, particularly in polycythemia vera. For too long, phlebotomy, while effective, has been a blunt instrument, trading thrombotic risk reduction for symptomatic iron deficiency. These new agents offer a more elegant solution, targeting the iron supply chain directly.

Clinicians should view these developments with cautious optimism. The promise of reducing phlebotomy burden and improving quality of life for patients with PV is substantial. But, the long-term safety profile and the impact on hard clinical endpoints like thrombotic events will be paramount. We need to see robust data (n=X, 95% CI: Y-Z) that positions these drugs clearly within existing treatment algorithms.

The pharmaceutical industry's focus on this pathway reflects a deeper understanding of iron biology in haematological malignancies. This is not merely another cytoreductive agent; it is a mechanistic intervention that could redefine how we manage chronic erythrocytosis. The challenge will be integrating these therapies effectively, ensuring they address the right patient populations without introducing unforeseen complications. The goal is to provide patients with better control over their disease and a better quality of life. If hepcidin

> mimetics can achieve this without the trade-offs inherent in current approaches, they will earn their place in our prescribing habits. Until then, careful monitoring and adherence to established guidelines remain essential, perhaps with the aid of a comprehensive reference like the Oxford Handbook of Clinical Haematology.

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REFERENCES

1. 1. Fox S, Griffin L, Robinson Harris D. Polycythemia Vera: Rapid Evidence Review. Am Fam Physician. 2021;103(11):680-687. PMID:34060791
2. 2. Ellis MH, Barbui T, Tefferi A. Polycythemia vera. Mayo Clin Proc. 2026;101(5):826-845. doi:10.1016/j.mayocp.2026.01.008
3. 3. Golden C. Polycythemia vera: a review. Clin J Oncol Nurs. 2003;7(5):553-6. doi:10.1188/03.CJON.553-556
4. 4. Spivak JL. Polycythemia Vera. Curr Treat Options Oncol. 2018;19(2):12. doi:10.1007/s11864-018-0529-x
5. 5. Stuart BJ, Viera AJ. Polycythemia vera. Am Fam Physician. 2004;69(9):2139-44. PMID:15152961
6. 6. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera: historical oversights, diagnostic details, and therapeutic views. Leukemia. 2021;35(12):3339-3351. doi:10.1038/s41375-021-01401-3

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