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Administration of vadadustat for anemia of chronic kidney disease; an updated review

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ABSTRACT

Chronic kidney disease (CKD) is a global health burden, often complicated by anemia due to impaired erythropoietin production and iron dysregulation. Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), has emerged as a promising therapeutic option for managing anemia in CKD patients. By stabilizing hypoxia-inducible factors, vadadustat enhances endogenous erythropoietin production and improves iron metabolism, offering a novel approach to treating CKD-associated anemia. Recent clinical trials demonstrate that vadadustat effectively increases hemoglobin levels, reduces the need for erythropoiesis-stimulating agents (ESAs), and improves patients' quality of life. However, concerns regarding its safety, including potential risks of thromboembolic events and hypertension, warrant careful patient selection and monitoring. Comparative analyses with standard therapies, such as ESAs and other HIF-PH inhibitors, highlight vadadustat's advantages in terms of oral administration and cost-effectiveness, while also identifying areas for further research.

Review

Implication for health policy/practice/research/medical education:
Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) which is administered to treat symptomatic anemia in adults with chronic renal failure. Clinical trials have shown that it effectively maintains hemoglobin levels within target ranges, offering a promising alternative for anemia management in chronic renal failure patients.

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Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by the gradual loss of kidney function over time (1). It is a significant global health concern, affecting approximately 10% of the world's populace, with prevalence rates continuing to rise due to aging populations and the increasing burden of diabetes and hypertension (2). CKD is associated with numerous complications, including cardiovascular disease, electrolyte imbalances, and metabolic disturbances (3). Among these, anemia is one of the most common and debilitating complications, associated with a significantly heightened risk of cardiovascular morbidity and higher mortality rates in individuals with advanced CKD (4). Anemia in CKD arises primarily from reduced erythropoietin production by the kidneys, iron deficiency, and inflammation, leading to fatigue, reduced quality of life, and increased cardiovascular risk (4). Current treatment options for CKD-associated anemia include erythropoiesis-stimulating agents (ESAs) and iron supplementation

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(5). While ESAs have been the cornerstone of anemia management, their use is limited by high costs, the need for frequent injections, and potential cardiovascular risks (5,6). Iron supplementation, though essential, often fails to address the underlying erythropoietin deficiency (7). These limitations have spurred the development of novel therapies, such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which offer a more physiological approach to managing anemia in CKD patients (8). Vadadustat is an oral HIF-PHI that has garnered significant attention as a potential alternative to traditional ESAs (9). By inhibiting prolyl hydroxylase enzymes, vadadustat stabilizes HIFs, leading to the upregulation of erythropoietin gene expression and enhanced iron mobilization (9,10). This dual mechanism not only stimulates erythropoiesis but also improves iron availability, addressing two key contributors to anemia in CKD (10). This property leads to a gradual increase in hemoglobin levels and the correction of iron metabolism (10). Moreover, this agent decreases hepcidin levels, which facilitates greater iron absorption and mobilization (11). Indeed, HIFs are transcription factors that mediate cellular survival under hypoxic conditions by regulating angiogenesis, cell growth and differentiation, metabolic processes, and erythropoiesis (12). Under normal oxygen conditions, HIFs are degraded through hydroxylation by prolyl-hydroxylase dioxygenases (12). Furthermore, vadadustat increases iron-binding capacity (10). Previous studies have demonstrated that vadadustat significantly decreases ferritin and hepcidin levels while increasing total iron-binding capacity (TIBC), promoting better iron utilization in CKD patients compared to placebo (13). By inhibiting HIF-prolyl-hydroxylases, vadadustat increases HIF levels, even without hypoxic conditions (10). This leads to increased endogenous erythropoietin production, improving iron mobilization and correcting anemia in patients with dysfunctional erythropoiesis due to CKD (9, 4). The rationale for using vadadustat in CKD patients lies in its ability to mimic the body's natural response to hypoxia, offering a more targeted and convenient treatment option compared to ESAs (15). Its oral administration route improves patient adherence and reduces the burden of frequent injections (9). Furthermore, vadadustat's potential to reduce the need for intravenous iron and ESAs makes it an attractive option for both non-dialysis-dependent and dialysis-dependent chronic renal failure patients (16, 17). This study investigates the mechanisms, efficacy, safety, and the clinical significance of vadadustat as a transformative therapy for CKD-related anemia.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords such as vadadustat, chronic kidney disease, anemia, chronic renal failure, hypoxia-inducible factor, prolyl hydroxylase inhibitors, erythropoiesis and iron-binding capacity.

Pharmacology of vadadustat

Vadadustat primary mechanism of action involves the inhibition of hypoxia-inducible factor prolyl hydroxylase enzymes, which are responsible for the degradation of HIF under normoxic conditions (18). By inhibiting these enzymes, vadadustat stabilizes HIF-α subunits, allowing them to translocate to the nucleus and form active transcriptional complexes with HIF-β (18,19). This stabilization leads to the activation of genes involved in erythropoiesis, including erythropoietin (20). The increased transcription of erythropoietin stimulates red blood cell production in the bone marrow (21). Additionally, vadadustat enhances iron utilization by upregulating the expression of proteins such as transferrin and transferrin receptors, which improve iron absorption and mobilization (22). The stimulation of erythropoiesis and optimizing iron metabolism, makes vadadustat an effective therapeutic option for managing anemia in CKD patients (23). Vadadustat is administered orally and is rapidly absorbed in the gastrointestinal tract, with peak plasma concentrations typically achieved within 1 to 4 hours post-administration (24). Vadadustat undergoes liver metabolism, mainly by glucuronidation and oxidation pathways (25). The metabolites of vadadustat are primarily excreted in the urine, with a smaller portion eliminated in the feces (26). The terminal elimination half-life (t½) of vadadustat is 4.7 hours in healthful adults; however, it ranges from 7.9 to 9.1 hours in individuals with non–dialysis- and dialysis-dependent CKD, respectively (24). The dosage is adjusted based on the patient's hemoglobin levels, iron status, and CKD stage (27).

Focus on erythroferrone

Erythroferrone is a hormone secreted by erythroblasts that suppresses hepcidin production, increasing iron availability for erythropoiesis (28). Vadadustat's effects on erythropoiesis and iron metabolism appear to be independent of erythroferrone (14, 29). A previous study found that, using erythroferrone knockout mice with CKD treated with vadadustat showed that vadadustat was still effective in normalizing hemoglobin concentrations, increasing the expression of duodenal iron transporters, lowering serum hepcidin levels, and decreasing tissue iron concentrations, similar to results seen in wild-type mice (14). This suggests that vadadustat increases iron mobilization independently of erythroferrone (14). Recent studies indicated that vadadustat suppresses CKD-induced hepcidin production, even in the absence of erythroferrone (30). It is possible that, vadadustat-mediated HIF stabilization directly or indirectly suppresses hepcidin expression (11).

Vadadustat in CKD

Chronic kidney disease is frequently associated with anemia, a condition characterized by decreased levels of hemoglobin due to inadequate erythropoiesis (31). Vadadustat being a novel oral therapeutic agent that has garnered attention for its efficacy in enhancing erythropoiesis in CKD patients (32). As mentioned earlier, this compound is designed as an oral HIF-PHI, which stabilizes the hypoxia-inducible factor pathway, consequently stimulating increased erythropoietin production (9). Under hypoxic conditions, HIF facilitates the transcription of genes that are crucial for erythropoiesis, thus promoting the production and mobilization of erythrocytes in the bone marrow (20,33). By enhancing endogenous erythropoietin levels, it supports one of the fundamental deficiencies in anemic CKD patients (34). Vadadustat has demonstrated significant efficacy in managing anemia in non-dialysis-dependent CKD patients (9). Clinical trials have consistently shown that vadadustat effectively increases and maintains hemoglobin levels within the target range 10–12 g/dL (6). For example, in the PRO$_2$TECT trials, vadadustat was non-inferior to darbepoetin alfa, an ESA, in correcting and maintaining hemoglobin levels over 52 weeks (35). Individuals who treated with vadadustat experienced a mean increase in hemoglobin of approximately 1.5–2.0 g/dL, with improvements observed as early as 4–6 weeks after initiation (35). Beyond hemoglobin correction, vadadustat has been associated with improvements in quality of life and symptom relief (9). These benefits are particularly important for non-dialysis-dependent CKD patients, who often experience a gradual decline in kidney function and worsening anemia over time (36). Likewise, in dialysis-dependent CKD patients, vadadustat has shown comparable efficacy to traditional ESAs in maintaining hemoglobin levels (37). The INNO$_2$VATE trials demonstrated that vadadustat was non-inferior to epoetin alfa in achieving and sustaining target hemoglobin levels over 52 weeks (38). Hemoglobin levels remained stable in the range of 10–11 g/dL, with no significant differences in transfusion requirements between vadadustat and ESA-treated groups (38). One of the key advantages of vadadustat in Dialysis-Dependent CKD patients is its oral administration, which eliminates the need for frequent injections required with ESAs (15). Additionally, vadadustat's ability to enhance iron utilization may decrease the need for intravenous iron supplementation, further simplifying anemia management in this population (36). Notably, hemoglobin levels in patients treated with vadadustat improved significantly from baseline, indicating its potent role in enhancing red blood cell production (39). Furthermore, vadadustat not only improves hemoglobin levels but also demonstrates benefits in iron metabolism (9), as evidenced by increased total iron-binding capacity and decreased hepcidin levels in treated patients (10). However, the safety profile of vadadustat has been increasingly scrutinized, especially with the backdrop of CKD management (40,41). Studies indicate that vadadustat is well tolerated and presents a safety profile comparable to that of darbepoetin alfa, with no significant increase in the risk of serious adverse cardiovascular events (41). In the phase three trials, patients treated with vadadustat did not exhibit a statistically significant increase in adverse events when compared to those receiving traditional ESAs therapy (42).

Adverse effects in vadadustat

Vadadustat is generally well-tolerated, but like all medications, it is associated with some common adverse effects (43). Vadadustat can lead to elevated blood pressure in some patients, likely due to increased erythropoiesis and blood viscosity (36). Also, elevated potassium levels have been observed in some patients, particularly those with advanced CKD (44,45). This may be related to improved erythropoiesis and increased red blood cell turnover, which can release potassium into the bloodstream (45). In addition, mild gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, have been reported in a subset of patients (46). These symptoms are typically transient and can often be managed with supportive care. It is notably to mention that these effects are generally manageable with appropriate monitoring and dose adjustments (41). While vadadustat is effective in managing anemia, it is not without risks of more serious adverse events. Like other therapies that increase hemoglobin levels, vadadustat may elevate the hazards of thromboembolic events, like deep vein thrombosis, pulmonary embolism and stroke (47). This risk is particularly relevant in CKD patients, who already have a higher baseline risk of cardiovascular complications (47,48). Hypoxia-inducible factor stabilization has raised theoretical concerns about promoting tumor growth (49). These factors play a role in angiogenesis and cell survival, which could potentially support the growth of existing malignancies (49). Although clinical trials have not shown a significant increase in cancer incidence with vadadustat, long-term data are needed to fully assess this risk (50).

Conclusion

Vadadustat is a pioneering therapeutic agent emerging in the treatment of anemia associated with chronic renal failure. As a HIF-PHIs, vadadustat has demonstrated unique benefits compared to traditional ESAs such as darbepoetin alfa. By effectively managing anemia, it not only aids in improving patients quality of life but also potentially mitigates the complications tied to untreated anemia, such as increased cardiovascular risks and diminished physical capacity. Moreover, the ability of vadadustat to enhance iron mobilization and reduce hepcidin levels provides additional clinical utility in

managing iron deficiency, a common comorbidity in CKD patients.

Authors' contribution

Conceptualization: Sajad Ataei Azimi and Shirin Shamsghahfarokhi.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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