kidney and dialysis

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Perspective

Is HIF-PHI the Answer to Tackle ESA Hyporesponsiveness in the Elderly?

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Abstract: Anemia in chronic kidney disease (CKD) has become an important clinical issue with the increased prevalence of elderly patients living with CKD progressing to kidney failure. The causes of anemia in elderly individuals tend to be multifactorial, exacerbated by the physiological effects of aging, frailty and declining kidney function. Erythropoiesis-stimulating agents (ESAs) are the conventional therapeutic option for anemia in CKD. However, ESA hyporesponsiveness is a commonly observed issue in clinical practice and an issue that is more challenging to resolve in elderly patients living with frailty, kidney disease, and multi-morbidities. Following the emergence of oral hypoxia-induced factor prolyl-hydroxylase inhibitors (HIF-PHI) in recent years, there is discussion on whether it is a solution to the conundrum of ESA hyporesponsiveness, as HIF-PHI treats anemia via an alternative physiological pathway. There remains uncertainty on the suitability of HIF-PHI use in elderly patients, given a lack of data on its safety over long-term follow-up for the elderly population. Further study is needed to provide answers, considering the clinical significance of this issue within a public-health scale.

Keywords: HIF-PHI; ESA hyporesponsiveness; anemia; chronic kidney disease; aging; multi-morbidities

Citation: Wu, H.H.L.; Chinnadurai, R.; Walker, R.J. Is HIF-PHI the Answer to Tackle ESA Hyporesponsiveness in the Elderly? *Kidney Dial.* **2022**, *2*, 446–453. https://doi.org/10.3390/kidneydial2030040

Academic Editors: Francesco Locatelli, Lucia Del Vecchio and Ciro Esposito

Received: 17 June 2022
Accepted: 3 August 2022
Published: 4 August 2022

1. Introduction

The prevalence of elderly patients with chronic kidney disease (CKD) and kidney failure has significantly increased since the turn of this century. Results from the third National Health And Nutrition Examination Survey (NHANES) in 2003 note the prevalence of CKD in the United States to be 39.4% for individuals aged ≥60 years (prevalence of CKD for individuals aged 40–59 and 20–39 is 12.6% and 8.5%, respectively) [1]. These numbers are believed to have risen to even greater levels in recent years, considering the exponential increase in the global geriatric population, most notable in elderly patients with kidney failure requiring dialysis. It has been highlighted following the Dialysis Outcomes and Practice Patterns Study (DOPPS) that adults aged ≥75 years form up to 30% of the global dialysis population [2]. CKD and kidney failure have strong associations with poor morbidity and mortality outcomes, in particular, for elderly individuals with a multi-morbid status. Anemia is a common sequela of CKD and the risk of anemia increases with declining kidney function and reduced erythropoietin production. NHANES data note that the proportion of anemic patients with CKD aged >65, as defined according to the World Health Organization Criteria (hemoglobin < 13.0 g/dL for males and <12.0 g/dL for females), has doubled from 8% between 1988 and 1994 to 15.4% between 2009 and 2010 [3,4].

2. Clinical Significance and Challenges of ESA Hyporesponsiveness in the Elderly

Finding an optimal management strategy for anemia in elderly patients living with CKD has become a topical issue. Erythropoiesis-stimulating agents (ESAs) are the most important therapeutic agents in anemia management for patients with CKD and kidney failure, alongside iron supplementation, since their introduction and approval by the United States Federal Drug Administration (FDA) in 1989. However, observational and randomized-controlled trials evaluating anemia management with ESA amongst elderly patients demonstrated mixed results in relation to their appropriate correction of hemoglobin levels for both non-dialysis and dialysis-dependent populations [5–7]. ESA hyporesponsiveness is of functional importance in the context of an elderly patient living with CKD or kidney failure, as inadequate treatment of anemia increases hospitalization and transfusion needs, reduces physical function, exacerbates frailty status and ultimately worsens health-related quality-of-life outcomes [7–11]. Simply escalating ESA doses to achieve hemoglobin targets is likely to pose greater cardiovascular, thrombotic and mortality risks, particularly in an elderly population living with multi-morbidities [12]. Various factors contribute to ESA hyporesponsiveness in elderly CKD patients, in whom the natural physiological decline associated with aging is a significant factor in itself. Outside of aging and uremia-iron deficiency, hepcidin accumulation, inflammation and infection, nutrition deficiencies, cancer, cardiovascular disease (i.e., heart failure), protein energy wasting, vitamin D deficiency and CKD-mineral bone disease (CKD-MBD), haematological disease (i.e., red blood cell aplasia, myelodysplastic syndromes and marrow hyporesponsiveness) and other factors of practical concern, such as drug compliance, contribute to ESA hyporesponsiveness in elderly individuals living with CKD [7,9,10,13].

Numerous ways to address ESA hyporesponsiveness have been suggested for patients needing long-term ESA treatment. Iron and other forms of nutritional supplementation have been touted to be key as part of the management strategy. However, a consensus approach for iron supplementation is not available [7]. Concerns over iron overload resulting in further oxidative stress, increased risk of infection, atherosclerosis and tissue–iron deposition are valid, particularly in the elderly CKD population [14]. Data supporting adjuvant vitamin D, folic acid, vitamin C, copper, α-lipoic acid, L-carnitine, vitamin B6 and vitamin B12 supplementation to improve ESA hyporesponsiveness remain not fully validated at present [15–17]. For dialysis-dependent patients, elevating dialysis intensity and dialysate flow to improve hepcidin clearance and clearance of other middle-weight inflammatory molecules may reduce ESA hyporesponsiveness [18]. This is often either achieved by convective hemodialysis or high-volume online hemodiafiltration with high-flux polysulfone membranes [18]. Cardiovascular risks are increased with elevated dialysis intensity and a cautious approach should be employed for elderly patients with kidney failure [19]. Anti-hepcidin and other anti-inflammatory medications are physiologically viable therapeutics to reduce ESA hyporesponsiveness, but evidence on their efficacy is premature [20,21]. Given the controversies surrounding treatment options to tackle ESA hyporesponsiveness, it is reasonable to search for avenues that avoid reliance on long-term ESA treatment altogether, considering the frailty and multi-morbid status of many elderly patients with CKD and kidney failure.

3. Potential Benefits of HIF-PHI for the Elderly

Anemia treatment via the hypoxia-induced factor prolyl-hydroxylase (HIF-PH) pathway offers an alternative option to the traditional ESA strategy. HIF-PH inhibitors (HIF-PHI) provide a pharmacological leeway to bypass the challenges brought on by ESA hyporesponsiveness. ESAs stimulate erythropoiesis by specifically acting on the erythropoietin receptors that are expressed on red blood cell precursors, whilst erythropoiesis through the HIF-PH pathway is dependent on oxygen levels in all cells [22]. Hypoxic status within the cellular environment controls the level of erythropoiesis enhanced through the HIF pathway [22]. There have been suggestions that HIF-PHI can restore erythropoiesis in a more consistent rate over time compared to ESA [23]. Such benefits have not yet been

convincingly demonstrated in direct head-to-head trials comparing HIF-PHI and ESA use in both non-dialysis and dialysis-dependent groups. More concrete evidence is needed to justify whether the physiological benefits are significant with HIF-PHI use compared to ESAs in the CKD and kidney failure populations.

Nevertheless, the superior performance of HIF-PHIs to regulate iron homeostasis and to meet the demands of iron supplementation is an important discussion point in relation to increasing erythropoiesis activity, particularly for elderly CKD and kidney failure patients with greater risks of functional iron deficiency due to poor intestinal intake and utilization of iron stores. HIF-PH pathway stabilization moderates genes, which are involved in iron metabolism and directly modulates iron handling by upregulating transferrin, cellular membrane transferrin receptor 1, and ceruloplasmin in allowing greater transport of iron to tissues [24–28]. Intestinal absorption of iron is increased via upregulation of duodenal cytochrome B and divalent metal transporter 1, together with the downregulation of hepcidin [29]. HIF-PH-mediated regulation of hepcidin is dependent on erythropoietin-stimulated erythropoiesis, very likely mediated via erythroferrone secretion from the bone marrow [30,31]. This is the primary mechanism by which global hypoxia, or when HIF-PHIs are administered to stabilize the HIF-PH pathway, mediates decreases in hepcidin levels [24,30]. Therefore, the administration of HIF-PHI may avoid excess iron administration, given increased iron absorption, increased accessibility to iron stores, and increased efficiency in iron transport. This reduces the need for increased ESA dosing and the associated morbidity and mortality risks of doing so. Although such benefits are indicated from basic studies, direct head-to-head clinical trials have not yet validated this and further study is required.

There is early optimism that numerous clinical trial data have demonstrated a comparable efficacy and safety profile between HIF-PHIs and ESA for anemia treatment in CKD and kidney failure [32,33]. A pooled analysis of four phase 3 clinical trials comparing the efficacy and cardiovascular safety of Roxadustat with ESAs in dialysis-dependent patients suggested Roxadustat improved hemoglobin similarly to ESAs while demonstrating comparable cardiovascular and overall safety profiles in a wide spectrum of dialysis-dependent patients with anemia of CKD [34]. At this point, the conclusions from this analysis by Barratt and colleagues should not be fully interpreted as such for patients switching from ESA to Roxadustat [34]. In the included trials, patients allocated to Roxadustat were switched from ESA at the start of each study, whereas patients randomized to ESA remained on the same ESA dose, and the impact of a potential risk in switching to any new treatment versus remaining on a treatment with stabilized hemoglobin may confound the observed results [34]. Comparisons of treatment–effect estimates between Roxadustat and ESA could not be reliably concluded as of yet [34]. Clinical trials for both non-dialysis and dialysis-dependent populations also observed significant associations between HIF-PHI and improved micro-nutritional status and bone health [35,36]. However, perhaps it is the practical benefits of HIF-PHI compared to ESA that attracts supporters of HIF-PHI use in the context of an elderly patient with CKD or kidney failure. The ease and comfort of oral administration in comparison to the injectable route with ESA can be important for elderly individuals, who may have significant functional limitations and cognitive deficits.

4. Safety Concerns of HIF-PHI Use in the Elderly

There have been documented concerns over the use of HIF-PHIs, despite their potential advantages. A frequently discussed issue is the extent of major adverse cardiovascular events (MACE) and thrombotic risk with these novel medications. Elderly patients with moderate CKD or kidney failure are likely to have other co-morbidities, which may present as independent risk factors for MACE and thrombotic events, superadding to the risks brought by HIF-PHI use. Although pooled data of phase 3 clinical trials for Roxadustat suggest comparable cardiovascular safety profiles to ESA, results from phase 3 clinical trials for the other five HIF-PHIs in late-stage development programs worldwide (Vadadustat, Daprodustat, Molidustat, Enarodustat, Desidustat) have reported the onset of MACE and

thrombotic events in non-dialysis and dialysis-dependent cohorts [37–46]. Conclusions from combined pooled data analyses of the various HIF-PHIs may not be reliable, as different molecular compositions for each HIF-PHI leads to slight differences in their pharmacodynamics. Several of these HIF-PHIs have global development programs, with sufficient statistical power to examine their individual MACE and thrombotic risks versus ESA, and findings from pooled data analysis for each of these agents are anticipated [47]. Recommendations from the Asian Pacific Society of Nephrology on the appropriate use of HIF-PHIs advised clinicians to be aware of MACE and thrombotic risks when considering the prescription of HIF-PHI for patients [48]. For one, HIF-PHI prescription for patients with iron deficiency should be approached with greater caution due to increased thrombotic risks. Despite the potential ability of HIF-PHIs in increasing efficiency of iron utilization for erythropoiesis, there are simultaneous concerns that its actions deplete iron stores, leading to iron deficiency [49]. Corresponding increases in platelet and transferrin levels may induce greater risks of thrombosis. Sufficient iron supplementation should be provided prior to HIF-PHI prescription in these instances to avoid iron deficiency as much as possible.

Another concern relates to elevated transcription of the vascular endothelial growth factor (VEGF) gene. VEGF gene transcription activity is regulated by HIF binding to hypoxia response element at target gene regulatory regions (following dimerization between HIF-α and HIF-β in the cell nucleus) amongst other genes, with this being an essential step for EPO activation [50]. Increased VEGF gene transcription activity heightens the risk of neoplasia and proliferative diabetic retinopathy, as VEGF promotes angiogenesis, vascular permeability and tumor growth [50]. Given the increased risks of malignancy and diabetes mellitus in elderly individuals generally, this is of relevant concern as HIF-PHI may add toward these risks.

Pulmonary hypertension has been speculated as another potential safety profile concern in relation to effects of HIF-PHI on pulmonary vascular remodeling, although the intricacies of this mechanism require further validation [51]. It may be of genuine concern if such associations are significant, considering the cardiopulmonary fragility in many elderly patients living with CKD and multi-morbidity. Metabolic acidosis, hypertension, liver dysfunction, hyperkalemia, and greater incidence of upper-respiratory-tract infections were all reported previously in clinical trials, but more substantive conclusions are still needed to fully establish their links with HIF-PHI use [37,52–55].

Polypharmacy in the elderly CKD and kidney failure population may present as another problem. Drug–drug interactions between HIF-PHI and other medications may result in a myriad of novel adverse effects, much of which is not fully known yet currently. For elderly individuals without an established family support network at home, long-term compliance with HIF-PHI treatment could be an issue. From a public-health perspective, there remain uncertainties on the cost effectiveness of HIF-PHI compared to ESA for anemia management in CKD [56].

5. Future Directions to Consider HIF-PHI Use in the Elderly

We have highlighted both sides of the debate on the use of HIF-PHI in anemia management for elderly people living with CKD and kidney failure (Table 1).

Because of the aforementioned safety concerns, universal approval of HIF-PHI in clinical practice has not been achieved as of yet. Roxadustat, for example, has been approved for clinical use in some countries, such as China, Japan, and Brazil. However, one of the most high-profile incidents in disapproving its use is the recent United States FDA Cardiovascular and Renal Drugs Advisory Committee voting against support of Roxadustat use, with an overwhelming majority (13 to 1) in July 2021. With most HIF-PHIs having completed or currently in the latter stages of phase 3 clinical trials, time will tell if HIF-PHI is the superior solution for anemia management in CKD compared to ESA within the complex clinical environment. There has been a greater focus on evaluating the outcomes of HIF-PHI, specifically for the elderly population, recently. Pollock and colleagues presented data comparing outcomes between Roxadustat treatment versus placebo (non-dialysis-

dependent CKD G3b-5 patients) versus epoetin alfa (dialysis-dependent CKD patients) in patients aged ≥65 and <65 from pooled data amongst pivotal phase 3 studies, presented at the American Society of Nephrology Kidney Week, November 2021 [57]. Results suggest Roxadustat is well tolerated and effective, regardless of age, in patients with CKD and anemia. These preliminary findings provide the platform for further work to be performed and determine whether HIF-PHI could breakthrough as the optimal anemia treatment option in elderly patients over long-term ESA use.

Table 1. Potential benefits and remaining safety concerns of HIF-PHI prescription for elderly patients with CKD and multi-morbidities.

Potential Benefits	Remaining Safety Concerns
Suitable alternative option for elderly individuals who are experiencing difficulties in achieving satisfactory erythropoiesis due to ESA hyporesponsiveness	Documented risks of MACE and thrombotic (e.g., when prescribed for those with iron deficiency without sufficient iron supplementation) events following prescription of the various HIF-PHIs, despite early pooled data analysis suggesting Roxadustat's comparable cardiovascular safety to ESA. Pooled data analysis is required for other HIF-PHIs (Vadadustat, Daprodustat, Molidustat, Enarodustat and Desidustat) individually to provide greater clarity regarding its extent of cardiovascular safety. Elderly individuals with CKD or kidney failure are at greater risk due to likely increased multi-morbid status.
May potentially avoid requirements for excess iron and ESA administration in elderly individuals, due to the ability of HIF-PHI on increasing iron absorption, and improving functional iron utilization.	Increased VEGF gene transcription activity elevates the risk of neoplasia and proliferative diabetic retinopathy even further for elderly people with CKD.
Ease of orally administered treatment for elderly individuals instead of regular injections.	Increased risk of pulmonary hypertension, metabolic acidosis, arterial hypertension, liver dysfunction, hyperkalemia and upper respiratory tract infections.
	Polypharmacy drug-drug interactions, with concerns regarding compliance and drug cost-effectiveness particularly for the elderly patient population living with multi-morbidities in addition to CKD.

CKD: Chronic Kidney Disease; ESA: Erythropoietin-Stimulating Agents; HIF-PHI: Hypoxia-Induced Factor Prolyl-Hydroxylase Inhibitors; MACE: Major Adverse Cardiovascular Events; VEGF: Vascular Endothelial Growth Factor.

Author Contributions: Conceptualization, H.H.L.W.; resources, H.H.L.W.; writing—original draft preparation, H.H.L.W.; writing—review and editing, H.H.L.W., R.C. and R.J.W.; visualization, H.H.L.W. and R.C.; supervision, R.C. and R.J.W.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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