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Efficacy of novel drugs hypoxia inducible factor prolyl hydroxylase inhibitor in therapy of posttransplant anemia. A review

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Abstract

Aim of the study

The aim of our study was to evaluate the efficacy of novel drugs from the group of hypoxia-inducible factor prolyl hydroxylase inhibitors, using roxadustat as an example, in the treatment of anemia occurring in kidney recipients. In the study, we included data from recent original papers that examined the efficacy of these drugs in the treatment of post-transplant anemia. We assumed an absolute increase in hemoglobin concentration as a factor expressing the effectiveness of the therapy.

Materials and Methods

This review was conducted using publications available in databases such as PubMed, Google Scholar, Scopus and ScienceDirect. These databases were searched using keywords such as hypoxia-inducible factor prolyl hydroxylase inhibitor, roxadustat, anemia, kidney transplant, posttransplant anemia, chronic kidney disease. The time range of published articles was set to 2017-2024, and some older publications were included if they were considered to bring valuable background information necessary for understanding the issue. Articles written in English and Polish were sought; however, all publications used in this review were in English.

The main reason of bias of this study may be the limited group of participants that may not be sufficiently representative, the lack of randomization in some studies, and the limited number of publications in the problem area.

Keywords: Prolyl hydroxylase inhibitor, Hypoxia inducible factor, Anemia, Kidney transplant, Chronic kidney disease

Introduction

Anemia in the course of chronic kidney disease (CKD), defined as a decrease in hemoglobin concentration according to WHO criteria (Hb) <12mg/dl in women and <13mg/dl in men [1], is a common symptom accompanying the disease.

Although the issue of anemia in the course of baseline CKD seems to be an apparent matter, post-transplant anemia (PTA) remains a relatively rarely addressed issue. Exacerbation

of anemia can be expected in the postoperative period. This is primarily attributed to the initial low Hb concentration, which is compounded by the loss of whole blood occurring in the perioperative period, as well as depletion of iron stores resulting from underlying disease in the preoperative period. In addition, it would seem that the graft should also undertake its function in terms of adequate EPO synthesis, however, this is not always the case [2].

Basically, according to Gafter - Gvili et al. (2017), we can divide PTA into early PTA, that is up to 6 months after surgery, and late PTA, which is more than 6 months after surgery [3]. The prevalence of early PTA oscillates around 50% while late PTA is between 23-35%. Overall, the problem of anemia in general may affect 20-51% of patients after allotransplant [4].

The distinction between early and late anemia is important insofar as it is important to thoroughly understand the underlying causes, which will translate into actual implications in the form of adequate clinical decisions. As it was mentioned, in the case of early PTA, the main source of the problem is related to the surgical procedure and acute blood loss, earlier depletion of iron reserves, and inadequate nutrition of the patient, as well as toxic causes resulting from medications such as angiotensin-converting enzyme inhibitors (ACEIs), and postoperative phlebotomy [4,5,6]. In contrast, failure or deterioration of graft function, with secondary renal failure developing, play an important role in the development of late PTA, although other factors such as pharmacological agents such as ACEIs, antimicrobial drugs as trimethoprim-sulfamethoxazole, antiviral drugs especially gancyclovir, immunosuppressive treatment [8], or disease as the initial cause of nephropathy remain important [9]. In addition, factors such as infections or vitamin D deficiency may also play a role [10]. PTA is associated with increased morbidity, mortality and decreased quality of life [11] and therefore should be treated.

Drugs commonly used to treat anemia in CKD are erythropoiesis stimulating agents (ESA), the use of which has the beneficial effect of reducing the need for blood product transfusions [12]. However, some may develop ESA resistance, with serious complications in the form of increased mortality [13]. However, there is a lack of clear treatment for PTA [14]. For this reason, researchers and clinicians are looking for new therapeutic solutions with satisfactory efficacy and safety profile. A new orally administered drug with registrations in China, Chile, the European Union, Japan and South Korea, roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), holds some promise [15]. The mechanism of action of HIF-PHI essentially involves stimulation of endogenous EPO secretion in the kidney [16]. The pathway for the synthesis of this hormone is regulated in the oxygen dependent manner in the kidney [17,18] and mediated by activity through hypoxia inducible factor (HIF). HIF is a

protein heterodimer composed of 2 subunits, HIF-α and HIF-β. While HIF-β is subject to permanent expression, the expression of HIF-α is oxygen dependent. Under normoxia, HIF-α is synthesized and hydroxylated continuously with the participation of prolyl hydroxylase (PHD), which then promotes the fusion of the product with von Hippel-Lindau protein (VHL) leading to ubiquitination and subsequent proteosomal degradation. In contrast, under hypoxia, reduced oxygen availability leads, as a substrate deficiency, to subsequent inhibition of PHD resulting in increased amounts of active HIF-α, promoting activation of the gene for EPO. Subsequently, EPO binds to the EPO receptor (EPOR) of marrow red cell progenitor cells leading to their growth [20].

Literature review results

In a single-center randomized study conducted by Kong et al. [21] a 150-person group of renal transplant patients who had not previously received ESA for at least 4 weeks prior to randomization, aged 15-75 years, with CKD, more than 6 months after kidney transplant, with stable graft function for at least 3 months, Hb levels of 9-11 g/dl were divided during the 12-week randomization period into a 100-person trial group receiving HIF-PHI along with iron supplementation, and a 50-person control group receiving iron supplementation alone. During randomization, of the initial group of n=150, 9 participants did not receive the trial regimen, and 13 did not report for follow up, leaving the study group n=90, and the control group n=38. Subsequently, after the randomization period, HIF-PHI was administered to all study participants for an additional 12 weeks at an initial dose of 100mg and then modified at a 4-week interval to maintain Hb levels >12g/dl, a follow up every 4 weeks was established. In the baseline measurement of Hb concentration in the study group n=90, the mean Hb concentration was 10.43 g/dL (SD 0.59) in the control group n=38 10.56 g/dL (SD 0.44) p-value 0.22, in the study group Hb concentration <10 g/dL was found in 22 patients, control group 6 p-value 0.28, while Hb concentration ≥10 g/dL was found in 68 participants of the study group and 32 participants of the control group. Changes in mean Hb concentration in the study and control groups measured every 4 weeks of the randomization period are shown in the figure (Figure 1).

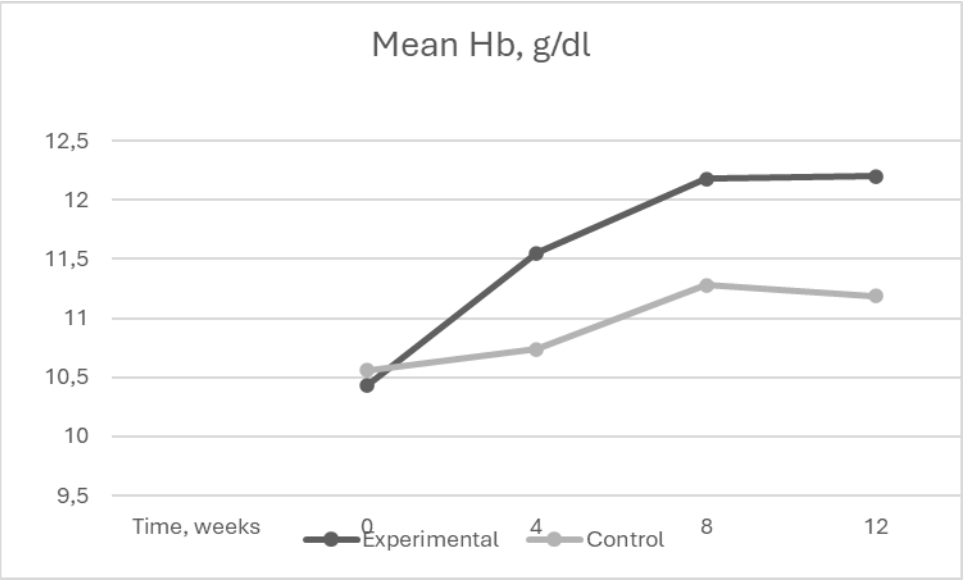

Figure 1. Changes in mean Hb levels in patients of the experimental group receiving HIF-PHI with iron supplementation and the control group supplementing with iron alone. Based on Weiwei Kong, Xiaoying Wu, Zhuowei Shen, Meifang Wang, Xinyu Liu, Xiaoli Lin, Yingyin Qiu, Hong Jiang, Jianghua Chen, Yan Lou, Hongfeng Huang, The Efficacy and Safety of Roxadustat for the Treatment of Posttransplantation Anemia: A Randomized Study, Kidney International Reports, Volume 9, Issue 6, 2024, Pages 1705-1717, ISSN 2468-0249, https://doi.org/10.1016/j.ekir.2024.04.021.

In the follow-up measurement after the 12-week randomization period, the mean Hb concentration in the study group was 12.2 g/dl (SD 1.25) the absolute increase compared to the baseline measurement was 1.76 (SD 1.36) showing statistical significance, p-value <0.01, while in the control group it was 11.19 g/dl (SD 0.94) representing an absolute increase of 0.69 (SD 0.97), but not representing statistical significance, p-value=0.87 [21].

In a study conducted by Katsuyuki et al [22] on a group of 31 renal transplant patients regardless of graft function with baseline Hb levels <11g/dl, HIF-PHI was administered at a dose of 20-100 mg according to the manufacturer's recommendations. Patients with Hb levels <10g/dl were started on ESA, while with iron levels <50 µg/dl and ferritin <100 ng/ml, iron supplementation was included. In addition, 50mg of sodium ferric citrate was supplemented once a day to maintain iron concentrations. The dose of HIF-PHI was adjusted individually to maintain an Hb concentration of 11-13 g/dl. Out of a group of 31 patients, HIF-PHI treatment was continued in n=25, not continued in n=6. The mean time from the transplant for the whole population was 8.2 years, in the group where HIF-PHI treatment was continued 7.8 years (SD 9.7) with 7 having early PTA, in the group where HIF-PHI was not continued 10 years (SD 10.9) with 1 having

early PTA. Mean values of Hb concentration at baseline in all patients was 9.8 g/dl (SD 0.86), concentration ≤9 g/dl in n=6, >9g/dl in n=25, in the study group mean Hb concentration was 9.8 g/dl (SD 0.78), concentration ≤9 g/dl was found in n=5, >9g/dl in n=20, while in the control group the mean concentration was 9.7 g/dl (SD 1.2), concentration ≤9 g/dl was found in n=2, and >9g/dl in n=4, however, no statistical significance was obtained for these results. A follow up every 4 weeks was established. During the study, 1 participant was excluded from the group taking HIF-PHI between weeks 4 and 8, while 5 participants were excluded from the group not receiving HIF-PHI between weeks 0 and 4.

The mean Hb value in the HIF-PHI continuation group was calculated based on the mean Hb measurements on the day the HIF-PHI supply was started, and at 4, 8, 12, 16, 20 weeks respectively. The results are summarized in the table (Table 1.) [22].

	Hb Mean (SD), g/dl	p value
Time, weeks		
0	9,8(0,86)	ns
4	10,6 (0,67)	0,0025
8	11,3 (1,15)	<0,001
12	12,1 (1,44)	<0,001
16	12,3 (1,47)	<0,001
20	12,4 (1,09)	<0,001

Table 1. Changes in mean Hb levels in patients receiving HIF-PHI with iron supplementation. Based on Katsuyuki Miki, Yuki Nakamura, Takayoshi Yokoyama, Manabu Kamiyama, Yasuo Ishii, Therapeutic Effect of Roxadustat on Patients With Posttransplant Anemia, Transplantation Proceedings, Volume 54, Issue 3, 2022, Pages 671-677, ISSN 0041-1345, https://doi.org/10.1016/j.transproceed.2022.02.004.

In a case series described by Naganuma et al [23], the efficacy of using HIF-PHI was evaluated in a group of 5 patients after kidney transplantation and prior treatment with ESA for 3 months, after which time treatment was changed to HIF-PHI. The dose of HIF-PHI was 100 mg administered 3 times a week on non-consecutive days. In Patient 1, the dose of HIF-PHI was reduced after 1 and 3 months. In Patient 2, the dose was reduced after month 6. In Patient

3, the initial dose was maintained, In Patient 4, the dose was reduced after month 3. In Patient 5, iron was supplemented concurrently, due to a significant increase in Hb HIF-PHI was discontinued after 1 month and restarted after 6 months. Hb concentration was measured in all subjects at the time of HIF-PHI inclusion, and sequentially after 1, 3, 6 and 9 months, Hb values at follow-up measurements are summarized in the table below (Table 2.) [23].

	Patient	1	2	3	4	5	
Time, months							
0		12,9	10,7	8,7	10,3	12,3	Hb, g/dl
1		15,1	10,9	9,1	12,2	15,9	
3		15,5	11,9	11,3	13,5	10,6	
6		11,8	14,3	11,6	12,8	10,7	
9		12,5	14,2	10,8	13	14,4	

Table 2. Changes in mean Hb concetration in 5 pateints receiving 100mg of HIF-PHI. Based on Toshihide Naganuma, Tomoaki Iwai, Yoshiaki Takemoto, Junji Uchida, Experience With the Use of a Novel Agent, Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, for Posttransplant Anemia in Renal Transplant Recipients: A Case Report, Transplantation Proceedings, Volume 54, Issue 2, 2022, Pages 544-548, ISSN 0041-1345, https://doi.org/10.1016/j.transproceed.2021.10.022.

Ishiyama et al [24], in a retrospective comparative analysis, evaluates the efficacy of HIF-PHI (roxadustat or daprodustat) in the treatment of CKD grade 3-5 anemia among dialysis non-dependent kidney transplant reciepients and non-recipients. The group analyzed, n=82, consisted of n=43 kidney transplant recipients (KTRs), and n=39 non-KTRs (n-KTRs). Data compared were values measured 3 months before HIF-PHI inclusion, and 6 months after. Follow up was set at 6-8 weeks, depending on the patient's condition. The evaluation population was included in the study regardless of prior ESA use. The dose of HIF-PHI was adjusted to achieve an Hb concentration of 11-13 g/dl. The most frequent primary cause of CKD in the n-KTR group was chronic glomerulonephritis, while diabetic nephropathy in the KTR population.

Of the HIF-PHI group, roxadustat was used predominantly in the KTR group (88.4%), while daprodustat was used in the n-KTR group 94.9%). The median Hb concentration at baseline in the overall population was 10.1 g/dl (IQR 9.4-10.6), in the KTR group 10.3 g/dl (IQR 9.7-10.7), and in the n-KTR group 9.9 g/dl (IQR 9.3-10.3). In the n-KTR group, the median time since transplantation was 78.6 months (IQR 3.8-178.1). A significant increase in Hb concentration (p-value for the whole period <0.001) measured at baseline and sequentially after 1,3,6 months was observed in both groups, the results are summarized in the figure below (Figure 2.).

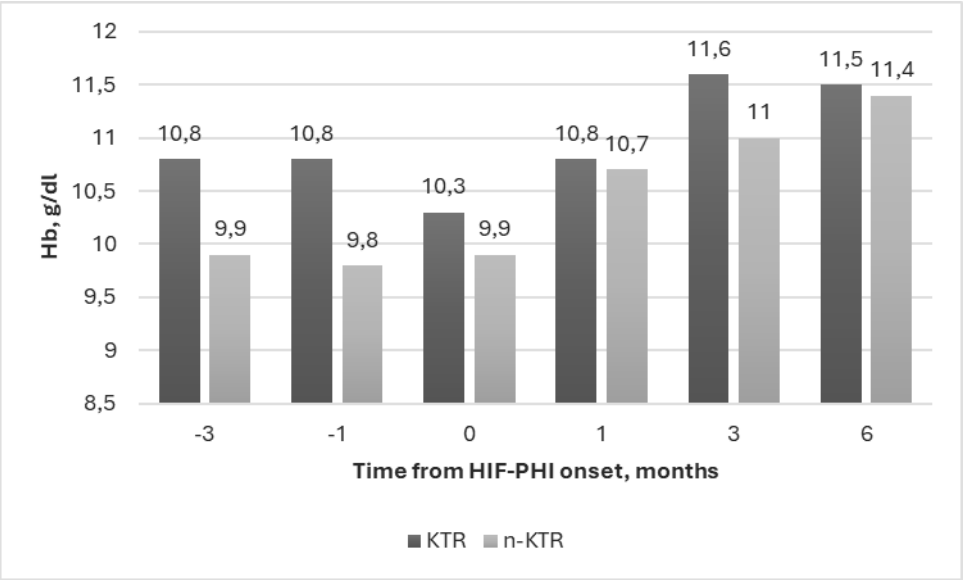

Figure 2. Changes in median Hb concetration in patients receiving HIF-PHI from the KTR and n-KTR group. Based on Yudai Ishiyama, Takafumi Yagisawa, Makiko Ichioka, Ayumu Hagiwara, Tomokazu Shimizu, Kazuya Omoto, Taiji Nozaki, Masashi Inui, Jun Ino, Kazuhiro Takeda, Hiroshi Toma, Shoichi Iida, Comparative Analysis of Real-World Efficacy and Safety of Hypoxia-Inducible Factor Prolyl-Hydroxylase Inhibitors in Kidney Transplant Recipients Versus Nontransplant Individuals: A Single-Center Study, Transplantation Proceedings, 2024, ISSN 0041-1345, https://doi.org/10.1016/j.transproceed.2024.05.029.

Conclusions

The use of HIF-PHI in treatment appears to be a more effective treatment for PTA compared to iron supplementation alone. Drug dosage should be adjusted individually to maintain stable Hb levels, and the patient's laboratory parameters such as Hb iron levels should be monitored. Iron supplementation also seems to be reasoned. In addition, this type of treatment may be applicable to the treatment of both early and late PTA and has shown similar efficacy in the treatment of anemia in the course of CKD. However, during our study, we

encountered limited data from original studies. The oral administration may improve patient cooperation and better tolerability of treatment, however, due to dosing on non-consecutive days, clinician control seems warranted. Further multicenter randomized trials are needed to verify the benefits of using HIF-PHI in clinical practice, the efficacy of this type of treatment, and its safety profile.

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