A Phase 3 Study of Enarodustat (JTZ-951) in Japanese Hemodialysis Patients for Treatment of Anemia in Chronic Kidney Disease: SYMPHONY HD Study

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\textbf{Keywords}
Enarodustat · Anemia in chronic kidney disease · Hypoxia-inducible factor-prolyl hydroxylase inhibitor · Iron utilization · Phase 3 study

\textbf{Abstract}

\textbf{Introduction:} Enarodustat (JTZ-951) is a new oral hypoxia-inducible factor-prolyl hydroxylase inhibitor for the treatment of anemia in chronic kidney disease (CKD). We conducted a phase 3 study to compare the efficacy and safety of enarodustat with darbepoetin alfa (DA) in Japanese anemic patients with CKD receiving maintenance hemodialysis. 

\textbf{Methods:} Subjects receiving maintenance hemodialysis were randomly assigned at a 1:1 ratio to receive oral enarodustat once daily or intravenous DA every week for 24 weeks with dose adjustment every 4 weeks to maintain hemoglobin (Hb) within a target range (≥10.0 to <12.0 g/dL). The primary efficacy endpoint was difference in mean Hb level between arms during the evaluation period defined as weeks 20–24 (noninferiority margin: –1.0 g/dL). The primary efficacy endpoint was difference in mean Hb level between arms during the evaluation period defined as weeks 20–24 (noninferiority margin: –1.0 g/dL). Intravenous iron preparations were prohibited during the screening period and during weeks 0–4. 

\textbf{Results:} The mean Hb level of each arm during the evaluation period was 10.73 g/dL (95% confidence interval [CI]: 10.56, 10.91) in the enarodustat arm and 10.85 g/dL (95% CI: 10.72, 10.98) in the DA arm. The difference in the mean Hb level between arms was –0.12 g/dL (95% CI: –0.33, 0.10), confirming the noninferiority of enarodustat to DA. The mean Hb level of each arm was maintained within the target range during the treatment period. Increased total iron-binding capacity and serum iron and decreased hepcidin were observed through week 4 in the enarodustat arm albeit after switching from erythropoiesis-stimulating agents. No apparent safety concerns of enarodustat were observed compared with DA. 

\textbf{Discussion/Conclusion:} Enarodustat was noninferior to DA for the treatment of anemia in CKD patients receiving maintenance hemodialysis and was generally well tolerated over 24 weeks.

\textbf{Introduction}

Anemia is a common complication of chronic kidney disease (CKD). The global all-age prevalence of CKD and the global all-age mortality rate from CKD have increased from 1990 to 2017, and 1.4 million deaths from cardiovascular disease were attributable to impaired renal func-
tion in 2017 [1]. Anemia in CKD is associated with increased cardiovascular disease, mortality, hospitalization, and reduced quality of life [2–9] and therefore is an important therapeutic target for patients with CKD. To date, erythropoiesis-stimulating agents (ESAs) have been widely used for the treatment of anemia in CKD. However, studies have suggested that the administration of higher doses of ESA to improve hemoglobin (Hb) levels increased the risk of mortality and cardiovascular events. Indeed, McCullough et al. [10] reported the risk of cardiovascular events with high doses of ESA. Koulouridis et al. [11] conducted a meta-regression analysis, which revealed that high doses of ESA might be associated with an increase in all-cause mortality and cardiovascular complications. Therefore, an alternative therapy to ESA is desired to reduce these risks.

Enarodustat (JTZ-951), a hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor, is an orally available compound [12–18]. Under hypoxic conditions, activity of the prolyl hydroxylase domain, which induces HIF degradation through hydroxylation of proline in HIF, is suppressed, thereby stabilizing HIF and promoting adaptive responses to hypoxia including erythropoiesis [19–21]. On the basis of these findings, enarodustat is being developed for the treatment of anemia in CKD. Phase 2b studies demonstrated that enarodustat corrected and maintained Hb levels within a target range in accordance with the Guidelines for Renal Anemia in CKD of the Japanese Society for Dialysis Therapy [22] for 30 weeks without apparent safety concerns [17, 18]. Enarodustat has been approved in September 2020 in Japan for the treatment of anemia associated with CKD and is currently being developed in South Korea [23]. Here, we report the results of a phase 3 study (SYMPHONY HD) to confirm the efficacy and safety of enarodustat compared with an active comparator, darbepoetin alfa (DA), for 24 weeks in Japanese anemic patients with CKD receiving maintenance hemodialysis.

**Materials and Methods**

**Study Design**

This active-controlled, randomized, double-blind, and parallel-arm phase 3 study consisted of a 4-week screening (Scr) period, 24-week treatment period, and 2-week follow-up period to confirm the efficacy (noninferiority to DA) and safety of enarodustat in Japanese anemic patients with CKD receiving maintenance hemodialysis. After informed consent acquisition and Scr procedures, the Interactive Web Response System was contacted by the site and randomly assigned the eligible subject with permuted block at a 1:1 ratio to receive once-daily oral enarodustat tablet(s) and weekly placebo injection(s) or weekly DA injection(s) and once-daily oral placebo tablet(s) for 24 weeks. DA and its placebo were supplied by Kyowa Kirin Co., Ltd. Initial doses were 4 mg/day in the enarodustat arm and 10–40 μg/week determined by the prior regimen of ESA in the DA arm. Dose adjustments were performed every 4 weeks during the treatment period in accordance with Hb levels. The details of initial dose of DA and dose adjustment steps are provided in online suppl. Tables 1 and 2 (see www.karger.com/doi/10.1159/000517053 for all online suppl. material). This study was registered with the Japan Pharmaceutical International Center Clinical Trials Information registry (JapicCTI-183938) in April 2018 and was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, the study protocol, and the Guidelines for Good Clinical Practice of Japanese Ministerial Ordinance. The study was approved by the institutional review board of each study center.

**Patients and Treatment**

Eligible patients were Japanese patients aged ≥20 years who received hemodialysis 3 times a week including hemodiafiltration for at least 12 weeks before Scr visit 1, had transferrin saturation (TSAT) >20% or ferritin >75 ng/mL at Scr visit 1, received recombinant human erythropoietin (epoetin alfa, beta, or kappa) in the range of 750–9,000 IU/week or DA in the range of 10–40 μg/week, and had Hb levels 9.5–12.0 g/dL during the Scr period (i.e., Scr visit 1 and Scr visit 2) with an absolute difference of ≤1.0 g/dL between Scr visits 1 and 2. Patients who had poorly controlled hypertension, severe hepatobiliary disease, congestive heart failure (New York Heart Association [NYHA] class III or more severe), or severe hyperparathyroidism (i.e., intact-parathyroid hormone ≥500 pg/mL at Scr visit 1), and were suspected to have anemia caused by noninfectious inflammatory disease were excluded. Further details of eligibility criteria are provided in online suppl. Table 3.

Intravenous iron preparations were prohibited between Scr visit 1 and week 4. Oral iron therapy initiated before Scr visit 1 could be continued without any change in the dose regimen between Scr visit 1 and week 4. Intravenous iron preparation or oral iron therapy including change in the dose regimen was allowed in principle between week 4 and week 24 (or at discontinuation) if ferritin was ≤100 ng/mL or TSAT was ≤20%. Note that the start or dose increase of intravenous and oral iron at the same time was restricted.

**Assessments**

Subjects were assessed every 2 or 4 weeks during the study. The primary efficacy endpoint was difference in mean Hb level between arms during the evaluation period (at 3 time points: week 20, week 22, and end of treatment [EOT, week 24 or at discontinuation corresponding to week 24]). Secondary efficacy endpoints included achievement of an Hb level within the range of week 0 ≥1.0 g/dL at week 4, achievement of an Hb level within a target range defined as ≥10.0 and <12.0 g/dL during the EOT period (at the EOT, a previous time point, and the second to last time point before EOT), and the mean prescribed dose. In addition, red blood cell (RBC)-related parameters and iron-related parameters were assessed as other efficacy endpoints. Safety assessments included adverse events (AEs) occurring after the start of treatment, laboratory tests, vital signs, standard 12-lead electrocardiogram, chest X-ray, and fundoscopy. Other assessments included vascular endothelial growth factor (VEGF).
Statistical Analysis

The per protocol set (PPS) included subjects who met the protocol requirements, had a treatment compliance rate of ≥75% for the study treatment, and were assessed for Hb level at week 20, week 22, and week 24 or at discontinuation corresponding to week 24 (i.e., evaluation period). The full analysis set (FAS) included subjects who received study treatment and were assessed for efficacy at least twice from week 4 onwards. The safety analysis population (SAF) included subjects who received study treatment and were assessed for safety at least once.

The analysis of primary efficacy endpoint was performed using the PPS. Before the verification of noninferiority, in accordance with the closed testing procedure, it was confirmed that the 95% confidence interval (CI) of the mean Hb level in the enarodustat arm during the evaluation period was within the target range because maintenance of the Hb level within the target range is important for the treatment of anemia in CKD. The point estimate of treatment difference (enarodustat arm − DA arm) and its 95% CI for Hb level during the evaluation period were determined by analysis of covariance with the treatment arm as the factor and baseline value of Hb level (the mean Hb levels at Scr visit 1, Scr visit 2, and week 0) as the covariate (significance level: 5%, 2-sided). When the lower limit of the 95% CI was above −1.0 g/dL, noninferiority to DA was demonstrated. Sensitivity analysis of the primary efficacy endpoint was performed using the FAS. In the sensitivity analysis, the EOT period was used instead of the evaluation period.

A sample size of 66 subjects per arm was required to demonstrate that enarodustat was as effective as DA, assuming a noninferiority limit of −1.0 g/dL, a 5% significance level with 90% power, and a difference between arms of −0.6 ± 0.7 g/dL. Considering 15% dropouts, the target number of subjects was set at 78 per arm. The simulation data generated from 10,000 runs with 66 subjects per arm indicated 100% power to demonstrate the 95% CI of the mean Hb level during the evaluation period was within the target range.

The analyses of secondary efficacy endpoints and other efficacy endpoints were performed using the FAS. Post hoc analyses of
changes in RBC-related parameters and iron-related parameters at week 24 and week 4 were performed, respectively. Intergroup comparisons between arms were carried out using the t test for RBC-related parameters and Wilcoxon rank sum test for iron-related parameters (significance level: 5%, 2-sided).

Safety assessments were performed using the SAF. AEs occurring from the start of study drug administration to the follow-up visit were summarized. All AEs were coded using the Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J), version 20.0. AEs of interest ("retinal disorders," "malignant or unspecified tumors," "hypertension," and "embolic and thrombotic events") were categorized with reference to the Standardized MedDRA Queries. All analyses were performed using SAS version 9.2 or higher (SAS Institute, Cary, NC, USA).

Results

Subject Characteristics

In total, 173 subjects were randomized into the study and administered the study drug (87 subjects in the enarodustat arm and 86 subjects in the DA arm). All subjects were included in the SAF. Overall, 172 subjects were included in the FAS because 1 subject in the enarodustat arm had <2 efficacy measurements. In the enarodustat arm, 79 subjects completed the treatment period, and 78 subjects were included in the PPS because 1 subject experienced protocol deviation. In the DA arm, 80 subjects completed the treatment period, and all were included in the PPS. Further details of the study flow of the participants are shown in online suppl. Figure 1.

Subject baseline characteristics and efficacy parameters at week 0 (FAS) are shown in Table 1. Overall, negligible differences in baseline characteristics between arms were observed.

Hemoglobin Levels

The mean Hb level during the evaluation period was 10.73 g/dL (95% CI: 10.56, 10.91) in the enarodustat arm, which was within the target range, confirming the efficacy of enarodustat. In the DA arm, the mean Hb level was 10.85 g/dL (95% CI: 10.72, 10.98). The difference in mean Hb level between arms during the evaluation period was −0.12 g/dL (95% CI: −0.33, 0.10). The lower limit of the 95% CI was above the prespecified noninferiority margin of −1.0 g/dL, indicating enarodustat was as effective as DA. Sensitivity analysis showed similar results (difference: −0.14 g/dL, 95% CI: −0.36, 0.08).

Change in Hb level from week 0 to week 4 was 0.21 ± 0.81 g/dL in the enarodustat arm and 0.21 ± 0.56 g/dL in the DA arm. The proportion of subjects with an Hb level within the range of week 0 ± 1.0 g/dL at week 4 was 80.2% (95% CI: 70.2, 88.0) in the enarodustat arm and 89.5% (95% CI: 81.1, 95.1) in the DA arm. Online suppl. Figure 2 shows a scatter plot of the relationship between change in Hb level and prior ESA dose.

The time course of mean Hb levels in each arm and mean dose of enarodustat and DA are shown in Figure 1. During the treatment period, mean Hb levels in both arms were appropriately maintained within the target range. The proportion that achieved an Hb level within the target range during the EOT period in both arms was high. The mean prescribed dose of enarodustat during the treatment period was 3.95 mg/day.
Fig. 2. Changes in iron-related parameters (FAS). Each point indicates the median value in each arm (closed circles: enarodustat arm; open circles: DA arm), and bars indicate the interquartile range. Intergroup comparisons of changes at week 4 between arms were performed for the post hoc analysis using the Wilcoxon rank sum test (significance level: 5%, 2-sided). *p < 0.05; **p < 0.0001. DA, darbepoetin alfa; TIBC, total iron-binding capacity; TSAT, transferrin saturation; F-up, follow-up; FAS, full analysis set.
RBC-Related Parameters
Mean values of RBC-related parameters at week 0, week 4, and week 24 are listed in online suppl. Table 4. The time course of changes in RBC-related parameters from week 0 is summarized in online suppl. Figure 3. Changes in hematocrit and RBC showed similar trends to the Hb level in each arm. Changes in mean corpuscular volume, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) in the enarodustat arm were numerically higher than those in the DA arm. Furthermore, the changes in MCH and MCHC at week 24 from week 0 in the enarodustat arm were significantly different from those in the DA arm (MCH: \( p = 0.0116 \), MCHC: \( p = 0.0345 \)).

Iron-Related Parameters
Median values of iron-related parameters at week 0, week 4, and week 24 are listed in online suppl. Table 5. The time course of changes in iron-related parameters from week 0 is shown in Figure 2. The median values of changes in hepcidin and ferritin were decreased and those of total iron-binding capacity (TIBC) and serum iron were increased in the enarodustat arm during weeks 0–4. A post hoc analysis to compare changes in the iron-related parameters between arms at week 4 showed changes in hepcidin, serum iron, TIBC, and TSAT in the enarodustat arm were significantly different from those in the DA arm (hepcidin: \( p = 0.0016 \), serum iron: \( p < 0.0001 \), TIBC: \( p < 0.0001 \), and TSAT: \( p = 0.0273 \)). The mean dose of in-
travenous iron between week 4 and EOT was 74.0 ± 147.3 mg in the enarodustat arm and 70.2 ± 150.2 mg in the DA arm. The number of patients who used oral iron before and during the treatment period was 40/86 (46.5%) in the enarodustat arm and 33/86 (38.4%) in the DA arm.

Safety

In this study, 76/87 subjects (87.4%) in the enarodustat arm and 72/86 subjects (83.7%) in the DA arm experienced at least 1 AE. No death occurred in this study. Serious AEs occurred in 13 subjects (14.9%) in the enarodustat arm and 12 subjects (14.0%) in the DA arm, none of which were judged to be related to the study drug. Four subjects (4.6%) in the enarodustat arm and 3 subjects (3.5%) in the DA arm discontinued the study due to AE. AEs that occurred in ≥5% of subjects in any arm are listed in Table 2. The most frequent AE was viral upper respiratory tract infection in each arm. Vomiting and gastroenteritis in the enarodustat arm were observed at least twice as often as in the DA arm, but were considered unrelated to the study drug in both arms. The AEs of interest (“retinal disorders,” “malignant or unspecified tumors,” “hypertension,” and “embolic and thrombotic events”) are listed in Table 2. No obvious changes were demonstrated by laboratory tests including VEGF, vital signs, standard 12-lead electrocardiogram, chest X-ray, and fundoscopy.

Discussion

SYMPHONY HD, the first study to evaluate the efficacy and safety of enarodustat compared with an active comparator in hemodialysis patients, demonstrated that enarodustat was as effective as DA for the maintenance of Hb level within the target range. The change in Hb level at week 4 from week 0 in the enarodustat arm was comparable to that in the DA arm. Online suppl. Figure 2 shows that the initial dose of enarodustat at 4 mg/day conserved Hb levels regardless of prior ESA dose. Throughout the treatment period, mean Hb levels were successfully maintained within the target range by orally once-daily administration of enarodustat, which was comparable to intravenous DA. The mean prescribed dose remained stable throughout the treatment period in the enarodustat arm. The study findings propose that enarodustat, administered orally with the simple dosage regimen, would be convenient to be prescribed because of the simple dose determination.

HIF is a master regulator of oxygen homeostasis including erythropoiesis, angiogenesis, energy metabolism, and iron metabolism [24]. In this context, the stabilization of HIF has a potential to not only increase Hb levels but also improve iron utilization. It was reported that erythropoiesis promoted by the stabilization of HIF increased the production of erythroferrone, thereby contributing to the suppression of hepcidin, a hormone secreted by hepatocytes, which regulates iron homeostasis by controlling the expression of ferroportin [25–28]. Indeed, we have already reported on the data suggesting the effect of enarodustat on improvement of the iron utilization [18]. In this study, hepcidin in the enarodustat arm was significantly decreased at week 4 compared with that in the DA arm. Significant increases of TIBC and serum iron at week 4 and week 24 from week 0 were also observed, which support the effect on iron utilization via HIF stabilization. Although it would be worthwhile to translate iron utilization effects based on iron-related parameters to clinical outputs, the mean dose of intravenous iron during the treatment period in the enarodustat arm was similar to that in the DA arm. Furthermore, the median value of ferritin at week 24 in the enarodustat arm was comparable to that in the DA arm. There were no apparent differences in the use of intravenous iron preparations and the change in ferritin, which raises a question of how iron in the body is utilized efficiently by enarodustat. We hypothesize that the erythropoiesis and iron utilization effects caused by enarodustat allow RBC to accommodate more iron. Indeed, RBC-related parameters were numerically higher in the enarodustat arm, and a post hoc intergroup comparison demonstrated that the change in MCH and MCHC at week 24 from week 0 in the enarodustat arm was significantly higher than that in the DA arm. Taken together, these data strongly suggest that enarodustat might be a new option for the treatment of anemia in CKD.

The expression of hepcidin is also induced by inflammation via IL-6 signaling and activin B signaling [25, 29, 30]. Inflammation is considered a factor of ESA hyporesponsiveness in conjunction with elevated C-reactive protein (CRP) [31]. The Hb level and dose of enarodustat or DA during the evaluation period stratified by CRP (high group: CRP ≥0.3 mg/dL; low group: CRP <0.3 mg/dL) in each arm were comparable although the number of subjects in the high CRP group was approximately only 15%.

The safety results demonstrated that enarodustat was generally well tolerated compared with DA and consistent with our phase 2b trial [18]. "Retinal disorders,"
“malignant or unspecified tumors,” “hypertension,” and “embolic and thrombotic events” were selected and summarized as AEs of interest based on potential risks derived from the administration of enarodustat and ESAs. A previous study reported that stabilization of HIF induced the expression of many genes involved in angiogenesis including VEGF [32], which prompted us to focus on retinal disorders and malignant or unspecified tumors. “Retinal disorders” were observed more often in the enarodustat arm (6.9% [6/87]) than in the DA arm (3.5% [3/86]), while the occurrence of “malignant or unspecified tumors” in the enarodustat arm was similar to that in the DA arm (2.3% [2/86] in the enarodustat arm and 1.2% [1/87] in the DA arm). Events observed in >1 subject among this category was retinal hemorrhage and its occurrence was similar in each arm (3.4% [3/87] in the enarodustat arm and 3.5% [3/86] in the DA arm). Of note, our preclinical study showed a high dose of enarodustat (>10-fold higher than that required for endogenous erythropoiesis) induced VEGF, but this increased level was unlikely to affect tumor growth. Furthermore, retinal VEGF mRNA levels were unchanged even at a high enarodustat dose [13]. However, further investigation with a larger population should be conducted to clarify the risk of retinal disorders. Hypertension and embolic and thrombotic events were categorized as side effects of ESAs according to the Japanese guidelines for renal anemia in CKD although it is unclear whether these events were caused directly by the administration of ESAs [22]. Hypertension was reported at a low frequency (<5%) in the enarodustat arm, and no apparent difference in frequency was noted between the arms. Moreover, the occurrence of embolic and thrombotic events in the enarodustat arm was comparable to that in the DA arm.

The limitations of this study are small sample size and short duration. Larger and longer-term studies are required to clarify the potential safety issues associated with chronic HIF stabilization by a HIF-PH inhibitor. In addition, the study was conducted in Japan exclusively, which would limit the generalizability of results to other ethnicities. Long-term studies of enarodustat (52 weeks) conducted in Japan have been already completed, which will be reported later. In conclusion, this study to assess the efficacy and safety of enarodustat compared with DA in Japanese hemodialysis patients revealed that the efficacy of enarodustat was noninferior to that of DA, without new safety concerns, for the treatment of anemia in patients with CKD receiving hemodialysis.

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Statement of Ethics

All patients provided written informed consent prior to participation. The study was registered with the Japan Pharmaceutical International Center (JapicCTI-183938), was conducted in compliance with the ethical principles of the Declaration of Helsinki, the study protocol, the Guidelines for Good Clinical Practice of the Japanese Ministerial Ordinance, and was approved by the institutional review board of each participating study site.

Conflict of Interest Statement

T.A. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Astellas, Bayer Yakuhin Ltd., Kyowa Kirin Co. Ltd., Kissei Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Fuso Pharmaceutical Industries Ltd., Torii Pharmaceutical Co. Ltd., GlaxoSmithKline, Nipro Corporation, Otsuka Pharmaceutical, Sanwa Chemical, Chugai Pharmaceutical Co. Ltd., and Mitsubishi Tanabe Pharma Corporation outside of the submitted work. M.N. is an Editorial Board Member of the journal Kidney Diseases and reports grants and personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Kyowa Kirin Co. Ltd., Astellas, Astra Zeneca, GlaxoSmithKline, Mitsubishi Tanabe Pharma Corporation, Akebia Therapeutics Inc., Bayer Yakuhin Ltd., and Torii Pharmaceutical Co. Ltd. and grants from Kyowa Kirin Co. Ltd., Astellas, Mitsubishi Tanabe Pharma Corporation, Bayer Yakuhin Ltd., and Torii Pharmaceutical Co. Ltd outside of the submitted work. T.Y. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Ono Pharmaceutical Co. Ltd., Kowa, Chugai Pharmaceutical Co. Ltd., TSUMURA&Co., CAC Croit Corporation, Kyowa Kirin Co. Ltd., Daiichi Sankyo, ASAHI INTECC, Asahi Kasei Corporation, Kaken Pharmaceutical, 3H Clinical Trial Co. Ltd., Welby, 3H Medi Solution, and Nipro Corporation and grants from Ono Pharmaceutical Co. Ltd., CAC Croit Corporation, Kyowa Kirin Co. Ltd., Daiichi Sankyo, 3H Clinical Trial Co. Ltd., AC Medical, A2 Healthcare, Facet Biotech, Japan Media Corporation, Luminary Medical, Medidata Solutions Inc., Senju Pharmaceutical, Otsuka Pharmaceutical, Eisai, FMD K&L Japan, Intellim, Welby, 3H Medi Solution, Nipro Corporation, Hemp Kitchen, NOBORI, Puravida Technologies LLC., and Medrio Inc. outside of the submitted work. H.H. reports personal fees from Japan Tobacco Inc. during the conduct of the study and personal fees from Kyowa Kirin Co. Ltd., Chugai Pharmaceutical Co. Ltd., and Torii Pharmaceutical Co. Ltd. outside of the submitted work. R.K., K.M., and Y.M. are employees of Japan Tobacco Inc.
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Author Contributions

All authors contributed to the final analysis and interpretation of data and had full access to the study data and analyses. All authors contributed to revising the article, providing intellectual content of clinical importance to the work described, and gave final approval for the version to be published.

References

1 GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020 Feb;395(10225):709–33.

2 KDOQI, National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis. 2006 May;47(5 Suppl 3):S11–145.

3 van Nooten FE, Green J, Brown R, Finkelstein EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a meta-regression analysis. Am J Kidney Dis. 2013 Jan;61(1):44–56.

4 Finkelstein FO, Story K, Firanek C, Mendelsohn D, Barre P, Takano T, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. Clin J Am Soc Nephrol. 2009 Jan;4(1):33–8.

5 Ofsthun N, Labrecque J, Lacson E, Keen M, Lazarus JM. The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. Kidney Int. 2003 May;63(5):1908–14.

6 Regidor DL, Koppel JD, Kovesda CP, Kilpatrick RD, McAllister CJ, Aronovitz J, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol. 2006 Apr;17(4):1181–91.

7 Akizawa T, Fison RL, Akiba T, Saito A, Fujikura S, Asano Y, et al. Japanese haemodialysis anaemia management practices and outcomes (1999–2006): results from the DOPPS. Nephrol Dial Transplant. 2008 Nov;23(11):3643–53.

8 Inaba M, Hayashino Y, Shoji T, Akiba T, Akizawa T, Saito A, et al. Disappearance of association in diabetic patients on haemodialysis between anaemia and mortality risk: the Japan dialysis outcomes and practice pattern study. Nephron Clin Pract. 2012;120(2):c91–c100.

9 Akizawa T, Saito A, Gejyo F, Suzuki M, Nishizawa Y, Tomino Y, et al. Low hemoglobin levels and hypo-responsiveness to erythropoiesis-stimulating agent associated with poor survival in incident Japanese haemodialysis patients. Ther Apher Dial. 2014 Oct;18(5):404–13.

10 McCullough PA, Barnhart HX, Inrig JK, Reddan D, Sapp S, Patel UD, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. Am J Nephrol. 2013;37(6):549–58.

11 Koulouridis I, Alifaez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a meta-regression analysis. Am J Kidney Dis. 2013 Jan;61(1):44–56.

12 Ogoshi Y, Matsui T, Mitani I, Yokota M, Terasita M, Motoda D, et al. Discovery of JTZ-951: a HIF prolyl hydroxylase inhibitor for the treatment of renal anemia. ACS Med Chem Lett. 2017 Nov;8(12):1320–35.

13 Fukui K, Shinozaki Y, Kobayashi H, Deai K, Yoshiuchi H, Matsui T, et al. JTZ-951 (enarodustat), a HIF prolyl hydroxylase inhibitor, suppresses renal interstitial fibroblast transformation and expression of fibrosis-related factors. Am J Physiol Renal Physiol. 2020 Jan;318(1):F14–24.

14 Saito H, Tanaka T, Sugahara M, Tanaka S, Fukui K, Wakashima T, et al. JTZ-951, an HIF prolyl hydroxylase inhibitor, suppresses renal interstitial fibroblast transformation and expression of fibrosis-related factors. Am J Physiol Renal Physiol. 2020 Jan;318(1):F14–24.

15 Pai SM, Connaire J, Yamada H, Enya S, Gaggar H, Maewaka M, et al. A mass balance study of 14C-labeled JTZ-951 (enarodustat), a novel orally available erythropoiesis-stimulating agent, in patients with end-stage renal disease on hemodialysis. Clin Pharmacol Drug Dev. 2019 Dec;9(6):728–41.

16 Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Matsui A, et al. Placebo-controlled, randomized trial of enarodustat in patients with chronic kidney disease followed by long-term trial. Am J Nephrol. 2019;49(2):165–74.

17 Akizawa T, Nangaku M, Yamaguchi T, Arai M, Koretomo R, Maeda K, et al. Enarodustat, conversion and maintenance therapy for anemia in hemodialysis patients: a randomized, placebo-controlled phase 2b trial followed by long-term trial. Nephron. 2019;143(2):77–85.

18 Minamishima YA, Kaelin WG Jr. Reactivation of hepatic EPO synthesis in mice after PHD loss. Science. 2010 Jul 33;239(5990):407.

19 Nangaku M, Eckardt KU. Hypoxia and the HIF system in kidney disease. J Mol Med. 2007 Dec;85(12):1325–30.

20 Wang GL, Jiang BH, Yue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5510–4.

21 Yamamoto H, Nishi S, Tomo T, Masakane I, Saito K, Nangaku M, et al. 2015 Japanese society for dialysis therapy: guidelines for renal anemia in chronic kidney disease. Ren Replace Ther. 2017;3(1):36.

22 Markham A. Enarodustat: first approval. Drug Des 2021;81(1):169–74.

23 Pugh CW, Ratcliffe PJ. New horizons in hypoxia signaling pathways. Exp Cell Res. 2017 Jul;356(2):116–21.

24 Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015 Jul;11(7):394–410.

25 Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anaemia in patients with CKD. Am J Kidney Dis. 2017 Jun;69(6):815–26.

26 Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythrophore as an erythroid regulator of iron metabolism. Nat Genet. 2014 Jul;46(7):678–84.

27 Sanghavi V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. Adv Nutr. 2017 Jan;8(1):126–36.

28 Nemeth E, Rivera S, Gavayen V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004 May;113(9):1271–6.

29 Besson-Fournier C, Latour C, Kautz L, Bertrand J, Ganz T, Roth MP, et al. Induction of activity of β2m in hematopoietic stimuli up-regulates expression of the iron-regulatory peptide hepcidin through Smad1/5/8 signaling. Blood. 2012 Jul;120(2):431–9.

30 Johnson DW, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology. 2007 Aug;12(4):321–30.

31 Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. Nat Med. 2003 Jun;9(6):677–84.