Post-marketing observational study on Management of Anemia in Chronic Kidney Disease patients with WEPOX® Pen (MAP II)

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Abstract

Objective: **To evaluate effectiveness and safety of WEPOX® Pen, a pre-calibrated pen device loaded with 30,000 IU cartridge of recombinant human EPO (rHuEPO), in management of anemia in CKD patients, in the real-world clinical settings.**

Material and Methods: **In this prospective, multi-center, open-label, post marketing surveillance study, ambulatory pediatric and adult patients of either gender, diagnosed with CKD and anemia were enrolled to access the effectiveness and safety of WEPOX® Pen. Patients were divided in two groups based on baseline Hb (g/dL) levels; Hb<10g/dL (Group 1) and Hb≥10g/dL (Group 2). Results were recorded in the follow up visits scheduled at weeks 5, and 12. Investigator had the choice to discontinue the patient from the study as per his/ her discretion based on significant adverse drug reaction or lack of expected effectiveness.**

Results: **A total of 409 patients were enrolled in the study; out of which 377 (92.2%) patients were enrolled in Group 1 and 32 (7.8%) patients in Group 2. Proportion of patients in Group 1 achieving ≥1 g/dL rise in Hb value from baseline were 70.3% and 86.5% at week 5 and 12, respectively. Similarly, proportion of patients in group 2 maintaining Hb levels of ≥10 g/dL were 68.7% and 96.8% at week 5 and 12 respectively. Overall compared to baseline, Hb (g/dL) levels increased in 366 (97.1%) and 30 (93.8%) patients, in group 1 and 2 respectively, at 12-weeks. No adverse events were reported during the study duration.**

Conclusion: **Treatment with WEPOX® Pen (rHuEPO Injection) in CKD patients with anemia was well tolerated and produced a clinically relevant improvement in Hb levels.**

Keywords: **Anemia, Chronic Kidney Disease, Erythropoietin Pen Device, Hemoglobin, Erythropoietin Stimulating Agent (ESA)**

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Introduction

Chronic kidney disease (CKD), with its high prevalence, morbidity and mortality, is an important public health problem, globally and in India.[1,2] The prevalence of CKD in India was observed to be 17.2% with ~6% having CKD stage 3 or worse.[2] Amid rising prevalence of diabetes and hypertension in India, the prevalence of CKD is expected to rise further in the country.[3] Anemia is a common complication among CKD patients,and begins to manifest atestimated glomerular filtration rate (eGFR) of <60ml/min/1.73m^2 (Stage III).[4,5] The reported prevalence of anemia in Indian CKD patients ranges between 94% and 100%.[6]

In CKD, anemia is characterized by a lack of synthesis of erythropoietin (EPO) leading to reduced red blood cell (RBC) formation and aberrant iron recycling.[7] The impact of anemia on patients with CKD is profound. Anemia contributes to an increased cardiac output, and the development of left ventricular hypertrophy, angina and congestive heart failure, leading to high morbidity and mortality in CKD patients.[8] The introduction of erythropoiesis-stimulating agents (ESAs) has transformed the management of anemia.[9] It has greatly benefited patients by decreasing debilitating symptoms, improving their quality of life, and freeing them from dependence on blood transfusions with their associated complications such as infections, sensitization impeding transplantation, and secondary iron overload.[10] Moreover, it has resulted in significant reduction in cardiovascular morbidity and mortality in CKD patients.[11]

Efficacy and safety of EPO is well established and drug has been widely used for the treatment of anemia in patients with CKD.[9-12] A growing body of evidence also indicates that the therapeutic benefits of EPO could extend beyond the improvement of anemia.[12] The ease of self-administration, less pain and discomfort, with WEPOX® Pen in the management of anemia in adult CKD patients have been reported earlier by Barkate *et al*.[13] However there is dearth of data about effectiveness and safety data of WEPOX® Pen in patients with CKD.

The objective of this post-marketing observational study was to evaluate effectiveness and safety of WEPOX® Pen, a pre-calibrated pen device loaded with 30,000 IU cartridge of recombinant human EPO (rHuEPO), in management of anemia in CKD patients, in the real-world clinical settings.

Material and Methods

This was a prospective, multi-center, open-label, post marketing surveillance study evaluating the effectiveness and safety of WEPOX® Pen (Erythropoietin Injection in pre-calibrated pen device) in the management of anemia in Indian patients with CKD. The study was conducted from 02/01/2017 to 15/11/2017 at 144 centers spread across 12 cities in India.

Ambulatory pediatric and adult patients of either gender, diagnosed with CKD and anemia, who were eligible to receive WEPOX® pen treatment as per investigator discretion and willing to give signed informed consent for study participation, were enrolled in this study. Patients with the history or evidence of hypersensitivity to any component of study medication/rescue medication to be used in the study, not willing to continue with same treatment without any addition of other therapy till study participation, with history or evidence of chronic abuse with alcohol, smoking, tobacco products or drugs, had participated in any other clinical trials 30 days prior to study enrolment date, pregnant or lactating women, and patients having any other condition deemed unfit by the investigator for the patients' participation in the study were excluded from the study. Dosage of WEPOX® was as per the prescribing information and based on the discretion of the treating physician.

The study duration was 12-weeks. Enrolled patients were prescribed WEPOX® Pen at a dose determined by the treating physician, in accordance to prescribing information. Patients enrolled in the study were divided in two groups based on baseline Hb (g/dL) levels; Hb<10g/dL (Group 1) and Hb≥10g/dL (Group 2). All the patients were counseled about general care, and use of concomitant and/or rescue medication, by treating investigator or study team member, at the time of enrolment. Follow-up visits were scheduled at weeks 5, and 12. The results of latest reported Hb (g/dL) not more than 7 days prior to day of baseline/ follow-up visit were recorded. In case of significant adverse drug reaction, Hb level ≥11.9 g/dL or lack of expected effectiveness, investigator could discontinue the patient from the study as per his/ her discretion.

The study was conducted in accordance with the principles of declaration of Helsinki and in compliance with Good Clinical Practice guidelines. Written informed consent was obtained from all study participants or legally acceptable representative of the patient, before being examined for eligibility criteria. The study protocol and the informed consent form were

Table 1: Patient Characteristics at Baseline

Variable(s)	Overall (N=409)	Group 1 (n=377)	Group 2 (n=32)
Sex, n (%)			
Male	259 (63.3)	241 (63.9)	18 (56.3)
Female	150 (36.7)	136 (36.1)	14 (43.8)
Age (years) (mean ± SD)	53.9±17.8	53.4±17.9	58.8±15.7
BMI (mean ± SD)	22.0±3.9	21.9±3.8	23.1±4.6
Hb (g/dL) (mean ± SD)	8.2±1.2	8.1±1.0	10.2±0.4
Concomitant Illness n (%)			
Diabetes+ Hypertension	7 (1.7)	7 (1.9)	-
Cardiovascular Disease	8 (2.0)	8 (2.1)	-
Diabetes+ Cardiovascular Disease	12 (2.9)	12 (3.2)	-
Hypertension	15 (3.7)	15 (3.4)	2 (6.3)
Diabetes	33 (8.1)	33 (8.8)	-

Group 1- Hb<10g/dL, Group 2- Hb≥10g/dL

reviewed and approved by the relevant Institutional Review Board before initiation of the study.

Study Endpoints

The primary endpoints were proportion of patients achieving>1g/dL rise of Hbin group 1 from baseline and proportion of patients maintaining Hb>10g/dL at week 5 and 12 in group 1 and 2. The secondary endpoints included mean change in Hb (g/dL) levels, mean change in dose of WEPOX® from baseline at Week 5 and 12 in group 1 and 2; and percentage of patients in both groups who required change in dose of Wepox at Week 5 and 12.

Statistical Analysis

Qualitative and quantitative variables are presented using descriptive statistics. Quantitative variables were evaluated using paired t-test at 5% level of significance and the corresponding p-value is presented. Data were analyzed using SPSS® statistics software, version 23.0.

Results

A total of 409 (Male: Female—259:150) patients with mean (SD) age of 53.9 (17.8) years were enrolled in the study, out of which 377 (92.2%) patients were enrolled in Group 1 and 32 (7.8%) patients in Group 2. All the enrolled patients completed the study as per protocol. The demographic and baseline characteristics of patients are summarized in table 1.

In group 1, 70.3% and 86.5% patients achieved ≥1 g/dL rise in Hb value from baseline, at Week 5 and 12, respectively. Likewise 68.7% and 96.8% patients in group 2 maintained Hb levels of ≥10 g/dL at 5 and 12 week, respectively (Figure 1). Overall compared to baseline, Hb (g/dL) levels increased in 366 (97.1%) and 30 (93.8%) patients, in group 1 and 2 respectively, at 12-weeks.

Mean Hb levels in group 1 and 2 at week 5 and 12 post treatment, are illustrated in Figure 2. In group 1, compared to baseline mean (SD) levels of 8.1(1.0), Hb (g/dL) levels increased significantly by 1.4g/dL(95% CI: 1.3 to 1.5; p<.001) and by 2.0g/dL (95% CI: 1.9 to 2.1; p<.001), respectively, at week 5 and 12 post treatment. However in group 2, Hb (g/dL) increased marginally by 0.2g/dL (95% CI: -0.1 to 0.5;p>.05) at week 5, but significantly by 1.0g/dL (95% CI: 0.8 to 1.2; p<.001) at 12-weeks, compared to baseline mean (SD) levels Hb levels of 10.2 (0.4)g/dL. Additionally, 73 (19.4%) and 21 (65.6%) patients in group 1 and 2 respectively, achieved Hb levels in range of 11.0 to 12.5 g/dL, at 12-weeks

The proportion of patients requiring change in WEPOX® pen dosage is presented in table 2. In group 1, effectiveness was maintained with minor changes in doses as observed on each visit. In the group 1 mean (SD) dose of WEPOX® pen was 4.42 (1.57) unitsat baseline, which increased significantly by 0.03 units (95% CI: .01 to .07; p<.05) at week 5 and by 0.05 units (95%

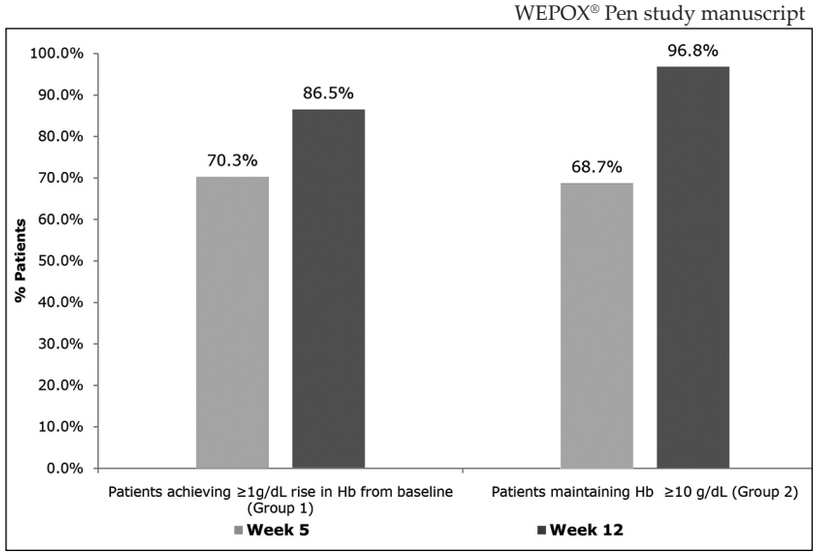

Fig 1: Percentage of patients achieving ≥1g/dL rise in Hb (Group 1) and maintaining Hb ≥10 g/dL (Group 2)

Table 2: Proportion of patients requiring changein Wepox® pen dose from baseline to week 5 and 12 in group 1 and 2

	Group 1 (n=377)		Group 2 (n=32)	
Variable n (%)	**Week 5**	**Week 12**	**Week 5**	**Week 12**
Increase in dose	13 (3.4%)	18 (4.8%)	0	0
Decrease in dose	04 (1.1%)	03 (0.8%)	0	0
No change in dose	360 (95.5%)	356 (94.4%)	0	0

Group 1- Hb<10g/dL, Group 2- Hb≥10g/dL

CI: .02 to .08; p<.01) at 12-weeks. However, in group 2 there was no change reported in dose of WEPOX® pen at week 5 and 12, from baseline mean (SD) dose of 3.88 (1.41) units. No adverse events were reported during course of study in both the groups.

Discussions

Anemia management was revolutionized in the late 1980s with the introduction of rHuEPO.[14] Erythropoietin and related ESAs greatly benefited patients by improving their debilitating symptoms, and freeing them from dependence on blood transfusions and its associated complications.[15,16,17] The correction of anemia with rhuEpo in patients with CKD also seems to improve cardiac performance and geometry.[18]

Wepox is the indigenously manufactured brand of Erythropoietin in India. The gene coding for erythropoietin is been inserted into mammalian cells to develop recombinant Wepox producer cell strain. This recombinant producer cells strain is employed to produce the secretory product which is purified to homogeneity.

The present study evaluated the effectiveness and safety of WEPOX® pen in CKD patients with anemia, over a medium-term observation period of 12-weeks.The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (2000) recommended that the selected Hb targets should generally be maintained in the range of 11.0 to 12.0 g/dL in patients with CKD, whether or not they were receiving dialysis.[19] In our study, 73 (19.4%) and 21 (65.6%) patients in group 1 and 2 respectively, achieved Hb levels in range of 11.0 to 12.5 g/dL, at 12-weeks.

The mean Hb levels in our study increased significantly (p<.001) by 2.0g/dLand by 1.0g/dL, at week 12, in group 1 and 2, respectively. These results are similar to those reported by other authors. Kristal *et al*. evaluated effect of EPO on biochemical parameters and GFR in CKD patients with anemia. Authors reported increase in Hb levels by 0.3 g/dL and 0.9g/dL, at week 10 and 20.[20] In a study by Schärer et al., Hb concentration increased by >2g/dL in all patients within 14-119 (mean 45) days, post treatment with rHuEPO injections.[21] In a systematic review by Cody *et al*., data of four studies reporting Hb levels at the end of study was evaluated; rHuEPO treatment significantly increased Hb compared to placebo or no treatment (Mean difference 1.90 g/dL, 95% CI 1.47 to 2.34).[22] Treatment with rHuEPO was reported to result in a significant increase in hemoglobin concentration (100% patients responded in a positive way to rHuEPO).[23]

Use of rHuEPOis reported to improve hemoglobin in 90-95% of the cases of anemia of CKD.[24] In our study also, Hb levels increased in 366 (97.1%) and 30 (93.8%) patients, in group 1 and 2 respectively, at Week 12. Additionally in our study, 86.5% patients in group 1 achieved ≥1 g/dl rise in Hb value from baseline at Week 12, and 96.8% patients in group 2 maintained Hb levels of ≥10 g/dl, at 12 weeks. WEPOX Pen, however, may elicit additional benefits over other EPO preparation due to itsease of administration, less pain and discomfort at the site of injection thereby making patients more confident with self-administration, resulting in improved patient compliance.[13]

Treatment of anemia in CKD patients has shown to improve their exercise capacity; physical performance features

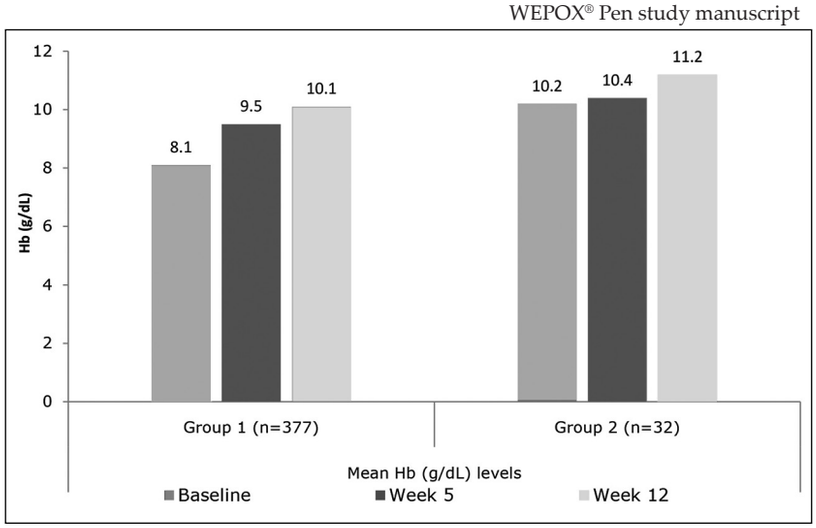

Fig 2: Mean Hb (g/dL) levels at week 5 and 12 compared to baseline in group 1 and 2

such as endurance; energy; and physical mobility.[25] Along with survival and other types of clinical outcomes, patient quality-of-life is an important indicator of the effectiveness of the medical care they receive.[26] Appropriate therapy with ESAs, can effectively treat anemia, thereby improving the quality of life in patients with CKD and anemia.[27] Treatment of anemia has also been shown to reduce hospitalization and mortality rates.[28] Moreover, patient's satisfaction also increases when anemia is corrected.[27]

In vitro tubular cell cultures as well as in vivo experimental studies in models of I-R injury have shown that EPO exerts a reno-protective effect during acute kidney injury.[29] Recognition of the reno-protective actions of EPO is considered even more important in the setting of CKD, mostly due to its widespread use in these patients for the purpose of anemia correction.[29,30,31] It has been suggested that direct reno-protective effects of EPO can delay the progress of renal disease and reduce morbidity and mortality irrespectively of complete or partial anemia correction.[30,31]

In conclusion, the results from our study suggest that treatment with WEPOX® Pen (rHuEPO Injection) in CKD patients with anemiawas well tolerated, and produced a clinically relevant improvement in Hb levels. Moreover, beside easeof usingWEPOX® Pen as also reported in pervious study [13], the present study further reinforces use of recombinant erythropoietin delivery device WEPOX® Pen, in management of anemia in CKD patients.

Our study has some limitations that need to be acknowledged. The main limitation is the relatively shorter follow-up period. The second limitation isabsence of group of CKD patients not treated with EPO. Despite these limitations, we believe that our findings are important and further support the previously reported beneficial effect of rHuEPO. Additionally, result from our study show an improvement in Hb levels though over a medium follow-up period of 12-week, in CKD patients with anemia. Additional large-scale randomized controlled studies are warranted to substantiate the finding of this study.

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