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Comparison of the effectiveness of equal doses of short and long-acting erythrocyte stimulating agents for managing anemia in chronic kidney disease adult patients

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ABSTRACT

Anemia is the most common side effect in patients with chronic kidney disease (CKD) mainly due to lower levels of erythropoietin (EPO) hormone. The aim of the present study is to compare the efficacy of equivalent doses of erythropoiesis stimulating agents (ESAs): short acting (Eprex®; Epoetin alfa) and long acting (Darbepoetin alfa: DA) in the treatment of anemia of CKD adult patients treated from September 2013 to January 2015. A total of fifty five patients were included; 22 patients were treated with Eprex®® (Epoetin alfa) and 33 patients received DA. Different blood indices were assessed in the initial 8 weeks. The equality of the doses was based on the conversion formula (1 µg of DA = 300 IU Eprex®). Treatment with lower dose of DA (0.64±0.07 µg/kg QW) induced a significant increase in hemoglobin (Hb) from week 4 through week 8, while red blood corpuscles (RBCs) and hematocrit (Hct) were significantly elevated in week 8. A significant increase in Hb and Hct were observed starting from week 2 through week 8 parallel with a significant rise in RBCs count, starting from week 3 through week 8 after treatment with DA (0.8±0.06 µg/kg QW), while a significant increment of Hb and Hct were noticed after treatment with DA (1.215±0.11 µg/kg QW) from week 3 to week 7. Administration of higher dose DA (1.37±0.22 µg/kg QW) led to a significant rise of RBCs in week 3, 6 and 7 while Hb and Hct in week 6 and 7. Treatment with equal doses of Eprex® (170.85±16.4 IU/kg and 238±25 .9 IU/kg) induced only a mild increase in RBCs in week 7 and 6 respectively, while higher dose of Eprex® (413±40.8 IU/kg) elevated RBCs significantly at week 8 and Hct in week 6 and 8. Administration of DA QW is more effective than Eprex® QTIW in terms of target anemia parameters: RBCs, Hb and Hct during the first 8 weeks of administration.

Keywords: Anemia; chronic kidney disease; Erythropoietin; Eprex®; Darbepoetin alfa; Erythropoiesis Stimulating Agents

INTRODUCTION

Deterioration in kidney function over time is the mainstay of chronic kidney disease (CKD) [1]. The gradual damage of renal parenchyma can lead to destruction of sufficient numbers of nephrons which causes progressive and irreversible decline in renal function that lead to reduced quality of life and eventually death [2]. The diagnosis of CKD is confirmed by elevated plasma level of creatinine, urea and lower glomerular filtration rate. There are several

diseases which could lead to CKD, the most likely are high blood pressure, diabetes mellitus, kidney stone and infection [3, 4].

Anemia in CKD is very common. The severity of anemia is usually parallel to the degree of renal impairment. It has been reported that lower kidney function was strongly associated with lower hemoglobin (Hb) level and higher prevalence and severity of anemia [5, 6]. The main causes of anemia are low renal erythropoietin (EPO) secretion, uremia, chronic blood loss, hemolysis and bone marrow suppression [7]. Accordingly, anemia is a major complication of CKD [8],which is mainly due to lower levels of EPO secreted by the damaged kidney together with low serum iron [9].

In the late 1980s recombinant human erythropoietin (rhuEPO) was introduced and the treatment of anemia in CKD patients was drastically changed as the treatment of anemia in CKD patients by EPO did not only lead to relief of fatigue and improvement of physical activity but also to enhancement of a broad spectrum of physiologic functions [7]. Treatment with EPO improves quality of life and symptoms of anemia in CKD patients as it raises Hb concentrations [10]. Short acting erythropoiesis stimulating agents, ESA (Eprex®; Epoetin alfa®) has the same amino acid sequence as endogenous EPO while long-acting ESA, Darbepoetin alfa® (DA) differs from endogenous EPO in terms of containing two additional N-linked oligosaccharide chain attachments to asparagine. The optimal administration schedule of Eprex®; Epoetin alfa is three times weekly because of its relative short half-life (6-8 hours i.v and 19-24 hours s.c), while the optimal administration schedule of DA is once a week because it has three to four times longer half-life (25 hours i.v and 48 hours s.c). It has been declared that rhuEPO improves anemia in CKD not only through stimulating erythropoiesis but also by decreasing one of the negative regulator of erythropoiesis transforming growth factor beta [11, 12]. Furthermore, it has been shown that erythrocyte membrane proteins in CKD patients with stage 5 are significantly altered which may be related to their interaction with hemodialysis membranes [13]. Patients with CKD have a significantly lower hematological indices including RBCs count, Hb, packed cell volume (PCV) and platelets while the total leukocyte count is normal [14]. In addition, there is a negative correlation between serum creatinine levels and all hematological parameters. Recently Dorgalaleh et al., [15] has reaffirmed the previous results and showed that accumulation of toxic metabolic products and deficiency of EPO secretion in acute and CKD lead to hematological changes including a significant decrease in RBCs count, Hb and hematocrit (Hct) compared to normal controls. In addition, patients with CKD showed a remarkable decrease in mean corpuscular hemoglobin concentration (MCHC), red blood cell distribution width (RDW%) and platelets count as compared to control group. To date and up to our best knowledge, there is a little information regarding the comparison of the efficacy of equivalent doses of the short acting ESA: Eprex® and long acting ESA: Darbepoetin alfa in the amelioration of different hematological changes in the initial 8 weeks of treatment in relation to serum iron status; serum iron, serum ferritin and calculated transferrin saturation (T-SAT) in CKD patients. Therefore, the aim of the present study is to compare efficacy of both Eprex® and DA on selected hematological parameters in the first 8 weeks in CKD adult patients.

MATERIALS AND METHODS

Study Design and Study Subjects

All clinical data were collected from Nephrology unit - King Abdulaziz Medical City at the National Guard Health Affairs, Riyadh, Saudi Arabia “between” September 2013 to January 2015. The study was approved by the King Abdullah International Medical Research Center (KAIMRC) and the Independent Ethics Committee of King Abdulaziz Medical City.

This is an observational study on 55 patients diagnosed with ESKD who are undergoing regular hemodialysis. The following were the inclusion criteria; patients should be on regular hemodialysis for at least 3 months and the age should be more than 18 and under medical treatment with Eprex®; Epoetin alfa or DA for the first time. While the exclusion criteria were the following; presence of certain established diseases as uncontrolled hypertension, heart diseases as congestive heart failure or those requiring an emergency transfusion of blood component or undergoing platelet transfusion, active neoplasia or with viral hepatitis or who were using certain drugs as cyclosporine. Before starting treatment with Eprex® or DA, serum ferritin was checked and if patient’s serum ferritin was less than 200 (µg/l), the patients were treated with i.v iron (a total dose 1 g) 100 mg for 10 days. More than 30% of the selected patients were receiving maintained dose 100 mg i.v of iron for 10 days.

The week before starting treatment was considered week 0. The administration frequency of Eprex® was 3 times/week, i.v. (QTIW) while DA was administered once weekly, s.c. (QW). The hematological parameters including red blood corpuscle (RBCs) count, Hb, Hct, PCV, MCH, MCHC, platelets count and total leukocyte count, serum iron, ferritin and total iron binding capacity (TIBC) were collected from medical record of the patients before starting treatment and at the end of every week for 8 weeks. Based on the data collected, T-SAT was calculated. The dose equivalence of both ESAs was based on recently published observation recommending the conversion factor: 300 IU Eprex®=1µg Darbepoietin [16].

Statistical Analysis

Descriptive statistical analyses were performed for the study sample. For continuous variables, measures of central tendency (e.g. mean, median) and range and standard deviation or standard error of mean (SEM) were provided. Proportions were used for categorical variables. The two groups (Eprex® and DA) were compared in terms of baseline characteristics including age, gender and body weight. Comparisons were made using the t-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Statistical comparison between measured bloods parameters over the follow up time were made using one way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison tests. Statistical significance was considered at $p<0.05$. All statistical analyses were performed using SPSS 21.0 [Release 21.0.0.0, IBM, USA].

RESULTS

After investigating all the files of CKD patients followed up in King Abdulaziz Medical City at the National Guard Health Affairs retrospectively, a total of 55 patients satisfying the study inclusion criteria were included in this study. Twenty two patients were treated with Eprex® (40%) and 33 patients were treated with DA (60%). Baseline characteristics of the study sample overall and by group are displayed in Table 1. Average age was 53.2 years (SD = 16.4), with 53% males. Average body weight was 74.1 kg (SD = 20.6). No statistically significant differences were found between the two groups in terms of baseline characteristics.

Table 1: Baseline Characteristics of the study sample. Total Number of Patients = 55.

Factor		All (N = 55)	Eprex® (N = 22, 40%)	Darbepoietin (N = 33, 60%)	p-value*
Age (years)	Mean ± SD	53.2 ± 16.4	52.8 ± 14.6	53.5 ± 17.7	0.87
	Median (range)	57 (23-91)	57.5 (24-72)	57 (23-91)	
Gender N (%)	Female	26 (47.3%)	10 (45.5%)	16 (48.5%)	0.83
	Male	29 (52.7%)	12 (54.5%)	17 (51.5%)	
Body weight (kg)	Mean ± SD	74.1 ± 20.6	76.9 ± 21.7	72.3 ± 20.1	0.52
	Median (range)	73 (39-147)	77 (46-147)	70 (39-115)	

**Based on t-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.*

Mean initial and weekly measured blood parameters indicated that starting treatment of 6 patients with DA 40-µg QW with mean dose/kg (0.64±0.07 µg/kg) induced a statistically significant elevation in Hb starting from week 4 through week 8 and a significant increase in RBCs number and Hct in week 8 although the mean initial serum iron (7.08±1.37 µmol/l) was lower than the normal level (9-30 µmol/l) (Table 2), while mean initial serum ferritin and calculated T-SAT were within normal range. Using the conversion factor (300 IU Eprex®: 1 µg DA), treatment of five patients with equal dose of Eprex® 4000 IU QTIW with mean dose/kg (170.85±16.4 IU/kg) induced a significant rise in RBCs count only in week 7 although mean initial serum iron, ferritin and calculated T-SAT were within normal range (Table 2).

Table 2: Comparison of the efficacy of Eprex® 4000 IU QTIW therapy with DA 40 µg QW therapy for treatment of anemia in CKD patients

	Hb (g/L)		RBCs ($\times 10^6$)		Hct (l/l)	
	Eprex® 4000 IU QTIW	Darbepoietin 40 µg QW	Eprex® 4000 IU QTIW	Darbepoietin 40 µg QW	Eprex® 4000 IU QTIW	Darbepoietin 40 µg QW
Week 0	77 ± 5.89	80 ± 3.56	2.77 ± 0.15	3.14 ± 0.25	0.25 ± 0.034	0.26 ± 0.020
Week 1	83 ± 6.78	86 ± 2.18	3.00 ± 0.14	3.43 ± 0.22	0.30 ± 0.021	0.26 ± 0.011
Week 2	86 ± 6.32	86 ± 1.88	3.09 ± 0.18	3.43 ± 0.16	0.27 ± 0.026	0.28 ± 0.009
Week 3	83 ± 3.50	92 ± 6.58	3.14 ± 0.03	3.49 ± 0.29	0.29 ± 0.038	0.30 ± 0.023
Week 4	98 ± 6.02	104 ± 8.8**	3.35 ± 0.18	4.04 ± 0.33	0.30 ± 0.015	0.33 ± 0.023
Week 5	102 ± 24.00	101 ± 5.87*	3.55 ± 0.72	3.90 ± 0.38	0.28 ± 0.020	0.33 ± 0.024
Week 6	93 ± 15.56	103 ± 6.22*	3.54 ± 0.23	3.77 ± 0.58	0.28 ± 0.014	0.31 ± 0.042
Week 7	121 ± 9.40	104 ± 5.00**	4.14 ± 0.34**	4.18 ± 0.51	0.26 ± 0.025	0.33 ± 0.027
Week 8	107 ± 4.30	108 ± 4.80**	3.75 ± 0.23	4.36 ± 0.40*	0.29 ± 0.020	0.30 ± 0.030**
					Serum Parameters at Week 0	
Iron (µmol/l)	10.09 ± 3.60	7.08 ± 1.37				
Ferritin(µg/l)	422 ± 118	826 ± 417				
T-SAT (%)	27.25 ± 7.40	21.5 ± 4.00				

*All data are expressed as Mean ±SEM, *p<0.05, **p< 0.001, [Compared to week 0 (baseline)]*

Administration of DA 60 µg QW to 11 patients with mean dose/kg (0.8±0.06 µg/kg), led to a remarkable increase in RBCs count starting from week 3 through week 8, and in Hb and Hct from week 2 through week 8, although the mean initial serum iron (7.5±1.65 µmol/l) was lower than the normal level while serum ferritin and calculated T-SAT were within normal range. In Eprex® treated group; the mean initial serum iron (5.12±1.15 µmol/l) and calculated T-SAT (17.7±4.7) were lower than the normal level (Table 3). Treatment with Eprex® 6000 IU QTIW (238±25.9 IU/kg) to 10 patients induced a significant increase in RBCs count only in week 6 (Table 3).

Table 3: Comparison of the efficacy Eprex® 6000 IU QTIW therapy with DA 60 µg QW therapy for treatment of anemia in CKD patients

	Hb (g/L)		RBCs ($\times 10^6$)		Hct (l/l)	
	Eprex® 6000 IU QTIW	Darbepoietin 60 µg QW	Eprex® 6000 IU QTIW	Darbepoietin 60 µg QW	Eprex® 6000 IU QTIW	Darbepoietin 60 µg QW
Week 0	84 ± 4.7	76 ± 2.26	3.10 ± 0.17	2.7 ± 0.09	0.28 ± 0.02	0.24 ± 0.01
Week 1	91.8 ± 4.7	82 ± 2.52	3.36 ± 0.16	2.88 ± 0.06	0.30 ± 0.02	0.26 ± 0.01
Week 2	89 ± 4.6	93 ± 3*	3.24 ± 0.14	3.26 ± 0.10	0.29 ± 0.02	0.30 ± 0.01*
Week 3	94 ± 6.3	102 ± 2.22**	3.45 ± 0.16	3.54 ± 0.07**	0.30 ± 0.022	0.32 ± 0.01**
Week 4	90.3 ± 4.3	105 ± 2.91**	3.36 ± 0.11	3.50 ± 0.09**	0.29 ± 0.16	0.33 ± 0.01**
Week 5	96.8 ± 7.2	114 ± 6.15**	3.59 ± 0.22	3.96 ± 0.20**	0.31 ± 0.03	0.37 ± 0.02**
Week 6	104 ± 4.4	109 ± 6.7**	3.92 ± 0.09	3.72 ± 0.20**	0.33 ± 0.02	0.34 ± 0.02**
Week 7	93.5 ± 5.9	117 ± 6.9**	3.60 ± 0.2	3.88 ± 0.36**	0.30 ± 0.03	0.34 ± 0.03**
Week 8	102.3 ± 5.2	115 ± 4.9**	3.77 ± 0.17	3.87 ± 0.20**	0.32 ± 0.02	0.35 ± 0.02**
					Serum Parameters at Week 0	
Iron (µmol/l)	5.12 ± 1.15	7.50 ± 1.65				
Ferritin (µg/l)	826 ± 290	839 ± 497				
T-SAT (%)	17.70 ± 4.70	22.00 ± 4.50				

*All data are expressed as Mean ±SEM, *p<0.05, **p< 0.001, [Compared to week 0 (baseline)]*

Similar results were observed after treatment with the higher dose of DA 100 µg (1.37± 0.22 µg/kg) to 7 patients, where RBCs count was significantly increased in week 3, 6 and 7, while Hb concentration and Hct level were elevated in week 6 and 7 respectively although the mean initial serum iron was lower than normal level. While, the iron status; mean serum iron, ferritin and calculated T-SAT were within normal range in patients receiving higher dose of Eprex® 10.000 IU (413± 40.8 IU/kg), a significant increase in RBCs counts in week 8 and Hct level in week 6 and 8 were observed (Table 4).

Table 4: Comparison of the efficacy Eprex® 10000 IU QTIW therapy with DA 100 µg QW therapy for treatment of anemia in CKD patients

	Hb (g/L)		RBCs ($\times 10^6$)		Hct (l/l)	
	Eprex® 10000 IU QTIW	Darbepoietin 100 µg QW	Eprex® 10000 IU QTIW	Darbepoietin 100 µg QW	Eprex® 10000 IU QTIW	Darbepoietin 100 µg QW
Week 0	73.3 ± 3.60	75 ± 3.54	2.50 ± 0.13	2.60 ± 0.09	0.23 ± 0.01	0.24 ± 0.01
Week 1	94.8 ± 5.60	80 ± 3.36	3.13 ± 0.30	2.79 ± 0.16	0.29 ± 0.02	0.26 ± 0.01
Week 2	62.3 ± 20.00	85 ± 2.72	2.67 ± 0.39	2.98 ± 0.08	0.29 ± 0.02	0.28 ± 0.02
Week 3	97 ± 7.20	91 ± 6.13	3.27 ± 0.27	3.20 ± 0.13*	0.24 ± 0.03	0.29 ± 0.02
Week 4	96 ± 6.90	84.7 ± 4.38	3.15 ± 0.17	2.89 ± 0.18	0.30 ± 0.02	0.26 ± 0.01
Week 5	101.5 ± 6.50		3.50 ± 0.06		0.33 ± 0.03	
Week 6	79 ± 38.50	104 ± 5.5**	3.67 ± 0.15	3.37 ± 0.18*	0.35 ± 0.04*	0.28 ± 0.02*
Week 7	98 ± 4.00	97 ± 8.17*	3.50 ± 0.20	3.34 ± 0.17**	0.32 ± 0.01	0.32 ± 0.02*
Week 8	113 ± 4.62		3.77 ± 0.12*		0.35 ± 0.01**	
			Serum Parameters at Week 0			
Iron (µmol/l)	9.70 ± 4.70	8.29 ± 1.70				
Ferritin (µg/l)	409 ± 157	567 ± 252				
T-SAT (%)	27.25 ± 10.00	21.00 ± 5.00				

*All data are expressed as Mean ±SEM, *p<0.05, **p< 0.001*

Also, while mean initial serum iron and calculated T-SAT were considerably lower than normal range (5.7±1.8 µmol/l) and (15±5.4) respectively, treatment with DA 80 µg (1.22± 0.11 µg/kg) led to significant increase in Hb concentration in week 3, 4, 6 and 7 and Hct level in week 3, 4 and 7 while having no significant impact on RBCs count (Table 5). Treatment with short or long-ESAs did not induce any changes in others hematological parameters; mainly PCV, MCH, MCHC, platelets count and total leukocyte count (data not shown).

Table 5: Effect of DA 80 µg QW therapy for treatment of anemia in CKD patients

	Hb (g/L)	RBCs ($\times 10^6$)	Hct (l/l)
	Darbepoietin, 80 µg, QW		
Week 0	75 ± 2.9	2.80 ± 0.26	0.25 ± 0.02
Week 1	81 ± 3.19	2.90 ± 0.21	0.25 ± 0.01
Week 2	88 ± 5.68	3.00 ± 0.37	0.27 ± 0.01
Week 3	102 ± 9.50*	3.90 ± 0.31	0.33 ± 0.03*
Week 4	104 ± 4.00**	3.20 ± 0.03	0.34 ± 0.03*
Week 6	103 ± 3.28**	3.70 ± 0.20	0.32 ± 0.01
Week 7	105 ± 4.00**	3.70 ± 0.24	0.33 ± 0.02**
		Serum Parameters at Week 0	
Iron (µmol/l)	5.7 ± 1.8		
Ferritin (µg/l)	466 ± 240		
T-SAT (%)	15 ± 5.4		

*All data are expressed as Mean ±SEM, *p<0.05, **p< 0.001, [Compared to week 0 (baseline)]*

DISCUSSION

Anemia remains an important challenge in CKD patients. Although several factors are implicated in the development of anemia, EPO deficiency remains the most important one. In the past, treatment of anemia was based on blood transfusion with the underlying risk of infection transmission in addition to other complications. However, with the introduction of ESAs in the late 1980's, it became the treatment of choice for management of anemia in CKD. DA and Eprex® are two different ESAs formulation with the same activity. However, DA has the advantage of being longer acting, and thus it is administered once weekly while Eprex® is given three times weekly.

The findings of this study indicated that treatment with different doses of DA 40,60, 80 and 100 µg QW, induced a remarkable and consistently significant elevation in Hb parallel with a significant increase in RBCs and Hct, although mean initial serum iron was lower than normal range. While, serum ferritin and calculated T-SAT were within normal range. It has also been observed that different doses of DA not only increased Hb but also maintained its levels within recommended target range (100-120 g/l). This was not the case for the Eprex® treated group, where the level of Hb was fluctuating and different doses of Eprex® induced an elevation in RBCs count in week 6, 7 or 8, although mean initial serum iron, ferritin and calculated T-SAT were within normal range.

Survival of RBCs is inversely proportional to levels of blood urea nitrogen (BUN) due to increased uremic plasma expression of phosphatidylserine on the outer surface of RBCs. This can enhance the identification of the RBCs and destruction by macrophages [17, 18]. Plasma level of BUN is elevated in both groups and the BUN level was double in DA treated group (data not shown).

The results of the present study confirm the basis for choice of the type of ESA used to maintain the target Hb; different doses of DA can achieve the desired elevation of the target Hb. Furthermore, the use of DA maintained Hb levels at the recommended range, while equivalent doses of Eprex® did not only fail to induce the desired elevation in the Hb levels but also failed to stop fluctuation in Hb levels. These results are in agreement with previously published studies which showed that longer dosing intervals may lead to less variability over time leading to stable Hb levels in the target range (110-120 g/l) [19]. The efficacy of DA over Eprex® may be related to difference in structure. DA contains two additional N-linked oligosaccharide chain attachments to asparagine. Sialic acid content of the carbohydrate moiety has significant effects on the biological activity and serum half-life but inverse relation with receptor affinity [20]. The longer serum half-life of DA may increase biological activity and allow less frequent administration. It has been shown that DA termination half-life was 25.4 h following i.v administration whereas for Eprex® is only one third of that period [21], which is the rationale behind using DA less frequently than Eprex® while maintaining the stable levels of Hb [22, 23].

Another important aspect of this study is the difference in route of administration of the two drugs and the conversion factor used. Eprex® was administered intravenously while DA was administered subcutaneously. Pharmacokinetic studies performed on Eprex® administered during hemodialysis indicated that the bioavailability of subcutaneous Eprex® was lower but its half-life was longer than intravenous Eprex® administration [24, 25].

The other factor relevant to current discussion is the conversion factor used in this study. The initial recommended conversion factor was 200 IU of Eprex® = 1 µg of DA. However, there are several conversion factors that were used in previous studies. The difference in the conversion factors may be due to different designs of the studies or the geographical area or the quality of dialysis. However, it was reported that using fixed conversion ratio does not always ensure an equivalent conversion between the two dosage forms [26]. Arrieta et al., [16] studied the dose equivalence in relation to Hb stability and showed that using conversion factor of 300 IU Eprex® = 1 µg DA seems to be suitable for most patients receiving low dose of Eprex® while 350=1 for higher doses. The difference between conversion factors used at different doses may be related to losses of some efficacy of Eprex® at high doses. In the current study, the calculated doses for Eprex® using conversion factor; 300 IU =1µg were adequate for maintaining Hb levels within the recommended range (100-120 g/l). The results of the present study clearly demonstrate that DA QW was adequately more efficient for maintaining Hb level, RBCs and Hct within recommended ranges. However, it was reported that the cost of DA is double that of Eprex®. Using higher conversion factor in the present study can explain in part low cost of DA as, it appears to be more cost effective than Eprex®. In addition less frequent administration of DA may decrease healthcare costs and save nursing time.

The results of the present study are consistent with the recently published data showing that DA QW is more efficient in achieving target Hb, with minor vascular access complications using the conversion factor 200:1 [27]. Although, a conversion factor of 300:1 was used in this study DA was still more efficient than Eprex® in the first 8 weeks of treatment. Moreover, the present study showed no major influencing factors as chronic inflammatory disease or malignancy reported in the study cases.

CONCLUSION

This study findings suggest that DA QW seems to be more efficient in ameliorating blood indices (RBCs, Hb, Hct) despite using equal doses of Eprex® QTIW. This may be due to longer duration of action of DA. No significant changes were observed in all other hematological parameters evaluated in this study. Further studies are highly warranted to elucidate the effects of both drugs for longer follow-up periods.

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Conflict of interest
The authors of this manuscript have no conflicts of interest to disclose.

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