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Research Article

PDpoetin immunogenicity compared with Eprex ,in patients undergoing maintenance hemodialysis

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ABSTRACT

Background: Anemia of chronic kidney disease(CKD)is primarily characterized by reduced erythropoietin production from the kidneys .Availability of recombinant human erythropoietin (rHu-EPO) has successfully changed the management of CKD anemia. Some erythropoietin products may elicit an antibody response in CKD patients which rarely result in pure red cell aplasia (PRCA).This study was conducted to compare the immunogenicity of two Epoetin alfa preparations, PDpoetin and Eprex. **Methods:** This experimental study was performed on 68 patients (40males and 28 females),undergoing conventional maintenance hemodialysis. The patients were randomly divided in two groups ,EP(31 subjects) and PD (37 subjects)who received 50-100 U/kg of subcutaneous Eprex and PDpoetin, thrice weekly. Data were collected by using a questionnaire. The anti-rHu-EPO antibody level, in all patients were measured by ELISA method, 3 months after EPO therapy. All data analyses were carried out using, the SPSS , Chi-square ,Fischer and t-tests. **Results:** Only one patient of PD group had positive level of anti-EPO antibody and no difference was found between PDpoetin and Eprex in immunogenicity($p>0.05$). PRCA did not occur in any patient. There were no correlation between age, gender, hemodialysis duration, CKD causes , previous history of renal transplantation, hemoglobin level, administered EPO dose and anti-EPO antibody level. **Conclusion:** PDpoetin has not more immunogenicity than Eprex. Subcutaneous administration of PDpoetin may be a safe route . Further researches with larger sample size are recommended.

Key words: Anemia, Chronic Kidney Disease, Erythropoietin antibody , Pure red cell aplasia.

INTRODUCTION

Anemia is a common accompaniment of chronic kidney disease (CKD) and is mainly due to inadequate production of erythropoietin (EPO) from damaged kidneys .EPO stimulates erythrocytes proliferation and maturation in the bone marrow[1].The mean hematocrit(Hct) value decreases progressively when creatinine clearance reaches below 60 mL/min in men and below 40 mL/min in women . Anemia with Hct<33%, presents in more than 20% of patients only when glomerular filtration rate (GFR) becomes severely depressed (<30 mL/min in women and 20 mL/min in men)[2-4] .On the other word ,anemia(according to 2006 NKF-K/DOQI guidelines, hemoglobin level < 13.5 g/dL in men and < 12 g/dL in women)[5]becomes more frequent as renal function declines ,becoming almost universal in end-stage renal disease (ESRD)[3,6] .Anemia develops earlier and more severe in CKD patients with diabetes mellitus than in non-diabetic subjects[7,8] .Untreated anemia can lead to a number of physiologic abnormalities , including cardiovascular complications ,decreased survival and impaired quality of life[9]. The management of CKD anemia has been greatly changed with availability of recombinant human erythropoietin(rHu-EPO) since 1986[10] .There are many commercially available rHu-EPOs such as epoetin alfa , epoetin beta and darbepoetin alfa. PDpoetin is a variety of epoetin alfa, manufactured in Iran by cloning and expression of EPO cDNA in eukaryotic cell lines of Chinese hamster ovary, which has similar peptides sequence and biological activity of Eprex(another form of epoetin alfa) ,but different glycosylation sites[11]. PDpoetin has passed all phases of clinical trial successfully and has been approved by Food and Drug Department of Ministry of Health and Medical Education of Iran[12].Unfortunately, administration of rHu-EPO has been accompanied with neutralizing anti-rHu-EPO antibody production in CKD patients .These antibodies inhibit erythroid colony formation from normal marrow[13]. Pure red cell

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aplasia (PRCA),an extremely rare antibody related side effect of rHu-EPO, has been reported only in 250 CKD patients worldwide, up to now[14].PRCA due to rHu-EPO has been almost exclusively observed in subcutaneous administration of Eprex and perhaps because of presence of leachates from uncoated rubber syringe stoppers, resulting in immunogenisity[15-17]. This study was performed to compare the immunogenicity of PDpoetin and Eprex.

MATERIALS AND METHODS

This experimental study was conducted on 68 anemic patients, undergoing conventional(3sessions/week) maintenance hemodialysis, at the Mustafa Khomeini Hospital ,Tehran , Iran . The participants were informed of study purposes and design and assured that participation was voluntary. A consent form was signed by each patient .The patients had to meet the following inclusion criteria:1-Undergoing maintenance hemodialysis for at least 3months.2-Lack of active systemic infection or immunologic diseases.3-Withdrawal from other rHu-EPO products at least 6weeks.4-Hct ⩽30% or Hgb level ⩽10g/dL.5-Basal serum ferritin >100ng/mL or «TSAT» >20%.On the other hand, the patients were excluded if there were any of the following:1-Malignancies, cerebrovascular accident(CVA),symptomatic ischemic heart disease(IHD) and systemic infection.2-Blood transfusion.3-Renal transplantation.4-Life threatening erythropoietin side effects such as seizures and vascular access thrombosis .The participants were randomly divided in two groups, including 31 Eprex receiving (EP) and 37 PDpoetin receiving (PD) subject.The patients of each group initially received subcutaneous doses[50-100U/kg/thrice weekly(after each dialysis session)] of Eprex[12] and PDpoetin[5], until achieving the target Hgb level of 11g/dL and not exceeding from 13g/dL(study end-point).Data were collected by using a questionnaire including, demographic variables, underlying disease, hemodialysis duration, past medical history(IHD,CVA, malignancies, hypertension and history of renal transplantation),drug history,blood pressure alterations, monthly iron parameters (ferritin, serum iron, transferrin saturation «TSAT», basal and weekly hematocrit/hemoglobin (in initial phase) and then 2weekly(in maintenance phase) measurements following subcutaneous erythropoietin administration. The anti-rHu-EPO antibody titer in all patients were measured(single blind manner)by Enzyme linked immunosorbent assays(ELISA) method at the manufacturer laboratory (Poyesh Daroo), after at least 3 months of EPO therapy. Also, according to 2006 K/DOQI guidelines, diagnostic criteria for anti-EPO related PRCA(for at least after four weeks of EPO therapy) were defined as following[5]:1-Decline in hemoglobin level of more than 0.5 to 1.0 g/dL/week, or transfusion requirement of at least one to two units per week to maintain adequate hemoglobin.2-Normal platelet and white blood cell count.3-Absolute reticulocyte count of less than 10,000/microL.All data analyses were carried out using, the SPSS *v* 11.5, Chi-square ,Fischer and t-tests .P value < 0.05 was considered statistically significant.

RESULTS

The study population consisted of 68 hemodialysis patients(40males and 28 females),aged 21-80 years with mean value of age 49.57 ± 15 years .The gender distribution in EP and PD groups was as following: 17 males-14 females and 23 males-14 females, respectively.Among 68 patients, only one patient who received PDpoetin had positive level (>1.5 ng/mL**)** of anti-EPO antibody and no significant statistical difference was found between PDpoetin and Eprex in anti-EPO antibody development .Therefore, PDpoetin had not more immunogenicity than Eprex [(p=0.07),mean level of anti-EPO antibody against PDpoetin and Eprex: 0.76±0.08 , 0.84±0.22 ng/mL, respectively].Pure red cell aplasia(PRCA) was not observed in any patient. The efficacy of PDpoetin in Hgb rising ,in comparison to Eprex, did not differ significantly(p>0.05) and at the endpoint there was no difference in hemoglobin levels between treatment regimens .There were no correlation between age, gender, hemodialysis duration, CKD causes , previous history of renal transplantation, C-reactive protein, Hgb level, administered EPO dose and anti-EPO antibody level.

DISCUSSION

This study revealed that PDpoetin has not more immunogenicity than the other Epoetin alfa preparation(Eprex) .Also, PRCA was not observed with PDpoetin administration. It seems the vast majority of cases of EPO-related PRCA have occurred in patients treated with a particular epoetin alfa preparation , Eprex (in single use syringes) .Altered antigenicity has been suggested as the underlying cause of anti-EPO antibody development. Although the precise mechanisms is unclear, possible explanations thus far include use of polysorbate as a stabilizing agent and the presence of organic compounds leached by polysorbate from uncoated rubber stoppers in prefilled syringes which act as adjuvants to increase the immunogenicity of Eprex [15,16,18].In addition, under conditions of inappropriate storage and handling, such as high temperatures, EPO molecules may aggregate and elicit an antibody response[19]. On the other hand, all reported cases of anti-EPO mediated PRCA have occurred in patients with

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CKD who have received the drug subcutaneously[20] and as we know ,subcutaneous administration of other drugs has been also associated with greater immunogenicity than with intravenous administration[21]. Replacement of uncoated rubber stoppers with fluoro-resin coated stoppers and intravenous administration of Eprex with polysorbate have been associated with lowering PRCA occurrence[22,23].However, there is no advantage for intravenous administration of EPO over subcutaneous administration, in 2006 K/DOQI guidelines[5]. In our study, despite subcutaneous administration of PDpoetin, because suggested above causes were absent, the incidence of anti-EPO antibody development was estimated 0.014.Whereas, our study population was small we can not judge about probable role of PDpoetin in PRCA occurrence and incidence, in comparison to other studies[24,25].The efficacy of PDpoetin and Eprex on Hgb rising did not differ and our previous study has demonstrated the favorable safety and tolerability profile of PDpoetin in CKD patients. During PDpoetin clinical trial study, no long-term adverse events were identified[12]. As with other rHu-EPOs, the most common adverse event was hypertension that may be attributed to increased blood viscosity secondary to anemia correction particularly when anemia correction is achieved rapidly or more than hemoglobin target. Also, enhanced vascular reactivity and vasoconstrictor responses have been thus suggested to play a role. The dose-related response harbors this idea that switching patients from intravenous to subcutaneous therapy, by lower doses, may reduce the incidence of adverse events including hypertension. This was suggested by Navarro et al study[26].Similar to Nicholas study, we did not find any correlation between age and anti-EPO antibody development[27].Lack of difference of anti-EPO antibody development between males and females ,while the females in our study had greater mean value of age ,compared with males(51.71 ± 16.9 *vs* 48.08 ± 13.7 years), confirms that the age could not impact on antibody development.

SUMMARY

PDpoetin has not more immunogenicity than Eprex which is attributed to cause the vast majority of EPO-related PRCA and antibody development . Subcutaneous administration of PDpoetin may be a safe route and PDpoetin is as effective as Eprex for hemoglobin rising in CKD patients without more serious adverse effects .However, further researches with larger sample population and longer duration are recommended.

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