

**Title of the study:** MIR-EPO study

**Efficacy of the Mircera® after switching from beta epoetin in chronic hemodialysis patients and analysis of the factors associated with the change in doses**

**PERIOD OF STUDY:**

Approval Protocol by ethical committee: 07/22/2009

Approval Protocol by Spanish Agency for Medicines and Health Products, Ministry of Health, Social Policy and Equality.AEMPS final Version: Version 2: 01/20/2010

Star of the study:10/24/2011.

First patient included: 06/07/2011.

Completion of patient's recruitment: 11/22/2011.

Notification of end of the trial to the ethical committee and to by Spanish Agency for Medicines and Health Products, Ministry of Health, Social Policy and Equality 10-30-2012.

Notification of the results to the ethical committee and to by Spanish Agency for Medicines and Health Products, Ministry of Health, Social Policy and Equality: 24/04/2013.

**OBJECTIVES:**

- **Primary:** Determine the percentage of patients who maintained stable plasma hemoglobin concentrations after the conversion of weekly epoetin beta (HrEPO) to monthly MIRCERA® and the average difference in the change of plasma hemoglobin (Hb) achieved between the two groups.
- **Secondary:** Analyze the factors associated with changes on erythropoietin stimulating agents (ESA) doses. The safety and tolerability of ESA was assessed by analysing the changes in office blood pressure along the study and by reporting serious adverse events.

**STUDY DESIGN:**

It is a clinical, descriptive and analytical study with a parallel design and randomized. Selected patients, were randomized by computer program in two groups. Group A: continued with three times weekly epoetin-beta (Neorecormón®) and Group B: changed to monthly beta methoxy-polyethylene-glycol epoetin (MIRCERA®) according to dose recommended by technical sheet.

The study protocol designed 24 weeks of follow-up. The 12 first weeks as a titration period and the last 12 weeks as an evaluation period. Clinical and analytical evaluation was performed every four weeks.

Hemoglobin stability was defined as change from baseline  $\leq 1$  g/dl.

**NUMBER OF SUBJECTS:**

The total planned recruitment (20 patients in each group) was not reached due to a warning report from the Spanish Medicines Agency (publication on January 19, 2012) about "*Quality deviations in Mircera® manufacturing and recommendations for changing to another epoetin*"

([http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/calidad/2012/NI\\_MUH\\_01-2012\\_calidad.htm](http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/calidad/2012/NI_MUH_01-2012_calidad.htm)).

**INCLUSION CRITERIA:** : i) same type of haemodialysis filter during the 12 weeks prior to their inclusion; ii)  $Kt/V \geq 1.2$  (Daugirdas-2<sup>nd</sup> generation); iii) plasma Hb ranged from 10.5 to 12.0 g/dl, during 12 weeks prior to inclusion; iv) treatment with stable doses of EB ( $\pm 1,000$  IU/week) with a dosage regimen of 1 to 3 times weekly for 3 months before inclusion; v) transferrin saturation (TSAT)  $\geq 20\%$  and/or serum ferritin  $> 100$  ng/ml.

**EXCLUSION CRITERIA:** i) New York Heart Association class IV congestive heart failure; ii) active bleeding episode or history of transfusion within 8 weeks prior to their possible inclusion; iii) other causes of anaemia (neoplasms, folic acid or vitamin B12 deficiencies, haemoglobinopathies or haemolysis); iv) acute or chronic infectious process; v) uncontrolled systemic inflammatory disease; vi) poorly controlled hypertension; vii) current immunosuppressive therapy; viii) thrombocytopathies; ix) aplastic anaemia; x) pregnancy or gestational desire; xi) refusal to participate in the study or to sign informed consent.

#### **TITRATION OF ERYTHROPOIETIC AGENTS PROTOCOL:**

The study protocol was made up of a 24-week evaluation period where clinical and laboratory data were collected in a monthly basis. Then, the first 12-week post-inclusion (titration period), we adjusted ESA dosage according to the following protocol: i) ESA dosages were increased by 25% for Hb decreases  $< 2$  g/dl or Hb  $\geq 9$  and  $< 11$  g/dl or by 50% when Hb decreases  $\geq 2$  g/dl or Hb  $< 9$  g/d; ii) ESA dosages were decreased by 25% for Hb increases  $\geq 1$  g/dl or Hb  $\geq 12$  and  $\leq 14$  g/dl, or by 50% for Hb increases  $> 2$  g/dl. If Hb was  $> 14$  g/dl, we temporarily stopped ESA for a month. Then, we restarted ESA administration with a 25% reduction of the lower dose previously administered. During the evaluation period (last 12 weeks), we only made further dose adjustment according to the same protocol if necessary.

Intravenous iron supplementation (100 mg of iron sucrose) was prescribed in order to maintain TSAT levels  $\geq 20\%$  during the study as needed.

#### **Statistical method:**

An analysis of the variables studied, demographic and concomitant treatments at the baseline time after randomization to determine the homogeneity of both groups, using Chi-square analysis or if necessary exact Test of Fisher, T's Student or Wilcoxon Test in case of non-parametric variables.

A general linear model for repeated measures has been implemented to assess the variation in the levels of Hb; as well as to identify the influence of different treatments both intra-group and inter-group, as well as it adjusted to the significant covariates.

The percentage of stable according to the assigned treatment group patients were evaluated with the Chi-square test.

#### **RESULTS:**

From 189 screened patients, 38 patients were included, one of them was incorrectly included; so only 37 patients started the study. 19 were allocated to Mircera® and 18 to continued with beta-epoetin and were included as intention to treat population. 15 patients at the Mircera® group and 16 from the beta-epoetin group completed the study (per protocol population).

No differences in the percentage of patients with stable Hb at month 3 and 6 at the Mircera® in comparison with beta-epoetin were observed [10(66%) versus 9(56%);  $P=0.55$  and 8(53%) versus 11(68%),  $P = 0.47$ , respectively].

The difference between EB and CERA in mean change (95% CI) in Hb concentration between baseline and evaluation was 0.28 g/dl (-0.46 to 1.03) and 0.18 g/dl (-0.50 to 0.87) for the PP and ITT analysis, respectively.

No differences in the percentage of patients who needed changes in ESA doses between the two ESA types was observed (beta-epoetin versus Mircera®: 38(40%) times versus 32(36%) times,  $P=0.78$ ).

As a whole, there was interaction between iron utilization at the time of the study and ESA doses ( $P$  interaction = 0.01), the mean difference on ESA doses along the study between those patients with or without iron supplements at the time of the inclusion was 36% (95% CI: 6 to 66).

#### *Safety and tolerability*

There were no significant differences in the office systolic or diastolic blood pressure in any arm of treatment throughout the study. However, the differences in systolic blood pressure among arms of treatment at baseline disappeared at the end of the study, driven by a greater increase in EB group ( $9.8 \pm 5.2$  mmHg) compared with the evolution of the patients on CERA ( $7.1 \pm 4.6$  mmHg), independently of the number of antihypertensive drugs used and without significant changes in the dry weight of patients.

The SAE requiring hospitalization or emergency room care were higher in the CERA arm, however there were no statistically significant differences in the frequency of the suspected adverse reactions between the treatment groups (Table 1).

**Table 1.** Safety Outcomes requiring hospital admission or care in the emergency department

	All patients (N= 37)	Epoetin-beta (N=19)	Mircera® N= 18	<i>P</i>
AE, n°(%)	10 (60)	7(39)	14(82)	<0.01
Required transfusion(s), n (%)	1	0(0)	1(6)	1.00
Any SAE, n(%)	7(19)	1(6)	6(35)	0.04
Vascular access complications*	6(17)	2 (13)	4(27)	0.40
Suspected adverse reaction	7(19)	2(13)	5(33)	0.39
Death, n(%)	2(6)	0(0)	2(11)	0.22

#### **CONCLUSIONES:**

- No differences on Hb stability between weekly beta-epoetin and monthly Mircers® was observed.

-No differences in the mean Hb change during the study was observed.

-Intravenous iron supplementation was the factor associated with the change in ESA doses.

- Serious adverse events was higher in the Mircera® group, however no differences at the related adverse events between the two groups of the study was observed.

**Disclosures:**

Nothing to declare.

The MIR-EPO trial was a non-commercial study.