

- **ERYTHROPOIETIN TREATMENT IN CHRONIC RENAL FAILURE ANAEMIA -  
BIOSIMILAR OPTION IN THE RATIONAL USE OF MEDICINE PROCESS IN  
ORDER TO REDUCED PUBLIC HEALTH ECONOMIC BURDEN**

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**ABSTRACT**

Biopharmaceuticals innovation molecules have changed the course of a large number of chronic diseases. Many of these molecules became Gold Standards in oncology, rheumatology and other illness. However, their cost makes these drugs unattainable for most patients, and often put the health systems' budgets at risk. This study takes the anaemia due to Chronic Renal Failure disease (CRFD) as an example to a rational selection of treatment with erythropoietin (EPO) and compares the trade brand mark of this drug with biosimilars option.

Prescriptions of EPO in 394 patients with CRFD were submitted to a protocol of rational selection based in efficacy/risk ratio demonstration. This protocol was able to reduce that initial number to 91 cases that could really benefited with EPO treatment. These patients were included in a cohort study that compared EPO trade mark with biosimilars option. The experience demonstrated equal clinical outcomes in both groups but a reduction to half the original cost when biosimilars were dispensed. Biosimilars demonstrated to be a cheap and safe option to increase medicine access for anaemia associated to CRFD.

**Key words:** *Biosimilars, anaemia, chronic, failure, renal, cost*

## INTRODUCTION

Biopharmaceuticals products are drugs containing substances derived from biotechnology as active ingredients<sup>1</sup>. These molecules were developed back in the early 1980s and certainly changed the course of a large number of chronic diseases and have inadvertently been introduced into the daily lives of patients suffering from hepatitis, rheumatoid arthritis, chronic kidney failure, diabetes, multiple sclerosis, cancer and other pathologies that were previously untreated.

Traditional medicines are made by chemical synthesis processes and have simple chemical structures. In contrast, biotechnology drugs are manufactured using microorganisms such as bacteria or mammalian cells. The success of this technology was such that in the last decade have introduced to the market more than 200 therapeutic molecules existing on a global scale.

Many of these molecules became Gold Standards in oncology, rheumatology and other high-impact diseases, however, their cost are up to 200,000 USD per year (almost 100 times cost of a traditional drug)<sup>2</sup>. This high cost is usually due to the complexity of its structure, as well as the manufacturing, the control and the research processes<sup>3</sup>. Those Pharmaceutical companies that develop a new products claim by itself the patent of the discovery<sup>4,5</sup>, and anyone that wants to produce these molecules, has to pay a high fee. Hence, this situation avoids market competition and sustain over time soaring prices that health systems may not assimilate in the future. For this reason, the access to these medicines will not be guarantee for everyone. Governments must arbitrate the measures to provide suitable coverage to the population with these needs. One of the best strategies to do so is the adoption of a policy on the rational use of medicines. This means select medicines with proven efficacy and with the best benefit/risk/cost ratio. Once the medicine is selected, other strategies are related to the choice of the medicine provided by the market. Due to the fact that some patents of the original biological molecules have recently expired, or are due to expire, it exists opportunities for small or local pharmaceutical companies to develop and produce either generic or biosimilars drugs.

Biosimilars differ from conventional generic drugs in various aspects, such as the size of the active substance, its complexity, the nature of the manufacturing process and the fact that they are not identical to the original products<sup>6</sup>. Biosimilars might be then pharmaceutical alternatives of "innovative" products at a lower cost<sup>7-10</sup>. In order to demonstrate so, we performed a strategy of RUM followed by a cohort study in which biosimilars were compared with original molecules in terms of clinical outcomes and cost of treatments to treat anaemia associated to Chronic Renal Failure disease.

## **METHODS**

### Type of study

The proposal of the study was framed in stages: the first one based in a rational selection of medicines strategy in order to validate the Erythropoietin (EPO) indication to treat the anaemia associated to Chronic Renal Failure disease (CRFD) in patients under haemodialysis. The second stage was the development of a cohort study in which patients were divided in two groups based on the type Erythropoietin (EPO) used to treat the disease either original trade mark or biosimilars molecule. Clinical outcome and cost of treatment were the main variables included in the analysis.

### Population

Social security beneficiaries of Buenos Aires State coverage, affected by anaemia associated with chronic renal failure in haemodialysis in whom EPO was indicated were included in the study.

### Inclusion and Exclusion Criteria of patients to the study

For the present study, authors adopted the recommendations of clinical practice of the Latin American Society of Nephrology and Hypertension (SLANH) for the treatment of anaemia in patients with chronic kidney disease<sup>8</sup>.

### Period of study

01/01/2015 to 31/12/2016

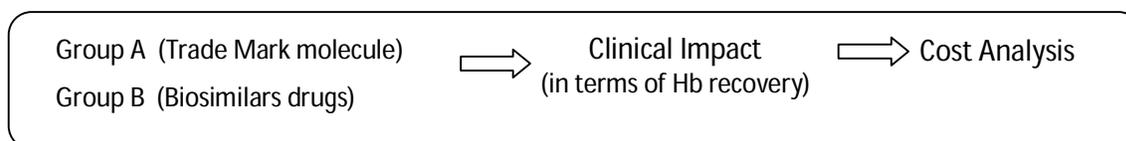
### Cost evaluation

The cost of the medicines was considered as defined daily dose (DDD) for patient treated. The baseline costs were extrapolated to a national coverage in order to determinate the global cost for Argentina. To compare the cost of each type of EPO ampoules, it was considered the commercial presentation of 2000 Units.

## RESULTS

The number of patients with CRFD in haemodialysis living in Buenos Aires State during the period of study was 10882 patients (4640 females / 6242 males). 1451 of those patients had social security coverage. Prescription of EPO was performed in 394 of those patients. However, after submitting the prescriptions to a RUM analysis the amount that really needed EPO were 91 patients. Patients excluded had either iron or folic acid deficiency or lack the strict criteria of use of EPO. From the 91 patients, only 60 of them had access to the EPO treatment and were included in the present study (35 men and 25 women). Their average age was 57 +/- 14 years old. Two groups were considered according to the type of EPO dispensed (either original molecule or biosimilars-figure 1). Basal blood test was performed in all cases (table 1).

**Figure 1. Cohort of Patients according to group of treatment**



**Table 1. Baseline data**

Group according to type of EPO	n	Hb gr/dl	Ht %	Ferritin ng/ml	Ferremia γ%	TSAT	TIBC
Trade mark	30	9.3 ± 0.9	28 ± 4	598 ± 303	88,4± 1	37 ± 13	159 ± 22
Biosimilars	30	9.1 ± 1.1	27 ± 1	584 ± 202	90,5± 7	36 ± 19	156 ± 46
Statistical difference		NS	NS	NS	NS	NS	NS

EPO: Erithropoietin; Hb: Hemoglobin; Ht: Hematocrit; TSAT: Transferrin; TIBC: total iron transport capacity

Ferritin values observed ranged from 173 to 987 ng/ml, transferrin saturation (TSAT) oscillated between 19 and 78%. Serum iron also showed marked oscillations (76,8-182  $\gamma\%$ ). Although serum iron profile disparity was observed in both groups, these results were similar in both groups and not find significant differences were detected (table 1).

The defined daily dose for Erythropoietin was 1000 Units (or its equipotent dose for biosimilars molecules), assuring a weekly dose of 6000 UI to complete the period of treatment established before the new blood control test.

After 4 weeks of treatment, five patients were excluded from protocol (2 from trade Mark drug and 3 from biosimilars). The cause of these exclusions was protocol violation in all cases (patients did not respect the weekly dose established in the protocol).

Results of blood test after a month of EPO treatment is shown in table 2. It is also shown in that table, the improvement of performance status referred by the patients in relation to basal survey.

**Table 2. Treatment Clinical and Laboratory Outcome**

Group according to type of EPO	n	Hb	Ht	Ferritin	Serum Iron	TSAT	TIBC	PS improvement from basal state
Trade mark	28	11.7 $\pm$ 0.6	35 $\pm$ 3	601 $\pm$ 275	78,4 $\pm$ 1	38 $\pm$ 12	159 $\pm$ 22	33,6%
Biosimilars	27	11.8 $\pm$ 1.6	34 $\pm$ 9	597 $\pm$ 263	70,5 $\pm$ 7	38 $\pm$ 16	156 $\pm$ 46	35,1%
Statistical difference		NS	NS	NS	NS	NS	NS	0.04

*EPO: Erythropoietin; Hb: Hemoglobin; Ht: Hematocrit; TSAT: Transferrin saturation; TIBC: total iron binding capacity test. PS: Performance Status*

In relation to the cost of EPO, the first surprising observation is that for the presentation of ampoules of 2000 U, there is a difference of 340% between the costs of the original biological molecule, but the most remarkable tip was that even between biosimilars, the

cost of more expensive option doubles the cheaper one. (21.77 USD vs 9.6 USD per ampoule of 2000 U) (table3).

**Table 3 Cost analysis of EPO molecules**

<b>Type of EPO</b>	<b>Price USD</b>
Original Brand	22.28
Biosimilar 1	12.26
Biosimilar 2	21.77
Biosimilar 3	9.6

*Presentation dose were syringe of 2000 UI for all cases  
USD: United States dollar.*

## **DISCUSSION**

Biosimilars pricing worldwide has commonly seen cost reductions up to 30% less than the reference products<sup>11-12</sup>, however our shows that there are still opportunities for biosimilars to provide even more significant discounts in certain countries.

Most of the available literature on biosimilars has focused on the critical analysis of their specific market authorization procedure. Only few papers are addressed to demonstrate biosimilars competition and its subsequent impact on price erosion<sup>11-13</sup>.

Companies that produce brand-name drugs are gradually abandoning their strategy of competing with their biosimilars counterparts for a policy aimed at improving their formulations, expression systems and the delivery methods<sup>20</sup>. For example, Amgen's first-generation epoetin alfa which has multiple weekly doses are changing its strategy towards the development of new products (second-generation epoetin alfa) that provides an only weekly injection. This fact opens an scenario that opens new opportunities to incorporate classical biosimilars products in emerging markets at a lower price to treat well known disease like anaemia in chronic renal failure disease (CRFD) in which outcome benefits was already demonstrated.

CRFD is a global public health problem. The most serious manifestation of renal disease is chronic renal failure that requires dialysis<sup>14,15</sup>. At the global level, the prevalence of Chronic Kidney Disease (CKD) in the elderly of 20 years is 17%. The CRFD

usually coexists with anaemia that needs high cost medicines like Erythropoietin (EPO) to be treated.

In our work is shown that the rational selection of patients that should receive EPO is the most cost/effectiveness decision to be made. In fact, after the selection process from the 394 prescriptions done, only in 91 patients the EPO was kept. That means that 76.9% of the prescriptions were inconsistent with the indication criteria.

On the other hand, once the validation of the treatment is demonstrated, the procedure of RUM continues with the selection of the type of EPO it should be used according to cost/effectiveness analysis. Here is where biosimilars have their place.

The present study shows that when biosimilars were used instead of brand market molecules, it could be obtained the same clinical outcomes and also save money of health service budgets in concept of treatment. In economical terms, it could be said that using the selection procedure, there is a net saving per year of 844.800 USD only in this drug and for this indication in the State of Buenos Aires, Argentina.

## **CONCLUSION**

This study reflects that rational use of medicine procedure may help to select the best treatment for anaemia in CRFD. The RUM procedure performed in this study included the use of a biosimilars selection, which was able to reduce the treatment cost by half of the original price. Policies that promote biosimilars use and production in developing countries like Argentina might be reflected in saving public budget of the health system, which can be a way of include more population into the health care coverage, increasing their access to health services.

Policy makers have then a challenge for in the coming years that will be to set effective measures leading to improved biosimilar uptake. Expectations on future savings for emerging markets la Argentina related to forthcoming biosimilars are a key driver for interest and concern from national authorities on biosimilar current market penetration, which becomes a clear opportunity in terms of savings cost in Health public Institutions.

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