A strategy to reduce inflammation and anemia treatment’s related costs in dialysis patients

ABSTRACT
This is a post-hoc analysis evaluating erythropoiesis stimulating agents’ (ESA) related costs while using an additional ultrafilter (Estorclean PLUS) to produce ultrapure dialysis water located within the fluid pathway after the treatment with reverse osmosis and before the dialysis machine. Twenty-nine patients (19 treated with epoetin alfa and 10 with darboepoetin alfa) were included in the analysis. We showed to gain savings of 210 € per patient (35 € per patient each month) with epoetin alfa during the experimental period of 6 months, compared to the control period and of 545 € per patient (90 € per patient each month) with darboepoetin alfa. Estorclean PLUS had a cost of 600 € (25 € per month per each patient) and was used for 6 months. Intravenous iron therapy with sodium ferrigluconate had a cost of 0.545 €/62.5 mg.

In conclusion, during the experimental period with the use of Estorclean, we obtained global savings of 11 € per patient per month with epoetin alfa and 30 € per patient per month with darboepoetin alfa to treat anemia in dialysis patients.

KEYWORDS: Anemia, costs, dialysis, dialysis bath
INTRODUCTION

Anemia is a relevant feature related to mortality and morbidity in Chronic Kidney Disease (CKD) (1). Already in 1905 Carnot and Deflandre hypothesized the existence of a humoral factor, called emopoietin, regulating red blood cells production (2). Later in 1977, Miyake and coll managed to purify the human erythropoietin (EPO) (3). In 1985 Lin and Jacobs cloned the gene of erythropoietin and developed transfected cells able to produce recombinant human erythropoietin. This innovation completely revolutionized the therapy of anemia in CKD and dialysis patients, reducing the frequency of transfusions, comorbidities and hospitalizations and ameliorating survival patients (4). On the other hand, the use of EPO increased global dialysis related costs. Since economic advantages deriving from reduced hospitalizations and transfusions rate is not always accounted in pharmacoeconomic evaluation by regulatory companies, there has been a continue disagreement between clinicians and health care organizers, particularly at the same of time of biosimilar erythropoiesis stimulating agents (ESA) marketing (5).

EPO amount needed to treat anemia in dialysis patients is conditioned by several factors (such as iron state, dialysis adequacy, inflammation) that may lead to increase the dose in order to achieve the therapeutic target. Our group showed that, besides the already known factors causing microinflammation, the presence of bacterial DNA in the dialysis bath is related to microinflammation and EPO resistance (6).

This is a post-hoc analysis of our previous study evaluating EPO costs related to the use of an additional ultrafilter (Estorclean PLUS) positioned within the fluid pathway after the treatment with reverse osmosis and before the dialysis machine (6).

Methods

The study had a cross-over randomized design. Details of the study and characteristics of the ultrafilter (Estorclean PLUS) were described elsewhere (6).

In the post-hoc analysis we included the patients treated with epoetin alfa (n=19) and darboepoetin alfa (n=10). Patients treated with methoxy-polyethylene-glycol-epoetin beta (n=3) were excluded because there is no correction factor to calculate the erythropoiesis resistance index (ERI: weekly dose of EPO/kg of body weight/hemoglobin levels) comparable to that of epoetin alfa and darboepoetin alfa.

The study was conducted at the Division of Nephrology of Solofra (Avellino, Italy). Thus, in order to evaluate costs related to the treatment of anemia in dialysis patients we considered reimbursement provided by ASL of Avellino for epoetin alfa (0,0037 €/UI) and darboepoetin (1,4045 €/mcg). We calculated monthly costs for each patients and separately for each type of erythropoietin; we also considered costs related to intravenous iron therapy with sodium ferrigluconate (0,545 €/ 62,5 mg of sodium ferrigluconate). We evaluated monthly hemoglobin levels and the correspondent ERI.

Since each Estorclean PLUS filter costs 600 € and can be continuously used over a period of 6 months for 4 patients using the same dialysis machine, its cost per patient is 25 € per month.
Statistical Analysis

Data were expressed as mean±standard deviation (SD) or median, as appropriate. Anderson-Darling method was used for normality test. We used the non-parametric Wilcoxon Signed Ranks Test to compare the distribution of matched measurement of a parameter in the two groups.

Results

Patients included in the analysis were 29, 19 out of them were treated with epoetin alfa and 10 with darboepoetin alfa. Eleven were men, with a mean age of 71±16 years and with a dialysis vintage of 48±32 months.

Figure 1 shows median values of hemoglobin of all patients for each month; significant changes appeared in the experimental phase from the third month after the use of Estorclean PLUS.

Figure 1

Median of hemoglobin per each month of the study

Figure 2 shows median values of ERI of all patients for each month; a reduction of resistance to erythropoietin was present after the third month.

Figure 2

Median of hemoglobin per each month of the study
Table 1 shows the amount of erythropoietin used each month for both groups of subjects treated with epoetin alfa (n=19) and darboepoetin alfa (n=10). All patients treated with epoetin alfa showed at the end of the experimental phase a reduction of EPO use of 1,084,000 UI, and those treated with darboepoetin alfa had a reduction of 388,000 mcg. The cost related to EPO during the experimental period varied from +163 to -1,302 € for epoetin alfa (with savings of 4011 € in 6 months, that is 211 € per patient), and from +674 to -1,460 € for darboepoetin alfa (with savings of 5449 € in 6 months and 545 € per patient).

<table>
<thead>
<tr>
<th>U of Epoetin alfa (n=19)</th>
<th>Control period</th>
<th>Experiment al period</th>
<th>Difference (Experiment al-Control)</th>
<th>€ saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>876,000</td>
<td>869,000</td>
<td>832,000</td>
<td>884,000</td>
<td>904,000</td>
</tr>
<tr>
<td>816,000</td>
<td>904,000</td>
<td>644,000</td>
<td>648,000</td>
<td>552,000</td>
</tr>
<tr>
<td>-60,000</td>
<td>-44,000</td>
<td>-18,000</td>
<td>-23,600</td>
<td>-352,000</td>
</tr>
<tr>
<td>-222</td>
<td>162.8</td>
<td>-695.6</td>
<td>-873.2</td>
<td>-1302.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mcg of darboepoetin alfa (n=10)</th>
<th>Control period</th>
<th>Experiment al period</th>
<th>Difference (Experiment al-Control)</th>
<th>€ saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>3200</td>
<td>3680</td>
<td>3360</td>
<td>3280</td>
<td>3120</td>
</tr>
<tr>
<td>3680</td>
<td>3280</td>
<td>2200</td>
<td>2240</td>
<td>2400</td>
</tr>
<tr>
<td>-480</td>
<td>-400</td>
<td>-1160</td>
<td>-1040</td>
<td>-720</td>
</tr>
<tr>
<td>674</td>
<td>-362</td>
<td>-1629</td>
<td>-1460</td>
<td>-1011</td>
</tr>
</tbody>
</table>

Monthly erythropoietin consumption in 19 patients treated with epoetin alfa and in 10 patients treated with darboepoetin alfa (expressed in units for epoetin alfa and mcg for darboepoetin alfa) and economic evaluation.

The reduction of pro-inflammatory cytokines levels observed with the use of Estorclean PLUS (6) allowed a better iron status, as shown in Table 2. During the experimental phase of the study, the total consumption of sodium ferrigluconate was of 52 phials with a monthly cost of 28,34 €, compared to 72 phials with a monthly cost of 39,24 € during the control period.

<table>
<thead>
<tr>
<th>Iron (mcg/dl)</th>
<th>Control</th>
<th>Experimental</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>48±24</td>
<td>64±18</td>
<td></td>
<td>0,006</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>175±47</td>
<td>214±40</td>
<td>0,001</td>
</tr>
<tr>
<td>Ferritin (ng/dl)</td>
<td>522±1219</td>
<td>350±328</td>
<td>0,466</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>21±14</td>
<td>31±11</td>
<td>0,004</td>
</tr>
</tbody>
</table>

Iron status of the included subjects (mean±SD) TSAT: transferrin saturation

Figure 3 shows savings gained with epoetin alfa, thus is about 11 €/patient/month, whilst Figure 4 shows savings gained with darboepoetin alfa, about 30 €/patient/month.
CONCLUSIONS

Inflammation has a relevant role in the pathogenesis of atherosclerosis and anemia, and is a risk factor for morbidity and mortality in CKD patients (7, 8). In dialysis population, the importance of sterility of the dialysis bath in the determination of inflammation is well known (6, 9, 10). In fact, there is a growing interest in the quality of dialysis water (11, 12, 13), and its impact on anemia in dialysis patients (14, 15), and also in the possible contamination of dialysis bath by bacterial DNA fragments (6, 16, 17).

We previously showed that the use of an additional ultrafilter to biosmosis improved inflammatory status of dialysis patients (6). In fact, we observed a reduction of pro-inflammatory cytokynes (-9.98 % for IL-6, -7.14 % for IL-8, -6.67 % for TNF-alfa) and an increase of anti-inflammatory cytokynes (+9.5 % for IL-4, +2 % for IL-17).

The benefit reached with the improvement of inflammatory status does not only impact on a better health state and improvement of anemia, but also the economic aspect with major savings.
and decrease of EPO costs related to dose reduction attained.

This post-hoc analysis showed during the experimental phase of 6 months, compared to the control phase, the possibility to achieve savings of about 210 € per patient (35 €/patient/month) with epoetin alfa and about 545 € per patient (90 €/patient/month) with darboepoetin alfa. Both amounts were higher than the cost of Estorclean PLUS (25 €/patient/month). Moreover, if we consider costs related to iron therapy, we obtained total savings of 11 €/patient/month with epoetin alfa and 30 €/patient/month with darboepoetin alfa.

This analysis is approximate because we did not measure the effect of using the ultrafilter on the cost-benefit ratio (that is, reduction of the number of hospitalizations, number of avoided deaths), neither the reduction of the risk related to fewer intravenous iron administrations (18). Therefore, further studies are needed to confirm the effects of Estorclean PLUS on cytokynes levels and inflammation status (19), and its economic impact.

Since the primary study was conducted at the Division of Nephrology of Solofra (Av), our economic evaluation for ESA and iron therapy was based on the exiting prices for the ASL of Avellino. Obviously, some differences may be found in other ASL or regions according to prices used.

Finally, the continuous use of Estorclean PLUS would lead to higher savings with a prediction of 27 €/patient/month using eritropoetin alfa and 115 €/patient/month using darboepoetin alfa.
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