

Cost-Minimisation Analysis of Erythropoiesis-Stimulating Agents in the Treatment of Anaemia in Dialysed Patients: A Pilot Study

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Abstract

Objective This study aimed to assess the cost impact of administering erythropoiesis-stimulating agents once every 4 weeks instead of one to three times a week to treat anaemia in patients undergoing dialysis.

Methods This was a monocentric retrospective study involving 27 patients who underwent haemodialysis between 2009 and 2013 in a university hospital in Angers, France. The study was a cost-minimisation analysis from the hospital perspective. Only direct medical costs were considered.

Results This study demonstrated that therapeutic management of anaemia with methoxy polyethylene glycol-epoetin beta would save medical and nurse time (7 days and 15 days per year, respectively) and reduce costs by €59,960 a year for an active file of 40 patients undergoing haemodialysis, assuming a 100% occupancy rate in the above-mentioned hospital.

Conclusion This study indicated that treating anaemia by administering erythropoiesis-stimulating agents once every 4 weeks instead of one to three times a week in patients undergoing haemodialysis would be beneficial for the hospital.

Key Points for Decision Makers

This study aimed to assess the cost impact of implementing a new therapeutic strategy for treating anaemia in patients undergoing dialysis.

Treating anaemia with methoxy polyethylene glycol-epoetin beta in patients undergoing haemodialysis may reduce costs related to the management of these patients in a hospital environment.

1 Introduction

The incidence of chronic kidney failure continues to increase in developed countries. This condition gradually progresses to end-stage chronic kidney failure, which requires replacement therapy—extra-renal purification or kidney transplant. This sustained increase in prevalence means that chronic kidney failure has become a significant public health concern in many countries, including France. According to the French National Authority for Health (Haute Autorité de Santé [HAS]) guidance note, *Medical and Economical Assessment of Kidney Failure Management Strategies in France* (September 2010), the prevalence of chronic kidney failure in France is one of the highest after the USA and Germany. French Renal Epidemiology and Information Network data from 31 December 2013 [1] estimated that 76,187 people were undergoing replacement therapy by dialysis or kidney transplant (i.e. 1163 people treated per 1 million inhabitants), 44% of whom were living with functional kidney grafts and 56% of whom were undergoing dialysis.

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One of the consequences of chronic kidney failure is anaemia caused by insufficient synthesis of erythropoiesis. It can cause systolic dysfunction and heart failure [2–4], and treating it in patients with chronic kidney failure increases the survival rate, reduces morbidity and improves quality of life.

In June 2013 [5], HAS published best practice guidelines for treating chronic kidney failure-related anaemia in order to slow the progression of heart complications and improve patients' quality of life. According to a recent HAS report [6], best practice guidelines set a target haemoglobin concentration of between 9 and 13 g/dl in patients undergoing haemodialysis being treated with an erythropoiesis-stimulating agent (ESA).

In 2007, a new ESA with a long half-life and a dosing schedule of one injection every 4 weeks reached the market. Therefore, an assessment of the cost impact of implementing a new type of management was justified.

Given the frequency of the disease and the cost of purchasing ESAs, treating anaemia in patients with chronic kidney failure is a major economic challenge. Evaluating the factors that define the medical costs related to ESAs can support decision making in the selection of the most efficient ESA for treating anaemia in patients with chronic kidney failure.

A literature review [7–9] indicated that administering methoxy polyethylene glycol (MPG)-epoetin beta once a month reduced costs and saved time; however, the results were not unanimous and key criteria were heterogeneous, making comparison difficult.

The Tempo [10] study assessed the amount of time that would be saved by switching from several injections a week (or twice a month) to one monthly injection. The results of this French study indicated that switching to one monthly injection would save up to 32.5 days of work per patient and per year for pharmacists/pharmacy technicians and nurses.

The results of these various works, combined with the current context of budget cuts and the search for efficiency, confirm the relevance of our study.

The objective of this study was to demonstrate whether treating anaemia with MPG-epoetin beta in patients undergoing dialysis reduced costs related to the management of these patients in a hospital environment. If so, this could translate into cost savings because of the time saved, mainly for nurses, which could in turn lead to a reorganisation of the haemodialysis service.

2 Methods

2.1 Design of the Study

Several studies [11, 12] have demonstrated that the efficiency and tolerance of MPG-epoetin beta is equal to that

of erythropoietins. Furthermore, on 19 December 2007, the French Transparency Committee [13] concluded that “MPG-epoetin beta has been as efficient as the other erythropoiesis-stimulating agents and has a similar tolerance profile,” confirming these results. Therefore, we chose to evaluate this new type of management using a cost-minimisation analysis.

A cost-utility analysis may have been possible. However, our study compared two therapeutic strategies (administration three times a week vs. once every 4 weeks) that have no direct impact on patients' quality of life. Indeed, patients are unaware of ESA administration because it occurs directly at the dialysis generator; neither the number of dialyses nor the general care of the patient changes. However, the literature review [2–5] did show that treating anaemia slows the progression of heart complications and reduces morbidity, thereby improving patient quality of life. Furthermore, the retrospective nature of our study meant we could not ask patients to complete a quality-of-life questionnaire, particularly as some of the patients had died.

This is a retrospective monocentric comparative ‘before/after’ study in which patients acted as their own control. We calculated only direct medical costs as defined in the traditional terminology of economic evaluation described in the French College of Health Economists methodological guide for the economic assessment of health strategies [14]. The study was conducted from the hospital's perspective and compared two methods of managing anaemia: administration of ESA one to three times a week (erythropoietin alpha or beta) versus every 4 weeks (MPG-epoetin beta).

Our hypothesis was that the implementation of a new administration method for treating anaemia in patients undergoing dialysis could reduce management costs in a French hospital environment.

2.2 Study Population

The population included patients aged >18 years undergoing haemodialysis who had anaemia that had been treated with an ESA one to three times a week over a 6-month period and a pegylated ESA once every 4 weeks over a subsequent 6-month period. This study enabled the comparison of two populations of patients (Fig. 1). Conversion from erythropoietin alpha or beta to MPG-epoetin

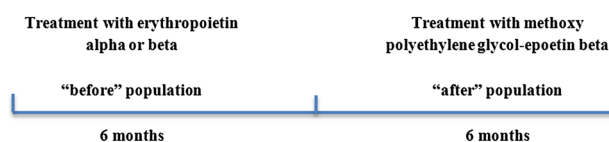


Fig. 1 Schema of the two periods of study

beta complied with the summary of product characteristics recommendations: The initial dose of MPG-epoetin beta was calculated based on the weekly dose of erythropoietin alpha or beta previously administered at the time of the substitution, and the first injection began on the date planned in the previous administration schedule for the erythropoietin alpha or beta.

Each patient acted as their own control. There were two types of measured parameters: fixed variables, measured once when the patient entered the study, and time-related variables, measured every month during the study. Data collection was retrospective over the period between 2009 and 2013.

2.3 Cost-Minimisation Analysis

The cost-minimisation analysis was carried out from the hospital perspective. Data were collected via follow-up of the cohort of patients undergoing haemodialysis who were treated with an ESA or a pegylated ESA between 2009 and 2013. The year of valuation corresponded to the year of ESA administration (2009–2013). Costs were calculated from negotiated real prices adjusted year to year. Unit cost values are detailed in Table 1. The evaluation was conducted over a 12-month period and assessed the direct medical costs (Table 2) related to resources that were likely to vary between the two therapeutic strategies over the time horizon. The costs were estimated according to a sophisticated approach to the real costs (micro-costing) and are expressed in €.

The average medical time per prescription of ESA represents the exclusive time for prescription with regard to the results of the biological balance sheet and was obtained

from real-world timing. The physician was the same person (a single physician) in both before and after groups.

We conducted a univariate deterministic sensitivity analysis (tornado diagram) using three relevant variables:

- time for ESA prescription per practitioner,
- time for ESA administration per nurse,
- cost of acquiring ESA.

Medical time includes the time from receiving the biological results and entering the data into the system until the prescription of ESAs. Nursing care time includes the time spent administering the ESAs, including removing the ESA from the refrigerator, disinfecting the injection area, preliminary control of the ESA according to the patient and the prescription (verifying concordance between patient identity and the dose prescribed for this patient before administering the ESA), administering the ESA (injection) and logging the administration (electronic traceability).

3 Results

3.1 Statistical Analysis of the Population

A total of 27 patients who underwent haemodialysis between 2009 and 2013 were eligible for this study (Fig. 2); 62% were men, and the average age was 70.3 ± 11.5 years. Diabetes (37.9%) and hypertension (58.6%) were the main cardiovascular risk factors. All patients were monitored in the haemodialysis service. The average ratio spKt/V (used to measure haemodialysis adequacy) was 1.6 ± 0.3 .

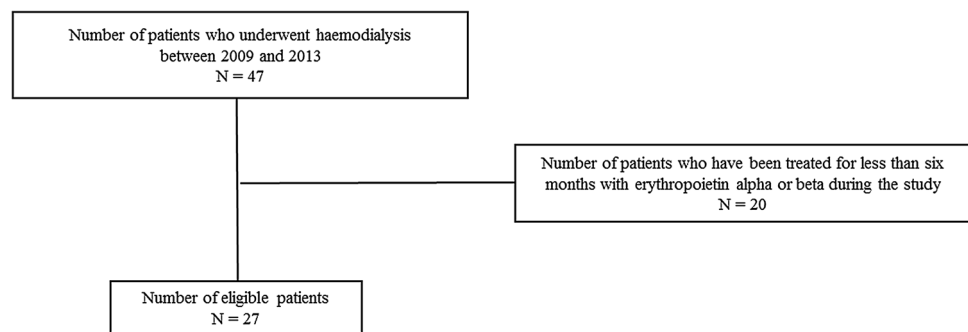
Table 1 Description of the unit cost values

Variable	Unit cost values (€)
Average hourly pay for hospital physician: 2010	42
Hourly pay for nurse: 2010	25
ESAs one to three times per week (varies according to year)	0.0035–0.0074 per IU
ESAs every 4 weeks (varies according to year)	1.4294–1.6234 per μg
Iron (varies according to year)	6.1260–13.2526 per vial
<i>ESA erythropoiesis-stimulating agent</i>	

Table 2 Description of the direct medical costs and method of their calculation

Cost description	Method of calculating the costs
Medical time for the prescription of ESAs	Average medical time per ESA prescription \times number of prescriptions
Nursing care time for the administration of ESAs	Average nursing care time per ESA administration \times number of administrations
Acquiring ESAs	Price, including all taxes, per unit \times number of units administered
Acquiring injectable iron	Price, including all taxes, per unit \times number of units administered
Administering ESAs (technical medical procedures)	Number of procedures for ESA administration \times two AMI
Administering injectable iron (technical medical procedures)	Number of procedures for injectable iron administration \times 2 AMI

AMI Acte Médico Infirmier (nursing procedure), ESA erythropoiesis-stimulating agent

Fig. 2 Cohort of eligible patients

No patients were naïve to ESAs. All patients had been treated with erythropoietin alpha or beta for at least 6 months then with MPG-epoetin beta for at least 6 months. The average administered dose of erythropoietin alpha or beta was 7389 IU per week or 29,556 IU per month. The average administered dose of MPG-epoetin beta was 148 µg per month (range 33–381).

The average blood haemoglobin level was 11.2 ± 1.1 g/dl in the ‘before’ population and 11.0 ± 1.2 g/dl in the ‘after’ population. Moreover, the haemoglobin level for 96% of patients matched the target of 9–13 g/dl recommended by the HAS, both in those following the 6-month treatment with erythropoietin alpha or beta and in those following the 6-month treatment with MPG-epoetin beta. Only one patient in the ‘before’ population did not reach (8.9 g/dl) the haemoglobin target recommended by HAS. This did not influence the cost-minimisation analysis of this group or the robustness of the cost-minimisation analysis in this study.

Iron supplementation was performed according to good practice and adjusted to maintain adequate iron status (ferritin > 100 ng/ml and transferrin saturation [TSAT] > 20%). The percentage of patients receiving supplementary iron at baseline was similar in each treatment group: MPG-epoetin beta 96% and erythropoietin alpha or beta 96%.

In total, 16 patients experienced one serious side effect and were hospitalised at least once in the course of the study. The most frequently observed serious side effects were influenza-like illness (five patients), deep vein thrombosis (two patients) and thrombosis at the fistula (two patients). Other less frequently observed serious side effects included sepsis, pulmonary oedema, respiratory distress, delirium and poorly controlled hypertension.

3.2 Results of the Cost-Minimisation Analysis

3.2.1 Cost Measurement

We considered only the direct medical costs related to the implementation of the two therapeutic strategies, which included all costs for hospital care (Table 3).

The cost-minimisation analysis showed that treating anaemia with MPG-epoetin beta in patients undergoing haemodialysis saved €40,464 per year (€133,166 vs. 92,702; Wilcoxon $p = 0.031$), corresponding to €1499 per patient per year. This represents savings of €59,960 per year for an active file of 40 patients (assuming a 100% occupancy rate).

A univariate deterministic sensitivity analysis (tornado diagram; Figs. 3, 4) carried out on three relevant variables (Table 4) confirmed these results were robust.

Table 3 Direct medical costs according to the type of anaemia treatment

Cost	‘Before’ group (6-month anaemia treatment with erythropoietin alpha or beta)	‘After’ group (6-month anaemia treatment with MPG-epoetin beta)
Medical time for ESA prescription	33.9 h	17.4 h
Cost of medical time for ESA prescription	€1424	€731
Nursing care time for ESA administration	39.4 h	5.5 h
Nursing care for ESA administration	€984	€138
Acquiring ESAs	€44,528	€38,058
ESA administration (AMI)	€13,054	€1134
Acquiring injectable iron	€4401	€3978
Injectable iron administration (AMI)	€2192	€2312
Total	€66,583	€46,351

AMI Acte Médico Infirmier (nursing procedure), ESA erythropoiesis-stimulating agent, MPG methoxy polyethylene glycol

Fig. 3 Graphical representation of the univariate sensitivity analysis (tornado diagram) on the ‘before’ population

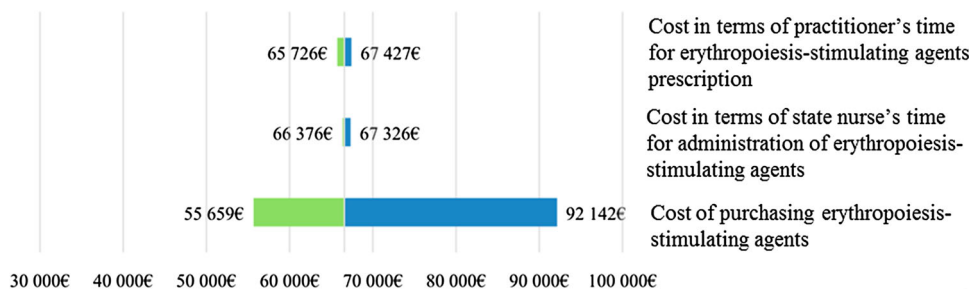


Fig. 4 Graphical representation of the univariate sensitivity analysis (tornado diagram) on the ‘after’ population

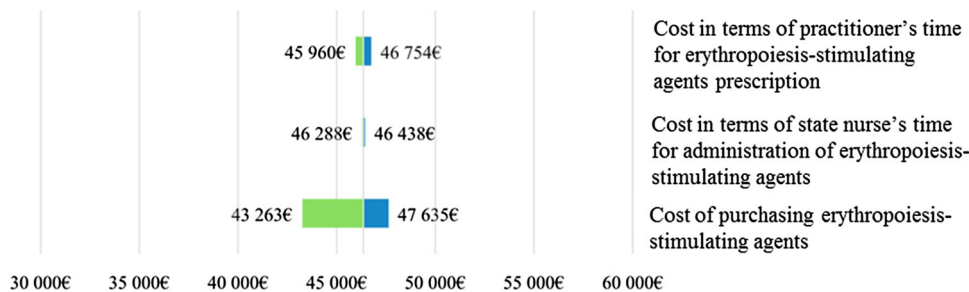


Table 4 Average value (€) and confidence interval of the variables used for the sensitivity study

Variables	Average value (95% confidence interval)	
	‘Before’ population	‘After’ population
Cost in time for ESA prescription per practitioner	1424 (567–2268)	731 (340–1134)
Cost in time for ESA administration per nurse	984 (777–1727)	138 (75–225)
Cost of acquiring ESA	44,528 (33,604–70,087)	38,058 (34,970–39,342)

ESA erythropoiesis-stimulating agent

These sensitivity analyses showed that the cost of acquiring ESAs had the greatest impact on the overall cost. This is particularly pronounced in the ‘before’ population. The results showed that treating anaemia with MPG-epoetin beta saved 49% of practitioner time over 1 year, representing 33 h per year or 1.2 h per patient per year. It also saved 7 days of medical time per year for an active file of 40 patients per year. The results showed that treating anaemia with MPG-epoetin beta saved 87% of nurse time over 1 year, representing 68 h per year or 2.5 h per patient per year. It saved 15 days of nursing care time per year for an active file of 40 patients per year.

The results of this study therefore confirm the hypothesis that treating anaemia with MPG-epoetin beta in patients undergoing haemodialysis may reduce the costs related to the management of these patients in a hospital environment.

4 Discussion

This study demonstrated that administering ESAs once every 4 weeks instead of one to three times a week saved 7 days of medical time and 15 days of nursing care time per year.

This result confirms those of Schmid [9] and the Tempo [10] study. Schmid [9] showed that changing the treatment of anaemia to MPG-epoetin beta could save a significant amount of nursing care time, but the majority of included studies were retrospective.

This result also confirms those of a recent prospective study [15] that found MPG-epoetin beta to be more cost effective than erythropoietin beta (incremental cost-effectiveness ratio continuous erythropoietin receptor activator vs. epoetin beta at –\$US6457.5, year 2013 values), making it the dominant treatment for the management of anaemia in patients receiving chronic haemodialysis.

Another recent cost-utility analysis [16] suggested that managing anaemia with MPG-epoetin beta compared with epoetin beta in patients receiving dialysis may result in better outcomes with higher overall costs, but there were limitations.

It is important to mention that patients receiving dialysis have a higher risk of mortality due to cardiac complications. Indeed, anaemia increases the work output of the heart by favouring left ventricular hypertrophy and remodelling the big arteries. Therefore, administration of erythropoietin would limit cardiac complications. Furthermore, erythropoietin, a hormone with antioxidant and anti-apoptosis effects, has a protective effect against ischemia

reperfusion. This hormone also controls angiogenesis and increases endothelial cells in the process of tissue repair. However, erythropoietin can also cause high blood pressure. Thus, it is important that haemoglobin concentration is stable around its target value. This indicates ESAs with a long half-life [4] are of clinical interest.

Treating anaemia with long half-life ESAs requires fewer administrations, which in turn appears to limit the risk of mortality by reducing variations in haemoglobin levels. Indeed, variations in haemoglobin concentrations appear to increase the risk of mortality, likely because of the repeated episodes of tissue ischemia that negatively affect organs such as the heart.

The amount of time saved (15 days per year for an active file of 40 patients per year) would allow nurses to allocate time to improving the quality of their work, in turn enhancing the quality and overall safety of care.

The change in management strategies also showed cost benefits: treating anaemia with MPG-epoetin beta in patients undergoing haemodialysis would save €59,960 per year for the 40 patients currently undergoing haemodialysis in this hospital.

These results confirm some results in the literature. Ranchon et al. [7] showed that direct medical costs, particularly the costs of purchasing ESAs, account for the largest portion of direct medical costs. Our sensitivity analyses also showed that the cost of acquiring ESAs had the greatest impact on overall costs.

In our study, the administered dose of MPG-epoetin beta varied between 33 and 381 µg per month, with an average administered dose of 148 µg per month. Our results showed that changing anaemia treatment to MPG-epoetin beta reduced treatment costs.

This study has limitations. We examined direct medical costs but not side effects associated with ESA treatment. Furthermore, the small size of our sample means these results only show a trend, and it would be interesting to undertake another study in several centres to increase the cohort size. This would strengthen the observations suggested by this pilot study. It would also be interesting to include side effects associated with anaemia treatment and data on patient survival and quality of life.

In conclusion, treating anaemia with MPG-epoetin beta in patients undergoing haemodialysis may reduce costs related to the management of these patients in a hospital environment.

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Author contributions The paper was conceived by A.D., C.C. and V.B. A.D. contributed the study design, statistical analysis and writing of the manuscript. C.C. brought her expertise as a health economist to the evaluation of medical economic. V.B. brought her clinical expertise as a physician in haemodialysis. C.C. and V.B. commented on initial drafts of the manuscript and approved the final version.

Compliance with Ethical Standards

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Conflict of interest Astrid Darsonval, Claire Cavalin and Virginie Besson have no conflicts of interest relevant to the content of this article.

Data availability statement The data that support the findings of this study are available from the corresponding author on request.

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