Erythropoietin Outcomes Assessment: Linking Clinical and Economic Parameters

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ABSTRACT

Human recombinant erythropoietin (Epo) is a mainstay in the treatment of patients with anemia of chronic renal failure (CRF), decreasing transfusions and improving the quality of life of patients who receive it. While Phase III trial-based cost-effectiveness studies have demonstrated the economic viability of prescribing Epo, post-marketing surveys which link drug utilization with clinical and economic outcomes are absent.

A retrospective assessment of Epo therapy was conducted in 68 hemodialysis patients. Clinical and economic outcomes were assessed to determine Epo's impact on health status and resource utilization. Overall, Epo increased hematocrit (Hct) and hemoglobin (Hgb) levels by an average of 25.1% and 24.4%, respectively. The mean (±standard deviation, (SD)) absolute Hct and Hgb levels achieved were 0.284 ± 0.04 and 96.3 ± 14.1 g/L, respectively, based on a mean Epo dose of 40.5 ± 21.1units/kg three times per week (3x/wk). Dosing requirements were also assessed in selected patient subgroups. The overall average Epo dose in patients with pre-existing hypertension (HTN) was 11.9 units (35.2%) more per kg 3x/wk than those with no underlying HTN. In patients without pre-existing HTN who then developed this condition, the average Epo dose was 12.1 units (42.8%) more per kg 3x/wk than in those patients who did not exhibit new onset HTN.

Considering drug costs and savings due to avoided transfusions and hospitalization, the total additional cost of Epo therapy from the perspective of the institution was $888 per patient per year. Thus, Epo improves hematologic indices in patients with CRF-induced anemia at an additional cost. Patients with HTN may require a different Epo dosing regimen, a previously unreported phenomenon which deserves further investigation.

Key Words: costs, erythropoietin, outcomes, utilization pattern

RÉSUMÉ

L'érythropoiétine recombinée humaine (Epo) est une pierre angulaire dans le traitement de l'anémie due à l'insuffisance rénale chronique (IRC). Elle permet de diminuer le nombre de transfusions et d'améliorer la qualité de vie des patients qui en reçoivent. Bien que des études coût-efficacité dans le cadre d'essais de phase III aient démontré la viabilité économique de l'administration de l'Epo, il n'y a toujours aucune étude post-commercialisation d'entreprise sur la relation entre l'utilisation du médicament et les résultats économiques et cliniques.

Une évaluation rétrospective du traitement à l'Epo a été menée auprès de 68 patients hémodialysés. Les résultats cliniques et économiques ont été évalués pour déterminer l'impact de l'Epo sur l'état de santé des patients et sur l'utilisation des ressources. Dans l'ensemble, l'Epo a accru les taux d'hématocrite (Hct) et d'hémoglobine (Hgb) en moyenne de 25,1 % et de 24,4 % respectivement. Les moyennes (±écart-type de la moyenne (ET)) des taux absolus d'Hct et d'Hgb qui ont été atteints étaient de 0,284 ± 0,04 et de 96,3 ± 14,1 g/L respectivement, en se fondant sur une dose moyenne d'Epo de 40,5 ± 21,1 unités/kg administrée trois fois par semaine (3 f.p.s.). Le schéma posologique a aussi été évalué chez des sous-groupes de patients choisis. La dose moyenne globale d'Epo chez les patients présentant déjà une hypertension artérielle (HTA) était de 11,9 unités (32,5 %) de plus par kg 3 f.p.s. que chez les patients ne présentant aucun antécédent d'HTA. Les patients qui ne présentaient aucun antécédent d'HTA et qui ont développé spontanément cette affection ont reçu une dose moyenne d'Epo de 12,1 unités (42,8 %) de plus par kg 3 f.p.s. que ceux qui n'ont montré aucun signe d'HTA.

En tenant compte des coûts des médicaments et des économies engendrées par l'évitement de transfusions et d'hospitalisations, le coût supplémentaire total du traitement à l'Epo, du point de vue de l'établissement, était de 888 $ par patient par année. Par conséquent, l'Epo améliore les indices hématologiques chez les patients ayant une anémie attribuable à l'IRC à un coût additionnel. Les patients hypertendus peuvent nécessiter un schéma posologique de l'Epo différent,

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The work outlined in this paper was supported by a summer student grant from Ortho Biotech (now Janssen-Ortho Inc.). The authors have no financial interest in Janssen-Ortho Inc., nor do they have any current contracts with or sponsorship from that company.

This paper is based on a study which was awarded the Merck Frosst Award for Rational Drug Use in the 1994-95 CSHP Awards Program.

une observation qui n'a jamais été rapportée jusqu'ici et qui mérite des recherches plus poussées.

Mots clés : coûts, érythropoiétine, profils d'utilisation, résultats.

Can J Hosp Pharm 1997;50:69-76

INTRODUCTION

Erythropoietin (Epo) is a hormone synthesized by the kidney which stimulates the production of red blood cells in bone marrow. In patients with chronic renal failure (CRF), damage to the kidneys decreases the amount of Epo produced, leading to chronic anemia and impaired blood oxygen carrying capacity.[1] In the past, the anemia of CRF has been treated with repeated blood transfusions, which have been associated with severe adverse effects and other undesirable therapeutic outcomes (e.g., iron overload, transmission of infectious diseases, antibody production and severe transfusion reactions).[2] Human recombinant Epo has proven to be a viable method of treating CRF anemia. It avoids the hazards associated with transfusion therapy, while improving patient quality of life (QOL) and care.[2-7]

The original economic evaluations of Epo therapy were based on efficacy data from randomized controlled trials in patients with CRF. A landmark Canadian study by Sheingold et al evaluated the potential effect of Epo on the utilization of health care services based on outcomes from a randomized clinical trial. Their analysis was based on the perspective of the health care system and they varied their major assumptions related to cost estimates for Epo therapy ($5,000 to $12,900 per year) and reductions in hospital days (four to eight days per year). The analysis demonstrated a range of effects on medical care costs: from a net savings of $1,775 per patient year (for patients with the lowest therapy costs and the greatest days of hospitalization avoided), to a net increase in medical care expenditures of $8,320 (for patients with the highest therapy costs and lowest days of hospitalization avoided)[base case net increase in costs of $3,425].[8]

The strict protocols used in clinical trials (i.e., efficacy studies) tend to bias pharmacoeconomic assessments, such that they may not reflect actual clinical use of the product. Decision makers need access to economic analyses which facilitate resource allocation in the real world. Two recent studies have reviewed the economics of the use of Epo from an effectiveness standpoint; that is, Epo's performance in usual practice outside the restrictions of a controlled trial. A British study examined the cost benefits of Epo and, like the Canadian study, there was an additional net cost to the health care system by using Epo in their population.[9] An American group assessed the cost effectiveness of Epo in peritoneal dialysis patients from an institutional perspective, and concluded that there was a net increase in costs within the first six months of Epo therapy.[10]

A recent drug use evaluation (DUE) involving a mixed group of renal patients assessed adherence to predetermined drug use criteria.[11] In addition, the investigators evaluated clinical outcome parameters achieved with this therapy. Hematocrit levels increased and transfusion rates decreased, but there was no attempt to link these outcomes to the funds invested into Epo therapy. Although Phase III trial-based, cost-effectiveness studies have reported the economic viability of prescribing Epo, and DUE studies have shown that the drug is effective when used appropriately, the literature reveals no post-marketing surveys which bring together economic and clinical outcome issues in patients treated with Epo.

The Health Sciences Centre (HSC) is the major purchaser of Epo for Manitoba, buying drugs for its own use and that of eight satellite dialysis centres. There have been notable increases (an average of 36% per year) in both total and HSC-specific purchases of the drug over the past few years (see Figure 1). This is a large increase which has accelerated over time, and is notably higher than the overall change in the drug budget for a comparable period (average increase of 16% per year). In addition to economic concerns, there is no in-house data regarding clinical outcomes associated with Epo use at HSC. Pharmacy and

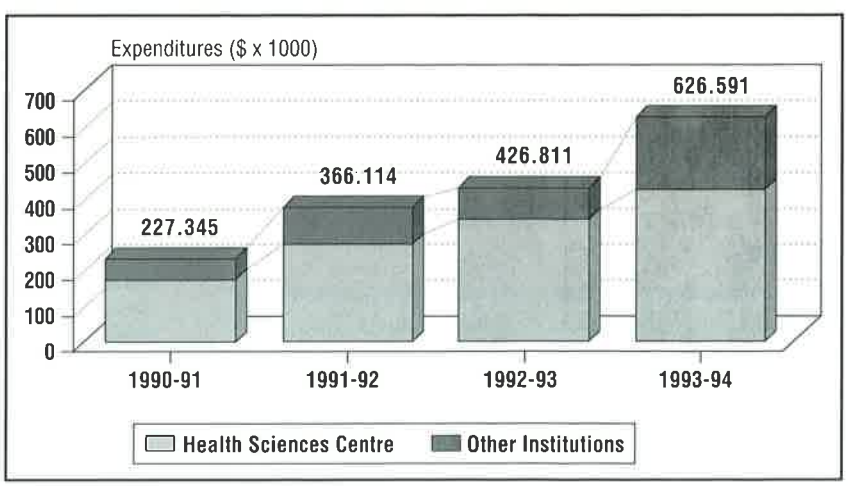

Figure 1. Erythropoietin Expenditures (HSC and other institutions serviced)

nephrology clinicians alike felt that the economic aspects of Epo therapy needed to be reviewed in the context of achieving acceptable clinical outcomes.

The purpose of the study was to survey the current utilization of Epo in patients with CRF undergoing hemodialysis at HSC, with the specific goal of determining the true costs of this therapy to the institution. Besides defining basic utilization patterns (i.e., dialysis site, patient population description), this study also describes outcomes in terms of administration issues (e.g., route, concurrent iron therapy, hematologic monitoring), clinical consequences (i.e., hematologic indices, transfusion rates, hospitalization and emergency room visits, adverse events) and the costs of therapy from the hospital's perspective (i.e., antihypertensive medications, Epo costs, iron therapy, per diem rates).

METHODS

A retrospective chart review was carried out and included the cohort of dialysis patients being treated with Epo on May 3, 1994. All patients were dialysed via HSC's Central Dialysis Unit (CDU) and Self-Care Dialysis Unit (SCDU). Since Epo prescribing is tightly controlled on a prospective basis, it was assumed that all patients met the criteria for Epo use (Appendix A). Data collection, collation and analysis were carried out from May to July 1994, inclusive. Information regarding patient demographics, Epo prescribing, hematologic outcomes and health care resource consumption were recorded. Epo data were recalculated based on the dose (in units, u) per kilogram (kg) three times per week (3x/wk) to standardize for the patient's dry weight and to allow for interpretation versus dosing guidelines in the product monograph (i.e., 50-100 u/kg 3x/wk). In those patients receiving Epo for less than three months, the investigators were not able to assess outcome data. However, baseline data for these patients were included. Analysis of the data was facilitated by using a relational database (R:Base®, version 3.5 for DOS, 1994, Microrim Inc., Bellevue, Washington).

Pre-existing HTN was defined by a diagnosis of HTN in the patient's chart and the presence of antihypertensive medications in the patient's therapeutic regimen. The development of Epo-induced hypertension was defined by the diagnosis of new-onset HTN in the patient's chart and/or the addition of (or the use of higher doses or more aggressive) antihypertensive agents to the patient's current therapeutic regimen.

Drug costs for iron products, antihypertensive medications and Epo were calculated based on HSC's acquisition costs for the lowest priced product (i.e., generic, where available). Epo treatment occurred over varying periods of time, so drug costs were annualized. Based on previous experience at HSC, it was assumed that there were no significant changes in hematologic monitoring before and after Epo therapy initiation. Thus, costs for laboratory tests were not evaluated.

Absolute values and descriptive statistics were used to summarize the majority of the data. Due to the observational nature of the study, limited statistical analysis was carried out (paired and unpaired t-tests).

RESULTS

General Results

A total of 70 cases of Epo therapy were reviewed in 68 hemodialysis patients. Two patients received two courses of Epo, separated by at least one year. Twenty cases were from the CDU while 50 cases involved patients from the SCDU. The demographics of these patients are outlined in Table I.

Epo Therapy Summary

The majority of patients (83%) received Epo via the subcutaneous route. The overall average current dose of Epo prescribed was 40.5 u/kg 3x/wk, corresponding to 38.2 u/kg 3x/wk in the SCDU and 46.0 u/kg 3x/wk in the CDU.

Hematologic Outcomes Summary

Table II outlines the physiologic response to Epo therapy. The average hemoglobin (Hgb) and hematocrit (Hct)

Table I. General Patient Demographics.

	Mean ± SD*	Range
male/female patients (number)	27/43	-
mean age (years)	50.3 ± 14.3	15.6 - 79.6
mean dry weight (kg)	64.7 ± 14.8	35.5 - 120.0
mean time on dialysis prior to initiation of Epo therapy (months)	35.5 ± 53.4	0.23 - 247.1
mean time on Epo (months)	18.3 ± 15.5	0.73 - 80.3

* SD = standard deviation

Table II. Overall Hematologic Response to Epo Therapy.

	Baseline (± SD)*	Initial (± SD)*	Current (± SD)*
Mean Epo Dose (u/kg 3/wk)	0	39.7 ± 17.7	40.5 ± 21.1
Mean Hct	0.227 ± 0.05 (n=66)$	0.274 ± 0.06	0.284 ± 0.04$
Mean Hgb (g/L)	77.4 ± 16.2 (n=67)$	92.7 ± 23.2	96.3 ± 14.1$

* "baseline" = value on initiation of Epo therapy; "initial" = value after a minimum of three months of Epo therapy; "current" = value at time of survey.
$ $p<0.05$
Note: "n" = 70 unless otherwise specified.

levels achieved on initial therapy (i.e., within the first three months on Epo), as well as on current therapy, are presented. In addition, the overall change in hematologic indices from baseline is summarized.

Epo Therapy in Hypertensive Patients

The additional antihypertensive costs attributable to the development or worsening of HTN after Epo therapy initiation was an average of $396.58 per patient per year. Because HTN is a known adverse effect of Epo therapy, the data were also evaluated in terms of the demography of HTN in the study population.

Thirty-nine cases (56%) involved patients with underlying hypertension (HTN) at the time of Epo therapy initiation. The incidence of HTN exacerbation by Epo in these cases was 41%. In the 31 cases without underlying HTN, the incidence of new onset HTN with the initiation of Epo was 47%. Tables III, IV, and V compare the differences in dosing requirements for the patients with and without preexisting HTN, and outline how these requirements varied depending on the incidence of Epo-induced HTN.

As noted in Table III, there were 16 patients who exhibited worsening of their preexisting HTN and 14 patients in whom new onset HTN developed subsequent to the initiation of Epo therapy. Key demographics and details regarding these patients and their therapy are listed in Tables IV and V.

Iron Therapy Summary

In 68 of 70 cases reviewed, patients had received some form of iron therapy at some point during their Epo therapy. Of these 68 cases, 47 (67%) started iron prior to the initiation of Epo treatment, eight (11%) cases started iron concurrently with Epo, 13 (19%) started after Epo was first prescribed. The overall average cost of iron therapy prior to Epo treatment was $46.47 per patient per year.

Table III. Effect of Hypertension on Epo Dosing Requirements (mean ± SD).

	Mean Current Epo Dose (u/kg 3x/wk)	Mean Current Hgb (g/L)@	Mean Current Hct
Underlying HTN (n=39)	45.7 ± 22.2*	95.7 ± 16.3	0.283 ± 0.049
No Underlying HTN (n=31)	33.8 ± 17.9*	97.0 ± 11.0	0.286 ± 0.029
Worsening of Underlying HTN (n=16)	46.5 ± 22.0$	96.9 ± 16.6	0.287 ± 0.048
No Worsening of Underlying HTN (n=23)	45.2 ± 22.8$	95.0 ± 16.5	0.280 ± 0.051
New Onset HTN (n=14)	40.4 ± 18.5$	94.4 ± 11.8	0.281 ± 0.032
No New Onset HTN (n=17)	28.3 ± 15.8$	99.1 ± 10.2	0.290 ± 0.027

@ patient groups had comparable baseline Hgb and Hct levels
* $p < 0.05$ (independent t-test, df = 68, power in the range of 80%)
$ $p = 0.05$ to 0.1 (independent t-test, df = 29, power in the range of 60%)
& not significantly different

Table IV. Parameters of Patients with Underlying Hypertension.

Parameter (mean ± SD, where applicable)	Underlying HTN Which Worsened on Epo Therapy	Underlying HTN Which Remained Stable on Epo Therapy
gender (m/f)	6/10	9/14
dialysis centre (SCDU/CDU)	11/5	18/5
mean dry weight (kg)	59.7 ± 12.7	66.2 ± 13.0
mean age (years)	50.9 ± 19.5	48.3 ± 13.4
mean time on dialysis (months)	45.0 ± 28.1	47.9 ± 53.3
mean time on Epo (months)	22.4 ± 13.7	11.38 ± 7.2
mean current Epo dose (u/kg 3x/wk)	46.5 ± 22.0	45.2 ± 22.8
mean current Hgb (g/L)	96.9	95.0
mean current Hct (%)	0.287	0.280

Table V. Parameters of Patients with No Underlying Hypertension.

Parameter (mean ± SD, where applicable)	New Onset HTN on Epo Therapy	No Underlying or New Onset HTN on Epo Therapy
gender (m/f)	5/9	7/10
dialysis centre (SCDU/CDU)	10/4	11/6
mean dry weight (kg)	59.8 ± 10.8	71.3 ± 19.1
mean age (years)	53.2 ± 12.7	50.1 ± 11.9
mean time on dialysis (months)	59.0 ± 58.9	66.2 ± 84.2
mean time on Epo (months)	25.1 ± 18.2	18.5 ± 19.7
mean current Epo dose (u/kg 3x/wk)	40.4 ± 18.5	28.3 ± 15.8
mean current Hgb (g/L)	94.4	99.1
mean current Hct (%)	0.281	0.290

compared to $203.07 per patient per year after the hormone was started (due to increased iron requirements for erythropoiesis).

Ferritin levels were regularly monitored in 24 (34%) cases. Total iron bending capacity was regularly monitored in only eight (9%) cases. Because of these low rates, it was difficult to assess the impact of these monitoring tools on changes in Epo therapy. The average ferritin level for those patients in whom it was assessed was 224 ±269 µg/L (normal = 12 to 300 µg/L), whereas, the average total iron binding capacity was 45 ± 6 µmol/L (normal = 45 to 72 µmol/L).[12]

Transfusion Requirements

Prior to the initiation of Epo therapy, transfusions were required in 56 cases (80%) from the overall study population, with an average of 7.9 transfusions required per patient per year. The administration of transfusions prior to Epo therapy could not be verified in the remaining 20% of the cases reviewed.

Subsequent to the initiation of Epo therapy, transfusion rates in the overall study population declined in frequency to an average of 4.9 transfusions per patient per year. There was also a decrease in the number of patients who required them: a total of 23 cases (33%) still required transfusions. In 47 cases overall (67%), transfusions were not required after the initiation of Epo therapy; that is, a total of 33 (i.e., 56 original minus 23 remaining cases) fewer patients required transfusion.

In cases where therapy achieved "target" Hgb and Hct levels within the first three months of Epo treatment, ten (14% of all cases) continued to receive transfusions. When current therapy was examined, it was found that eight of these ten patients (11% of all cases) continued to receive transfusions, even though "target" Hgb and Hct were being maintained.

Other Therapy Outcomes

Aside from HTN, there were few other adverse effects recorded in the patient charts. One patient experienced a seizure subsequent to Epo initiation and thrombotic vascular access blockage occurred in 15 cases (21%). Both of these adverse events have been previously attributed to Epo in the literature.[13-17]

Rates of hospitalization and emergency room visits (at the HSC) before and after Epo initiation demonstrated that, subsequent to Epo, there was a decrease in the average number of hospital admissions per year related to the patient's CRF (from 0.77 down to 0.71 stays per patient per year). Each admission was also shorter in the post-Epo initiation period, decreasing from 11.19 to 6.12 days for the average length of stay (LOS). CRF-related emergency room visits also decreased on average, from 1.58 to 1.35 encounters per year.

DISCUSSION

General Results

At the time of the survey, 191 patients were on hemodialysis (122 in SCDU and 69 in CDU). Based on the 68 individuals in the survey, this results in an Epo therapy adoption rate of 36%.

Overall, it is apparent that patients dialysed in the CDU require higher doses of Epo versus their SCDU counterparts. These are two inherently non-comparable patient groups, with the less medically stable patients being assigned to the CDU. It is likely that the differences in overall Epo dosing requirements reflect disease severity. This dosage discrepancy is not surprising, since the literature reports that acute processes increase Epo dosing needs.[18]

Epo Therapy

The product monograph and literature define target Hgb and Hct levels as one of the primary measures of the outcome of Epo therapy. In the survey, however, there were no predetermined "target" Hgb or Hct levels identified in the charts reviewed. Practitioners reported to the investigators that the "targets" used as goals in the treatment of the majority of patients were in the range of 100 g/L and 0.30 for Hgb and Hct, respectively. These "targets" are similar to the ranges outlined for "low dose" Epo therapy.[19]

Current Epo dosing at the HSC could be described as "low dose"[19] since current average Hgb and Hct levels are 96.3 g/L and 0.284 (see Table III), as opposed to normal minimal values for women (lower value) and men of approximately 120-135 g/L and 0.37-0.40, respectively.[12] There has been much discussion in the literature regarding the relative clinical and economic merits of "low dose" Epo treatment versus normalizing hematologic indices.[20] The "low dose" proponents suggest that increases in Hgb and Hct to the levels described above are clinically effective. Given the limited budgets allowed for Epo funding in most Canadian centres, from an economic perspective "low dose" Epo regimens may allow clinicians to use the drug in the maximum number of patients.

In contrast, many clinicians suggest normalizing hematologic values for Hgb and Hct in CRF patients.[21] There is concern, however, regarding the potential for more frequent serious Epo-induced adverse events which must be balanced with the fact that the clinical benefit

of these higher hematologic values has not been demonstrated. A preliminary investigation by Eschbach found that twice the dose of Epo is required to normalize Hgb and Hct when compared to "low dose" regimens (personal communication, Dr J. Eschbach, June 1994). Should normal Hgb and Hct goals be applied to patients with CRF, funding requirements would essentially double. Another factor to be considered is the QOL achieved by patients on these two dosing regimens. Neither side has conducted comprehensive assessments of the changes in QOL. The clinical, economic and health related QOL impact of adjusting target Hgb and Hct levels for CRF patients into the "normal" range is obviously an area for future research.

Epo Therapy in Hypertensive Patients

Our data suggest that the presence of underlying HTN or the development of new onset drug-induced HTN influences Epo dosing requirements. Patients who had underlying HTN required 35% more Epo (+ 11.9 units; $p<0.05$) per kilogram 3x/wk to maintain their hematologic indices (see Table III) than those with no underlying HTN. In patients whose HTN worsened, dosing requirements remained high and did not appear to increase significantly on Epo initiation versus those patients in whom HTN remained stable (see Tables III and IV). On the other hand, those with new onset Epo-induced HTN demonstrated a need for almost 43% more Epo (+ 12.1 units; tended towards but not statistically significant) to maintain hematologic indices in contrast to those who did not develop elevations in blood pressure (see Tables III and V).

While HTN is a commonly reported adverse effect associated with Epo therapy, such a discrepancy in dosing requirements based on pre-existing HTN or the development of drug-induced HTN has not been previously documented. The data were scrutinized to determine if there were any known underlying factors which could explain this discrepancy. There was a slight discrepancy in time on Epo therapy in the two subgroups with underlying HTN (22.4 versus 11.3 months), and a difference in weight (59.8 versus 71.3 kg) and time on Epo therapy (25.1 versus 18.5 months) in the two subgroups without underlying HTN. Neither of these factors, however, would lead one to suspect them as a cause for differences in Epo dosing requirements. Factors such as aluminum toxicity, prevalence of diabetes mellitus, ferritin, transferrin saturation, and the Hgb and Hct levels achieved did not account for this difference either. The standard deviations for the average Epo dose requirements tabulated are quite wide, indicating that this difference may be due purely to chance.

We cannot rule out disease progression as a cause for new onset or worsened HTN, although the time frame over which this outcome occurred would lead one to attribute the HTN to the drug rather than CRF. Error may also have been introduced by the fact that the investigators did not specifically examine the success of HTN control prior to Epo therapy initiation. It was assumed that antihypertensive therapy was being prescribed to keep HTN under the best control possible. Further investigation of this phenomenon is required.

Transfusion Requirements

The net benefit of Epo therapy can be tabulated in terms of direct costs for blood transfusions. If we assume that the direct cost of a unit of packed red blood cells is $180,[8] then: the decrease of 3.0 units per patient per year for the 23 patients still receiving transfusions translates into a savings of $12,420 per year; and the decrease of 7.9 units per patient per year for the 33 patients who no longer required transfusions translates into a savings of $46,926 per year. Overall savings of $59,346 per year (average of $847.80 per case) in transfusion costs accrues with Epo therapy. This value would likely be higher if one included the probabilities and costs of treating the infectious complications of transfusions in the analysis.

Epo Cost and Wastage Summary

The average cost of Epo per case per year was $6,308 when maximum wastage was assumed. However, this cost decreased to $5,062 per case per year when absolutely no wastage was included in the calculations. Given this difference of $1,246 in the 70 cases of Epo use reviewed, this would total $87,220 in potential savings per year if wastage were eliminated. A more conservative estimate, assuming that wastage was 25% of this total (in-house data), would translate into savings of $65,415 per year.

Other Therapy Outcomes

There was a trend toward a reduction in the number of HSC hospital admissions, LOS and encounters at the emergency room up to two years after therapy with Epo was initiated. In terms of hospital admissions, this translates into an overall decrease of 299 inpatient days (or 4.27 days per case) at the HSC. Given a per diem rate of $902, this extrapolates to a potential total savings of $269,698 per year.

This latter figure is theoretical for several reasons. First, such savings could be extracted within a globally budgeted health care system only by bed closures, specifically nephrology beds. One is also cautioned that the per diem rate is a global estimate of the cost of an average hospital bed for one day and, therefore, includes the cost of both more and less expensive admissions

(e.g., to critical care units versus chronic care beds). And finally, it is difficult to differentiate between the impact of Epo use versus recent health reform measures for this patient population, particularly regarding the decreased LOS. It is likely that some of these changes in resource utilization are not due solely to the introduction of Epo into the CRF therapeutic regimen. Figure 2 provides a summary of the sources of costs and savings associated with Epo therapy in the population surveyed.

Study Limitations

The drug costing exercise was limited to include Epo, iron, and antihypertensive therapy costs. Dispensing fees and drug costs incurred during hospital admissions and emergency room visits, or other outpatient drug therapies (e.g., multivitamins, Vitamin D supplements, antibiotics, etc.) were excluded from the analysis due to the limitations of the hospital database. In an additional related matter, there continues to be limited information regarding the infectious risks and costs (drugs and otherwise) which might be avoided by reducing the number of transfusions required by CRF patients.

The retrospective nature of the review made it difficult to find data related to the start of Epo therapy in patients who had been receiving Epo for several years. The transfer of patients in or out of the HSC dialysis network also may have lead to incomplete documentation. The retrospective design eliminated the investigators' ability to collect data regarding quality of life and return to work frequency, although such data have been documented in other Epo studies.[6,19] Finally, the direct impact of Epo on the dialysis process was not evaluated as it was felt that this was outside the investigators' expertise. This is an important issue, however, as there has been a question of whether or not the cost of dialysis increases with Epo therapy.

In conclusion, this study reviews current Epo prescribing, costs, and some basic outcome parameters in patients at the HSC. While Epo does improve hematologic indices, this comes at a price to the hospital and, therefore, the health care system. The discovery of elevated dosage requirements in patients with pre-existing HTN and in those with new onset HTN is an issue which should be investigated and corroborated by other researchers. To further delineate the impact of Epo in this population, prospective evaluation of QOL and clinical and economic outcomes should be carried out as new patients become eligible for Epo therapy.

Costs	
- Epo costs (assume no wastage)	+ $5061.55/year
- additional antihypertensive costs	+ $396.58/year
- additional iron costs	+ $156.60/year
Savings	
- avoided transfusion costs	- $847.80/year
- avoided hospital days	- $3851.54/year
Total Additional Cost of Epo Therapy	+ $888.39/year

Figure 2. Summary of Epo Costs and Savings (per patient).

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Appendix A. Current Epo Criteria

The Section of Nephrology of the University of Manitoba have agreed:

1) no physician other than a member of the Section of Nephrology may prescribe Epo for renal failure patients, except by special agreement;

3) no hospital, other than a teaching hospital or a hospital related to the Local Centre Dialysis Program of the Manitoba Renal Failure Program, shall supply Epo;

4) that, in descending order of importance, one or more of the following will be considered as reasons for commencing Epo therapy -
   i) transfusion dependency requiring one or more units of blood per month to remain free of anemia symptoms, such as angina, shortness of breath, severe weakness, and tiredness (i.e., normally a Hgb of not more than 75 g/L).
   ii) awaiting transplant to ensure that no transfusions are given which may cause pre-sensitization.
   iii) failure of (or side effects due to) all other forms of anemia therapy (other than frequent transfusion). These include iron (serum ferritin at least 100), folate, B_{12}, vitamins B and C, and androgens.
   iv) transfusion complications with iron overload (serum ferritin >1000).
   v) multiple red cell antibodies causing transfusion reactions.
   vi) evidence of cardiovascular disease which can be ameliorated by improving anemia (ischemic heart disease, cardiomyopathy, heart failure, peripheral vascular disease).
   vii) severe pulmonary disease.

5) Relative contraindications to Epo therapy will include:
   i) moderate or severe hypertension;
   ii) thrombotic tendency;
   iii) age > 70 years;
   iv) severe other disease with life expectancy < 3 years

   (Patients under iii & iv can be transfused to maintain comfort unless marked iron overload is already present.)

Revised 1992