Cost Implications to Medicare of Recombinant Erythropoietin Therapy for the Anemia of End-Stage Renal Disease

Neil R. Powe, Robert I. Griffiths, and Eric B. Bass

N.R. Powe, R.I. Griffiths, E.B. Bass, Department of Medicine, The Johns Hopkins University School of Medicine, Department of Health Policy and Management, The Johns Hopkins University School of Hygiene and Public Health, and The Johns Hopkins Program for Medical Technology and Practice Assessment, The Johns Hopkins Medical Institutions, Baltimore, MD (J. Am. Soc. Nephrol. 1993; 3:1660-1671)

ABSTRACT
The purpose of this study was to estimate the net cost effect to Medicare of the increasing use of recombinant human erythropoietin (EPO) instead of red blood cell transfusions or androgens in the management of anemia for the approximately 100,000 hemodialysis patients in the U.S. End-Stage Renal Disease (ESRD) program. A computerized decision model that takes into account the effectiveness and possible side effects of transfusions, androgens, and EPO and predicts 1- and 5-yr direct medical costs to Medicare associated with each therapy was constructed. Probability estimates for clinical events were derived from the literature. Costs were assigned by use of the amounts Medicare pays providers of ESRD care for: (1) use of EPO, transfusions, and androgens; and (2) health care services related to the treatment of anemia (including complications of treatment and possible reductions in morbidity). For every 10,000 hemodialysis patients treated with EPO, net Medicare expenditures will be much greater than if only transfusions are used by $42,530,000 at 1 yr (6% of ESRD program costs) and by $118,370,000 at 5 yr. The increase in cost was highly sensitive to the dose of EPO; moderately sensitive to changes in estimated anemia response rates for EPO, frequency of EPO-induced vascular access clotting, and reduction in cardiovascular or overall morbidity; and slightly sensitive to transfusion rates, estimated anemia response rates for androgens, frequency of EPO-induced seizure or hypertensive complications (stroke, myocardial infarction), frequency of transfusion-related viral infection, and frequency of androgen-induced virilization. Considering both effectiveness and side effects of alternative treatments for the anemia of ESRD, it was projected that the increasing use of EPO will markedly increase the cost to Medicare of ESRD medical care.

Key Words: Erythropoietin, recombinant erythropoietin, ESRD, anemia, Medicare, cost-benefit analysis, economic analysis

Anemia is a common comorbid condition in patients with ESRD, resulting largely from impaired production of erythropoietin (EPO) by the diseased kidneys. Until recently, red blood cell transfusions and androgen therapy have been the standard therapies for the treatment of anemia in ESRD. EPO can now be produced through recombinant DNA technology and, when administered to patients with ESRD, has been shown to increase hematocrit, ameliorate symptoms associated with anemia, and improve quality of life (1-6). Both old and new therapies for anemia are associated with the risk of side effects. For example, transfusions may transmit viral infections and may cause hemolytic reactions, whereas androgens may cause virilization and hepatotoxicity (7). EPO also has potential side effects including hypertension, iron deficiency, and possibly seizures and vascular shunt thrombosis (2). In addition, it has been suggested that EPO may be effective in reducing cardiovascular or overall morbidity in the ESRD population (8,9).

The Food and Drug Administration (FDA) approved EPO for use in clinical practice in June 1989. Pay-
ment for medical care provided to U.S. ESRD patients is primarily through Medicare, which paid out 3.8 billion dollars in 1988 for ESRD care (10). Shortly after FDA approval of EPO, the Health Care Financing Administration (HCFA) approved coverage of and reimbursement for EPO for patients in Medicare’s ESRD program.

HCFA initially provided reimbursement for EPO using a fee-for-service payment policy rather than incorporating payments into the capitation fee for providers of dialysis. The payment amount was set at $40 for up to 10,000 units administered at one of three weekly sessions and $70 per session for those receiving more than 10,000 units. After December 1990, HCFA began reimbursing for EPO at $11 per 1,000 units (11). The cost effect to Medicare could be substantial if EPO is prescribed widely for the nearly 100,000 hemodialysis (12) patients in the United States and if savings are not realized from avoidance of the side effects associated with standard therapy or reductions in ESRD morbidity.

We conducted a study to estimate the net cost effect to the Medicare program of substituting EPO for standard therapies of transfusions and/or androgens, in which we considered both the anticipated effectiveness and side effects of the alternative therapies.

METHODS
Target Population
The population we considered is patients with ESRD who receive hemodialysis and whose medical care is paid for by Medicare. Approximately 93% of all ESRD patients in the United States are entitled to Medicare benefits (10). The point prevalence of this population was 51,750 on December 31, 1981, and had risen to 97,346 on December 31, 1989 (12).

Therapeutic Options
We considered three therapeutic options for the treatment of anemia associated with ESRD: EPO, red blood cell transfusions, and androgens.

Structure of Decision Model
We used a decision analytic approach to depict the clinical paths that hemodialysis patients traverse and the associated costs that they incur when initially treated for anemia with one of the three therapeutic options over a time horizon of 1 to 5 yr (July 1989 through June 1994). To accomplish this, we constructed a computerized multistate transition model using Decision Maker 6.2 software (New England Medical Center, Boston, MA). Our model simulates how hemodialysis patients pass from one health state to another over an extended period of time after initial treatment of anemia with EPO, androgens, or transfusions. A simplified representation of the model is shown in Figure 1. Each health state in the model is assumed to cover one or more months of time, and each state is associated with a set of branching pathways that represent the possible complications that may follow from being in a particular state.

In this model, a choice is made between three alternative methods of treating anemia: EPO, androgen therapy, or red blood cell transfusions. After the initiation of therapy, the model accounts for patient response (increase in hematocrit) or lack of response to therapy on a monthly basis. In the model, patient response includes consideration of the possible beneficial effects of an increase in hematocrit on cardiovascular and overall morbidity. During each month of therapy, patients may or may not experience a side effect of therapy. If a side effect occurs with hormonal therapy (EPO, androgens), patients will either remain on hormonal therapy if the side effect is acceptable to the patient or the physician or switch to transfusions if the side effect is unacceptable. If there is no response to hormonal therapy after 3 months on EPO or after 6 months on androgen therapy, patient management is changed to transfusion therapy in the following month. In addition to accounting for the occurrence of side effects associated with each therapy, the model also accounts for patient mortality due to treatment-related complications and mortality due to other causes.

Response to therapy, occurrence of side effects due to therapy, and mortality are modeled as probabilistic events. Therefore, a probability estimate is assigned to each event considered in the model. Estimates of the direct cost from the perspective of Medicare are assigned to each of the three alternative anemia therapies and to each of the potential clinical events.

Assumptions
Several assumptions were made in this analysis. These are as follows: (1) selection of initial therapy is independent of patient characteristics; (2) only one treatment or side effect can occur each month; (3) patients starting EPO therapy will continue therapy for at least 3 months unless they experience a side effect, and patients starting androgen therapy will continue therapy for at least 6 months unless they experience a side effect; (4) patients with iron deficiency related to EPO therapy can be treated adequately; (5) the complication of iron overload will occur outside of the 5-yr time frame for our analysis (and therefore is not included in the model); (6) no deaths result from either abnormal liver function or virilization caused by androgen therapy; (7) all anemia therapy would be provided to patients on an outpatient basis, whereas side effects could be managed either on an outpatient or (if severe) inpatient
Cost Implications of Erythropoietin Therapy

Figure 1. Decision model for the treatment of anemia in ESRD patients.

basis; (8) for hepatitis, 80% of patients would have resolution and never require hospitalization (13), whereas for other side effects, such as seizure, myocardial infarction, and cerebrovascular accident, we assumed that patients would always be hospitalized.

Probability Estimates
For our baseline analysis, we derived probability estimates from published literature of the response expected with each anemia therapy, of the rate of side effects of each therapy, of the mortality rate due to side effects, and of the mortality rate due to other causes (Table 1). We identified the major studies of EPO and androgen therapy through computerized Medline searches, examination of review articles, and references of published studies. When literature was unavailable for estimates of event rates, assumptions were necessary (see above). If an event occurs at a fixed time (e.g., no response to androgen
### TABLE 1. Parameter estimates for decision model

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Probability Description</th>
<th>Baseline Values (High</th>
<th>Low</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPO</strong></td>
<td>No response to EPO</td>
<td>0.036</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency due to EPO</td>
<td>0.0466</td>
<td>0.0936</td>
<td>0.0234</td>
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<tr>
<td></td>
<td>Myocardial infarction given hypertension due to EPO</td>
<td>0.0004</td>
<td>0.0002</td>
<td>0.00005</td>
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<tr>
<td></td>
<td>Cerebrovascular accident given hypertension due to EPO</td>
<td>0.00004</td>
<td>0.0043</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Seizure due to EPO</td>
<td>0.0000</td>
<td>0.0043</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vascular access clotting due to EPO</td>
<td>0.0000</td>
<td>0.0043</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Death due to myocardial infarction</td>
<td>0.47</td>
<td>0.94</td>
<td>0.23</td>
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<tr>
<td></td>
<td>Death due to cerebrovascular accident</td>
<td>0.28</td>
<td>0.58</td>
<td>0.15</td>
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<tr>
<td></td>
<td>Continuation of EPO not acceptable given iron deficiency</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Continuation of EPO not acceptable given myocardial infarction</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Continuation of EPO not acceptable given cerebrovascular accident</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Continuation of EPO not acceptable given seizure</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Continuation of EPO not acceptable given vascular access clotting</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>Androgen</strong></td>
<td>No response to androgen</td>
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<td>0</td>
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<tr>
<td></td>
<td>Virilization due to androgen</td>
<td>0.0186</td>
<td>0.032</td>
<td>0.009</td>
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<td>Abnormal liver function due to androgen</td>
<td>0.0045</td>
<td>0.009</td>
<td>0.00225</td>
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<td>0</td>
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<td>Continuation of androgen not acceptable given abnormal liver function</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td><strong>Transfusion</strong></td>
<td>Severe transfusion reaction</td>
<td>8.33 x 10^-6</td>
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<td></td>
<td>Hepatitis due to transfusion</td>
<td>0.0010</td>
<td>0.002</td>
<td>0.0005</td>
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<tr>
<td></td>
<td>AIDS due to transfusion</td>
<td>1.0 x 10^-7</td>
<td>2.0 x 10^-7</td>
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<td>Death given severe transfusion reaction</td>
<td>1</td>
<td>1</td>
<td>0.8</td>
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<td></td>
<td>Death given hepatitis</td>
<td>0.0034</td>
<td>0.0068</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td>Death due to other causes</td>
<td>0.0210</td>
<td>0.04</td>
<td>0.01</td>
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<td><strong>All Other Parameter Description</strong></td>
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<td>Cardiovascular morbidity (admissions) reduction</td>
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<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Overall morbidity (hospital days) reduction</td>
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<td>0.50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dose of EPO (units/administration)</td>
<td>3500</td>
<td>5250</td>
<td>2570</td>
</tr>
<tr>
<td></td>
<td>Transfusion rate (units/year)</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

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*a* Model assumes lack of response is determined after 3 months of EPO therapy.

*b* Probability is 0 after 12 months.

*c* We estimated that all patients could be treated for iron deficiency and would remain on EPO therapy.

*d* We estimated the baseline probability as 0.20 and examined in sensitivity analyses the full range of probability from 0 to 1.

*e* Model assumes lack of response is determined after 6 months of androgen therapy.

*f* The definition of virilization was that which was severe enough to stop therapy; therefore, this baseline probability was 1.

*g* We estimated that all patients with abnormal liver function due to androgen therapy would not continue therapy.

*h* Estimate reflects considerations that EPO may reduce cardiovascular disease (angina pectoris, myocardial infarction, cerebrovascular accident, and peripheral vascular disease) hospitalizations or improve health status to result in fewer days in the hospital. High values represent a 50% reduction.

*Value represents dose per administration. We assumed three administrations per week.*
after 6 months), its probability of occurring was programmed to be in effect only at that time. In contrast, we assumed that other events, such as the probability of death from other causes, were constant over time. If event probabilities appearing in the literature had been computed for a yearly time period, we derived monthly probabilities by applying the Declining Exponential Approximation of Life Expectancy (DEALE) method (14).

Therapeutic Response Rates

We estimate that 97% of those receiving EPO will respond before the end of the third month after the initiation of therapy (2). We estimate that 100% of those who respond within this time period will continue to respond in the following months and will therefore remain on EPO indefinitely. Those who do not respond to EPO therapy after the first 3 months will be switched to transfusions.

Although not conclusively proven, we also consider possible beneficial effects of EPO on cardiovascular and overall morbidity (8, 9, 15). Cardiovascular disease (angina, myocardial infarction, cerebrovascular accidents, and peripheral vascular disease) admissions accounted for approximately 6% of all admissions in the U.S. ESRD program in 1988 (12). In our sensitivity analyses, we estimated that EPO might reduce the number of admissions for cardiovascular disease by 50%. We also considered the possibility that the average duration for all causes of hospitalization, which occur in 50% of ESRD patients annually (16), might be reduced by the use of EPO through improvements in patient well-being (e.g., appetite and nutritional status).

Fifty percent of patients receiving androgens will respond by the sixth month after the initiation of therapy (17–22). Patients who respond within this time period will continue to respond, whereas those who do not respond will be switched to receive transfusions. We estimate that 100% of those receiving red blood cell transfusions respond.

Side Effects of Therapy

Potential serious side effects of EPO therapy include hypertension and its sequelae of cerebrovascular accident and myocardial infarction, seizures, and clotting of vascular access for dialysis. However, results of clinical trials with EPO suggest that there may be only a slight additional risk of hypertension and no additional risk of clotting or seizure (2). Therefore, in our model, we assigned a value of 0 to the baseline probability estimates of both clotting and seizure due to EPO. The probabilities of a myocardial infarction or a cerebrovascular accident are conditional on, first, developing new or exacerbated hypertension from EPO (0.32) (2), and, second, developing a myocardial infarction (0.0037) or cerebrovascular accident (0.0014) from hypertension. Because data on the risks of myocardial infarction due to hypertension were not available specifically for ESRD patients, we used the risks from literature examining non-ESRD populations (23). We assigned a value of 0.0001 to the baseline probability of myocardial infarction given new or exacerbated hypertension due to EPO and 0.00004 to the baseline probability of cerebrovascular accident given new or exacerbated hypertension. These events were expected to be acute or subacute effects of EPO and therefore were programmed to occur only during the first year of therapy.

Iron deficiency is a more common, yet less severe side effect of EPO. We assigned a baseline monthly probability of 0.0468 to this side effect (2). No transition from EPO therapy to transfusions because of the occurrence of iron deficiency is expected.

On the basis of the clinical literature, we also computed the probability of death, given each of the serious side effects associated with EPO therapy. We also estimated the probability of finding each side effect of EPO not acceptable, given that the patient survived the side effect.

The most significant complications of androgen therapy are abnormal liver function and, in women, virilization. We estimated a baseline monthly probability of abnormal liver function associated with androgen therapy of 0.0045 and a baseline monthly probability of virilization in women of 0.0186. The baseline probability of virilization was adjusted to account for the fact that not all ESRD patients receiving androgen therapy will be women. We also estimated that 20% of those experiencing virilization will find it an unacceptable side effect and will switch to transfusions.

The most prevalent complication of transfusion is hepatitis infection. We estimated that the baseline monthly probability of transfusion-associated hepatitis is 0.001 (24–26). We also included probabilities of transfusion-related HIV infection with subsequent acquired immunodeficiency syndrome (AIDS) and fatal transfusion reaction in our model, although the probability of either of these events is extremely low (26, 27) and AIDS is not likely to occur until at least 2 yr after a transfusion.

Finally, on the basis of data from the U.S. Renal Data System (12), we estimated a baseline monthly mortality rate in ESRD of 0.021, irrespective of anemia treatment modality.

Cost Estimates

Taking the perspective of Medicare, we estimated direct medical costs (1989 dollars) for each of the alternative anemia therapies and for treatment associated with each side effect of therapy. The perspective of Medicare was taken because the Medicare
program is the predominant payer of ESRD care in the United States. We included both hospital services (part A) and outpatient and physician services (part B) in all cost estimates for services. We attempted to estimate what Medicare actually pays providers (cost to Medicare) rather than simply charges submitted by providers that Medicare may or may not pay.

In deriving cost estimates, the following facts were taken into account. Under Medicare ESRD outpatient reimbursement regulations, facilities receive a fixed payment per patient per dialysis session for dialysis-related care. According to Medicare regulations, there is additional, but limited reimbursement for outpatient care associated with managing the side effects of anemia therapy. Nephrologists also receive a fixed payment per patient per month for managing dialysis care. They do not receive additional payments for the administration of EPO anemia therapy. In addition, outpatient services are subject to a 20% copayment for which the patient, not Medicare, is responsible. Drugs are subject to a 875 annual deductible, and there is an annual 3-U deductible for blood transfusions. Medicare does not pay for outpatient drugs administered by the patient (with the exception of EPO), such as oral antihypertensive therapy needed to treat EPO-induced hypertension.

Cost of Anemia Therapy

Table 2 lists the cost estimates used in the model. The monthly cost of EPO was computed as follows. We estimated that the average dose of EPO would be 3,500 U for a 70-kg patient based on a recommended dose of 50 U/kg. Relatively low dosing, compared with the doses of 50 to 100 U/kg recommended in product labeling, has been observed (28,29). The Medicare allowable charge for EPO during the first year and a half of Medicare coverage was $40 per administration for doses of less than 10,000 U. We estimated three administrations per week for a total of 152 administrations per year. Laboratory fees for monitoring iron therapy (iron levels, ferritin) were included in the cost of EPO therapy and were estimated at an allowable charge of $44.17 for each treatment. The monthly cost of EPO during the first year was computed as the sum of the annual Medicare allowable charges less than 20% copayment and the 875 deductible, divided by 12. This amounted to $432.

After the first year and a half of Medicare coverage, reimbursement policy changed. Rather than paying a lump sum for EPO, irrespective of doses less than 10,000 U, Medicare changed its policy to one of reimbursement on the basis of incremental doses. $11 per 1,000 U administered. Depending on the dose of EPO that is administered, this policy could have an effect on the total cost of EPO to Medicare. For our baseline analysis, the estimate for the cost of EPO after 18 monthly cycles of our model reflects the revised Medicare payment policy for an average dose of 3,500 U. The use of smaller doses of EPO with either sc or iv administration is currently under investigation. In our sensitivity analysis, we address the expected economic effect of a change in dosing practices by adjusting the second-through fifth-year EPO cost estimates to reflect changes in the average dose of EPO. We estimated the lowest dose under revised sc dosing practices to be 2,570 U on the basis of 110-U/kg weekly doses for a 70-kg patient (30). Alternatively, the change in Medicare payment policy could lead to an increase in dosing. We estimated a high dose of 5,250 U (75 U/kg for a 70-kg patient).

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
<th>Value (1989 U.S. Dollars)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO</td>
<td>EPO therapy (per month)</td>
<td>432</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Declotting a shunt (per episode)</td>
<td>8,537</td>
<td>34, 35</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular accident (per episode)</td>
<td>4,466</td>
<td>34, 35</td>
</tr>
<tr>
<td></td>
<td>Managing iron deficiency (per month)</td>
<td>4</td>
<td>33, 10</td>
</tr>
<tr>
<td></td>
<td>Managing myocardial infarction (per episode)</td>
<td>7,228</td>
<td>34, 35</td>
</tr>
<tr>
<td></td>
<td>Managing a seizure (per episode)</td>
<td>3,409</td>
<td>34, 35</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease admission</td>
<td>4,832</td>
<td>12, 34, 35</td>
</tr>
<tr>
<td>Androgen</td>
<td>Androgen therapy (per month)</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Abnormal liver function (per month)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Virilization (per episode)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Transfusion</td>
<td>Transfusion therapy (per month)</td>
<td>16</td>
<td>10</td>
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<tr>
<td></td>
<td>AIDS (per month)</td>
<td>1,693</td>
<td>37</td>
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<td></td>
<td>Hepatitis (per episode)</td>
<td>907</td>
<td>10, 34, 35</td>
</tr>
<tr>
<td></td>
<td>Managing a transfusion reaction (per episode)</td>
<td>2,677</td>
<td>34, 35, 10</td>
</tr>
</tbody>
</table>

* Includes cost of facility and physician services.

* Seventy-fifth percentile of Medicare prevailing fees for Baltimore metropolitan area. See Methods section (cost estimates) for full descriptions of calculations.

* A weighted average of the cost of admission for angina pectoris, myocardial infarction, cerebrovascular accident, and peripheral vascular disease was used. The weights were derived from the relative frequency of each of these four types of admissions, based on data from the United States Renal Data System.
The monthly cost of transfusion was computed as follows. First, on the basis of an estimate from the U.S. literature, anemic ESRD patients receive an average of six red blood cell transfusions per year (31). Studies in Canada and the United Kingdom, where the severity of illness for ESRD patients and the transfusion practice may be different than those in the United States, have indicated slightly lower annual rates of four to five transfusions per patient (9,32). The effect of using a lower average number of transfusions \((N = 4)\) was explored in our sensitivity analyses. Medicare regulations include a transfusion deductible, which does not allow payment for the first 3 U transfused in any year. We assigned a Medicare allowable charge of \$49\) per transfusion for three transfusions plus \$15.25\) in type and cross-matching laboratory fees for six transfusions, because Medicare does not pay ESRD providers for laboratory fees associated with transfusion. After subtracting the 20% copayment from the total Medicare allowable charge, we estimated the monthly cost of treating anemia with transfusions at \$15.90. In computing the cost of androgen therapy, we estimated the cost of weekly doses of nandrolone at \$6 per administration (33). Allowing for the 20% copayment and \$75\) deductible, we estimated the monthly cost of androgen therapy to be \$15.

**Cost of Managing Side Effects**

Because Medicare reimbursement for ESRD outpatient (physician and facility) care is paid by capitulation (fixed amount per patient), there is limited payment for outpatient care resulting from the side effects of therapy. In our analysis, we accounted for limited payments, such as the cost of iv iron therapy for iron deficiency. We assumed that each EPO recipient who developed iron deficiency, on average, required four annual supplemental iron treatments. The monthly material costs of the iv iron dextran therapy were estimated at \$4.

We accounted for more serious side effects of each alternative anemia therapy, which are expected to result in hospitalization in the following way. Medicare pays the hospital component of inpatient care for ESRD patients according to the Prospective Payment System in which hospitals are reimbursed a predetermined amount for care based on a diagnosis-related group (DRG) (34,35). Therefore, we used the DRG payment rate (for large urban area) in assigning costs for hospitalization due to side effects. Medicare payment for the physician component of hospital care is fee for service. We used the median length of stay for specific DRG (Baltimore metropolitan area) to assign initial and subsequent days’ costs of physician care during hospitalization. Physician payments were multiplied by a factor of 0.80 because the patient is responsible for a 20% copayment for physician services. There is no corresponding copayment for the hospital component of inpatient care.

In estimating an EPO-induced cost saving associated with a reduction in average length of stay for hospitalizations, only the physician component of inpatient care is affected because length-of-stay reductions do not affect hospital DRG-based prospective payment.

**Baseline Analysis**

Using our decision model, we calculated the net cost (material cost plus cost due to side effects and related services) per case for treatment with each of the three alternative therapies for 1 yr (12 cycles of the model) and 5 yr (60 cycles of the model). These estimates were then used to calculate the incremental net cost per patient and per 10,000 patients of using EPO as compared with using transfusions (net cost of EPO therapy minus the net cost of transfusion therapy) or as compared with using androgens (net cost of EPO therapy minus the net cost of androgen therapy). We estimated the incremental net cost per 10,000 patients treated because this is a convenient divisor of the approximately 100,000 patients who receive dialysis each month in the ESRD program and who might possibly receive EPO (12,36). We discounted costs at 5% per year to adjust for the greater relative value of present dollars compared with future dollars.

**Sensitivity Analysis**

In sensitivity analysis, we examined the sensitivity of our results to alternative probability and cost estimates of the events. The ranges (low, high) used in the sensitivity analyses are also shown in Table 1. In one-way sensitivity analyses, we examined the change in incremental net cost associated with a change in several estimates (one at a time) in the model. The variables producing the greatest change in cost in several one-way sensitivity analyses were then used in two- or three-way (change in two or three variables simultaneously) sensitivity analyses to estimate the maximum differences between the costs of the strategies.

**RESULTS**

**Baseline Analysis**

As shown in Figure 2, the 1-yr net cost to Medicare of treating anemia with EPO (\$4,428), which includes the expected material cost of treatment, the cost of related services, and the cost of treating potential side effects, is much greater than for transfusion therapy (\$175) and androgen therapy (\$158). The 5-yr net cost for EPO is \$12,327, compared with \$522 for transfusion and \$490 for androgen. The average
TABLE 3. Incremental cumulative costa to Medicare of treating 10,000 patients with EPO versus transfusions or androgen.

<table>
<thead>
<tr>
<th>Time Frame (yr)</th>
<th>EPO vs Transfusion</th>
<th>EPO vs Androgen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$42,530,000</td>
<td>$42,700,000</td>
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<tr>
<td>2</td>
<td>$71,880,000</td>
<td>$72,120,000</td>
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<tr>
<td>3</td>
<td>$92,100,000</td>
<td>$92,380,000</td>
</tr>
<tr>
<td>4</td>
<td>$107,030,000</td>
<td>$107,330,000</td>
</tr>
<tr>
<td>5</td>
<td>$118,050,000</td>
<td>$118,370,000</td>
</tr>
</tbody>
</table>

* 1989 U.S. dollars.

yearly cost of each therapy decreases over time mainly because future costs are discounted to account for the time value of money.

The incremental net cost, per 10,000 patients, of EPO relative to transfusions and to androgen therapy is shown in Table 3. The 1-yr incremental cost per 10,000 patients of EPO relative to transfusion is $42,530,000, and the 5-yr incremental cost is $118,050,000. The incremental cost of EPO relative to androgen therapy is slightly greater but similar in magnitude to the incremental cost of EPO relative to transfusion: $42,700,000 per 10,000 patients at 1 yr and $118,370,000 at 5 yr.

One-Way Sensitivity Analysis

We tested the sensitivity of our baseline results to changes in our cost and probability estimates (Figures 3 and 4). The sensitivity analysis indicates that the baseline 5-yr incremental cost per 10,000 patients is highly sensitive to changes in the estimated average dose of EPO, as expected. With a low estimate of the average EPO dose (2,570 U), the estimated 5-yr incremental cost of EPO relative to transfusion decreased 10% (from the baseline of $118,050,000 to $106,440,000), and the estimated incremental cost of EPO relative to androgen therapy decreased 10% (from the baseline of $118,370,000 to $106,760,000). With a high estimate of the average dose of EPO (5,250 U), the estimated 5-yr incremental net cost of EPO relative to transfusion increased 32%
Cost Implications of Erythropoietin Therapy

Figure 4. Effects of variation in estimates for probability of side effects, response to therapy, or cost of therapy on the 5-yr cumulative incremental net cost to Medicare per 10,000 ESRD patients treated with EPO versus androgens. The bars define the range of cost when using the high and low estimates for a given parameter in Table 1, and the midpoint represents the cost ($118,370,000) using baseline parameter estimates. For low and high estimates of the cost of EPO therapy, see Results (one-way sensitivity analysis) section. SM, millions of 1989 U.S. dollars; CVD, cardiovascular disease; Hosp, hospital; Pr, probability of; MI, myocardial infarction; CVA, cerebrovascular accident; LFTs, liver function tests.

Our baseline estimates of incremental net costs per 10,000 patients were also slightly sensitive to changes in the estimated rate of EPO response and the estimated probability of seizures or vascular access clotting associated with EPO therapy. As the EPO response rate increased from 97 to 100%, the estimated 5-yr incremental net cost of EPO relative to transfusion increased 3% to $121,330,000. The projected 5-yr incremental net cost of EPO relative to androgen therapy increased 3% to $121,650,000. When the monthly probability of seizure was increased from a baseline of 0 to 0.0043, the projected 5-yr net incremental cost of EPO relative to transfusion increased 1.4% to $119,730,000 and the projected 5-yr cost relative to androgen therapy increased 1.4% to $120,050,000. Increasing the estimated monthly probability of vascular access clotting due to EPO from a baseline value of 0 to 0.0043 increased the projected 5-yr incremental net cost of EPO per 10,000 patients relative to transfusion by 7% to $126,600,000 and increased the projected incremental cost relative to androgen therapy by 7% to $126,920,000. If one considers that vascular access declotting can be performed on an outpatient basis at half the cost of an inpatient admission, the incremental costs would increase by only 2.4%.

We also considered that the average hemodialysis patient might receive fewer transfusions per year, four instead of six, as suggested by studies performed in Canada and the United Kingdom. In this case, the estimated 5-yr incremental cost of EPO relative to transfusion increased 2% (from the baseline of $118,050,000 to $120,640,000) and the estimated incremental cost of EPO relative to androgen therapy increased 1.3% (from the baseline of $118,370,000 to $119,870,000).

The projected incremental net cost to Medicare was not very sensitive to rates of hepatitis, AIDS, EPO-induced hypertensive complications (cerebrovascular accident and myocardial infarction), androgen responsiveness, or androgen-induced virilization. Incremental net cost to Medicare was also not sensitive to assumptions regarding the acceptability of continuing therapy in the face of a recent severe side effect and the frequency of iv iron therapy.

Two- and Three-Way Sensitivity Analysis

We also performed two- and three-way sensitivity analyses to determine the effect on 5-yr incremental net cost per 10,000 patients of simultaneously changing more than one variable demonstrated to significantly influence the incremental cost. When the low estimate for the average dose of EPO and a 50% reduction in cardiovascular disease attributable to EPO therapy are used in the model, the 5-yr incremental cost of EPO relative to transfusion decreased 13% from a baseline of $118,050,000 to $102,930,000, and relative to androgen, the incremental cost of EPO decreased 13% from a baseline of $118,370,000 to $103,250,000. When three estimates in the model are adjusted to provide the most optimistic economic outcome for EPO versus transfusions or androgens (low estimate for average dose
of EPO, 50% reduction in admissions for cardiovascular disease, and 50% reduction in annual total number of days in the hospital), the 5-yr incremental cost of EPO relative to transfusion decreased 16% from a baseline of $118,050,000 to $98,886,000, and relative to androgen, the incremental cost of EPO decreased 16% from a baseline of $118,370,000 to $99,180,000.

When the monthly probability of seizure due to EPO use was increased from a baseline of 0 to 0.0043 and the dose of EPO was set to its upper limit (as described above), the 5-yr incremental cost of EPO relative to transfusion increased 32% from a baseline of $118,050,000 to $156,020,000, and relative to androgen, the incremental cost of EPO increased 32% from a baseline of $118,370,000 to $156,340,000. A similar analysis, in which the monthly probability of clotting due to EPO was increased from a baseline of 0 to 0.0043 and the average dose of EPO was increased to its upper bound, resulted in an increase in 5-yr incremental net cost of EPO relative to transfusion from a baseline of $118,050,000 to $163,120,000 (38% increase), and the incremental net cost relative to androgen increased from $118,370,000 to $163,430,000 (38% increase).

DISCUSSION

With the growing concern about drug costs, there is a greater need to understand the magnitude of changes in the cost of treatment when a new drug, such as EPO, is substituted for more standard therapies. Estimates of drug costs do not often consider the cost effect of rates of responsiveness, side effects of the new therapy, avoidance of side effects associated with older therapies, and potential improvements in morbidity. Our study was designed to estimate the net cost effect to Medicare of the introduction of EPO, while accounting for these types of considerations.

In contrast to suggestions that the use of EPO might result in significant cost savings from avoidance of transfusion-related morbidity (15), we conclude that there are very large increases in the expected cost to Medicare for EPO compared with those for the previous standard therapies for anemia (transfusions and androgens) for ESRD patients when effectiveness and side effects are taken into account. Cost differences were highly sensitive to changes in the dose of EPO. This finding has important implications for potential changes in dosing practices and Medicare reimbursement policy for EPO. Because reimbursement for EPO recently changed to a smaller incremental scale for both increments of revenue and increments of dose, the dose of EPO administered and the frequency of administration are important determinants of the total incremental net cost to Medicare. Cost differences between anemia therapies were also moderately sensitive to EPO response rates, the frequency of EPO-induced vascular access clotting, and potential beneficial effects of EPO on ESRD morbidity, emphasizing the need for improved information regarding these aspects of the effectiveness and safety of EPO in routine clinical practice.

The total incremental net cost to Medicare will also depend on how widely EPO is prescribed for ESRD patients. If used for 50,000 (50%) of the nearly 100,000 hemodialysis patients in the United States, Medicare costs for ESRD care before EPO of $3.8 billion dollars (36) will rise by $213 million dollars or 6% in 1 yr and by a total of $590 million dollars over 5 yr. This is an extremely large percent increase in annual or 5-yr health care expenditures for ESRD care that is solely attributable to the introduction of medical practice of one therapy. If EPO is also increasingly used for patients undergoing peritoneal dialysis, the percent increase in ESRD program costs would be even greater.

Our analysis considered the incremental net cost of EPO from the perspective of Medicare, because Medicare bears a substantial amount of the material cost of EPO and the total cost of ESRD care in the United States. As such, we did not include societal indirect costs such as those related to work productivity (time lost from work) or the cost to providers such as the time that dialysis nurses spend administering anemia treatments to patients. An analysis from the perspective of the patient, provider, or society that includes such costs (including unreimbursed costs) might yield somewhat different results.

Some aspects of our study are worth emphasizing. First, our probability estimates are based on the efficacy of EPO and androgen therapy as demonstrated in clinical trials rather than on effectiveness demonstrated under conditions of routine use. In our sensitivity analysis, we adjusted for the possibility that the effectiveness of EPO therapy in routine practice may differ from that in clinical trials and found that changes in the estimated efficacy of EPO were associated with moderate variability in the incremental net cost of EPO therapy relative to transfusions or androgens.

Second, our analysis was designed to measure the overall cost effect to the Medicare program rather than the cost effectiveness of EPO versus standard therapies. We therefore did not consider all improvements in the quality of life that EPO provides or the value that patients attach to being treated with each type of therapy. To compare costs and benefits of EPO with those of other therapies covered by Medicare, the assessment of these improvements should be combined with our estimates of net costs.

Third, our baseline results also make use of current data about the effect of EPO and standard therapy.
It is possible that EPO could have important protective effects on morbidity such as a reduction in hospitalization. For example, increased oxygen delivery to tissues could bring long-term benefits of reduced cardiovascular disease (8). EPO could also influence survival rates for kidney transplants. Alternatively, increased blood viscosity could result in an increased long-term risk of thrombosis-related cardiovascular disease. A consideration of such potential influences, as demonstrated in our sensitivity analyses, could result in higher or lower estimates of the relative cost effects of EPO compared with those of transfusions or androgens.

Another important consideration is the recent changes that are occurring in the methods by which Medicare-participating physicians are paid. We used physician payment based on previous payment regulations. The new Resource-Based Relative Value Scale payment system will decrease physician costs for services provided by some specialists and could have an effect on our incremental cost estimates for EPO versus transfusions or androgens.

In summary, our analysis indicates that the expected incremental net cost to Medicare over the 5 yr after EPO was introduced will be substantial. The estimated cost differences were highly sensitive to the dose of EPO administered (and the amount that Medicare will pay for each use of EPO) and moderately sensitive to estimated rates of morbidity reduction and side effects requiring hospitalization.

ACKNOWLEDGMENTS

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REFERENCES

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