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Abstract

Purpose: One third of hemodialysis patients have high serum ferritin levels and low transferrin saturation (TSAT). The purpose of this analysis was to determine the cost effectiveness of administering 1g of sodium ferric gluconate complex (SFGC; also referred to as ferric gluconate) to patients with serum ferritin >500ng/mL and TSAT ≤25% based on the Dialysis Patients Response to IV Iron with Elevated Ferritin (DRIVE) study and its 6-week observational extension (DRIVE-II). In these studies, IV iron administration resulted in reduced epoetin requirements.

Methods: Decision analysis was performed using a time horizon of 12 weeks, consistent with the combined duration of DRIVE and DRIVE II. Treatment effectiveness was based on mean increase in hemoglobin (Hb) for each group (SFGC plus epoetin or epoetin alone) in the intention to treat populations. Costs included drugs (SFGC and epoetin) and hospitalizations due to serious adverse events (SAEs) reported. The primary cost effectiveness measure was cost per g/dL of Hb increase at 12 weeks. Costs were computed from a Medicare perspective using projected 2007 reimbursements. Sensitivity analyses were performed to test the impact of using the safety population, median epoetin and SFGC doses, actual 2005 Medicare reimbursements, median increases in Hb, and SAE rate changes. The model was constructed using TreeAge Pro software.

Results: Total cost per patient receiving SFGC plus epoetin was $3675 per g/dL Hb increase, while the total cost per patient receiving epoetin alone was $5065 per g/dL Hb increase. Net savings for SFGC plus epoetin was $1390 per g/dL Hb increase over the 12 week period Sensitivity analyses affirmed the robustness of the model.

Conclusion: Administering 1g of SFGC plus epoetin in patients with high ferritin and low TSAT as defined in the DRIVE studies resulted in significant cost-savings compared to epoetin alone.

Background

Significant policy issues surround the management of anemia with epoetin and iron;

- Medicare is developing a bundled payment scheme for dialysis services
- The safety of epoetin has been called into question[1]

The DRIVE Studies were conducted to determine the best treatment options for a subgroup of anemic end stage renal disease (ESRD) patients with high ferritin, but low to low-normal TSAT levels

- DRIVE I:
  - A 6 week randomized controlled trial
  - Measured the effect of adding SFGC to epoetin
  - Patients included in this trial were on hemodialysis, anemic (Hb < 11g/dL) despite an epoetin dosage >22,500 IU/week (or >225 IU/kg per week), and had high ferritin (500-1200ng/mL) and low TSAT (≤25%) measures
  - The intent to treat population included 64 participants in the SFGC and epoetin group, and 65 participants in the epoetin alone group
  - Patients were prescribed set doses of epoetin, 25% greater than their pre-trial dosing
  - This study found that patients receiving SFGC had significantly greater increases in Hb than those who did not[2]
- DRIVE II:
  - A 6 week observational follow-up study to DRIVE
  - During this phase of the trial, physicians were free to adjust epoetin doses as they saw fit
  - At the conclusion of this trial, patients who had received SFGC during DRIVE I received less epoetin on average, and experienced a greater increase in their Hb levels[3]

Objective

To determine if the addition of SFGC to epoetin is cost effective for anemic hemodialysis patients with high ferritin and low TSAT.

Methods

Model Design:

- A cost effectiveness analysis was conducted utilizing a decision tree framework
- Cost effectiveness was measured as the cost per unit of Hb increase observed in the DRIVE studies for the SFGC plus epoetin versus epoetin alone, and reported using the incremental cost effectiveness ratio (ICER)
- This model used the perspective of a Medicare payer because that program bears a majority of the cost of ESRD treatment in the U.S.
- The model was constructed to simulate the treatment groups in the DRIVE studies
- Data from the DRIVE studies were used to populate the variables in the model
- The model is presented in Figure 1

Assumptions and Costing Procedures:

- Hospitalizations associated with serious adverse events (SAEs) were coded using diagnosis related groupings (DRGs). The average national reimbursement for each DRG was then used to estimate the cost for each SAE. The DRG codes applied and estimated costs are listed in Table 1.
- Current Medicare reimbursement levels were used to estimate the cost of epoetin and SFGC based on the mean dose of medication used.
- Adverse event probabilities were based on the percent of patients hospitalized for a SAE in each group.
- Treatment efficacies were based on the mean change in Hb level from baseline to week 12 (the beginning of DRIVE I to the end of DRIVE II).

Sensitivity Analyses

- Univariate (one –way) Sensitivity Analyses
  - Each variable was replaced individually with a range of possible values. These values are listed in Table 2.
- Probabilistic Sensitivity Analysis
  - Simulations of this model were run taking into account the estimated variability around each input.
  - Simulations were run using a Monte Carlo method, to test 1 million random iterations of the model.

Disclosure

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Figure 1: Decision Tree Framework

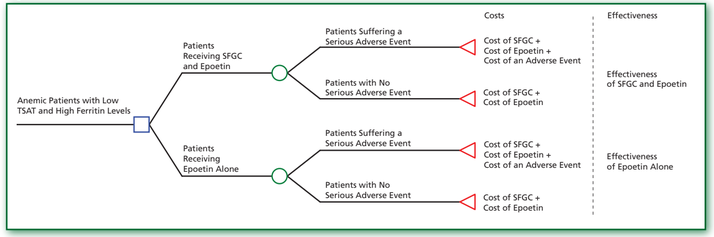


Figure 2: Results of Decision Tree after Roll-Back Calculations

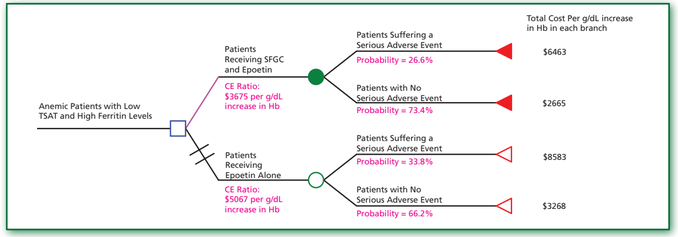


Table 1: Assigned DRG codes and estimated costs*

Treatment	Adverse Event Description	Assigned DRG Code	Assigned DRG Description	Estimated 2007 Reimbursement for This DRG ($US)
SFGC and Epoetin	Syncope	141	Syncope and Collapse with CC	3,720.45
	Abdominal Pain NOS	463	Signs and Symptoms with CC	3,491.67
	Endocarditis NOS	126	Acute and Subacute Endocarditis	12,986.21
	Implant Infection	120	Other Circulatory System O.R. Procedures	11,777.93
	Kidney Transplant Rejection	442	Other O.R. Procedures for Injuries with CC	12,446.22
	Cardiac Arrest	121	Circulatory Disorders with Acute Myocardial Infarction and Major Complications, Discharged Alive	7,883.34
	Hypertension NOS	134	Hypertension	3,020.95
	Cardiac Failure Congestive	127	Heart Failure and Shock	5,114.58
	Skin and Subcutaneous Tissue Abcess	277	Cellulitis, Age Greater than 17 with CC	4,365.81
	Clotted Tesio Catheter	317	Admission for Renal Dialysis	3,935.08
	Gangrene	130	Peripheral Vascular Disorders with CC	4,736.05
	Fluid Overload	317	Admission for Renal Dialysis	3,935.08
	Pleural Effusion	85	Pleural Effusion with CC	6,076.52
	Coagulation Time NOS Prolonged	397	Coagulation Disorders	6,477.98
	Implant Infection	120	Other Circulatory System O.R. Procedures	11,777.93
	Congestive Cardiac Failure Aggravated	317	Admission for Renal Dialysis	3,935.08
	Hypoglycemia NOS	296	Nutritional and Miscellaneous Metabolic Disorders, Age Greater than 17 with CC	4,065.33
Epoetin Alone	Peritonitis	572	Major Gastrointestinal Disorders and Peritoneal Infections	6,525.79
	Gastric Erosions	182	Esophagitis, Gastroenteritis and Miscellaneous Digestive Disorders, Age Greater than 17 with CC	3,831.67
	Nodal Arrythmia	138	Cardiac Arrhythmia and Conduction Disorders with CC	4,079.47
	Sepsis NOS	120	Other Circulatory System O.R. Procedures	11,777.93
	Pancreatitis Acute	204	Disorders of Pancreas Except Malignancy	5,360.43
	Cerebrovascular Accident	14	Intracranial Hemorrhage or Cerebral Infarction	5,907.25
	Cardiac Failure Congestive	127	Heart Failure and Shock	5,114.58
	Pneumonia NOS	89	Simple Pneumonia and Pleurisy, Age Greater than 17 with CC	5,061.41
	Pneumonia Staphylococcal	565	Respiratory System Diagnosis with Ventilator Support < 96 Hours	25,509.01
	Pulmonary Edema	87	Pulmonary Edema and Respiratory Failure	6,748.71
	Colitis Ischemic	182	Esophagitis, Gastroenteritis and Miscellaneous Digestive Disorders, Age Greater than 17 with CC	3,831.67
	Cardiac Failure Congestive	127	Heart Failure and Shock	5,114.58
	Dyspnea NOS	317	Admission for Renal Dialysis	3,935.08
	Cellulitis	277	Cellulitis, Age Greater than 17 with CC	4,365.81
	Skin and Subcutaneous Tissue Abcess	277	Cellulitis, Age Greater than 17 with CC	4,365.81
	Failure to Thrive	172	Digestive Malignancy with CC	6,965.78
	Sepsis NOS	576	Septicemia without Ventilator Support 96+ Hours, Age Greater than 17	7,781.87
	Blood Culture Positive	576	Septicemia without Ventilator Support 96+ Hours, Age Greater than 17	7,781.87
	Cellulitis	277	Cellulitis, Age Greater than 17 with CC	4,365.81
	Pulmonary Edema NOS	87	Pulmonary Edema and Respiratory Failure	6,748.71
	Sepsis NOS	120	Other Circulatory System O.R. Procedures	11,777.93
	Fluid Overload	317	Admission for Renal Dialysis	3,935.08

*NOS: not otherwise specified; CC: complicating condition

Table 2: Values used for each model input , base case and sensitivity analyses*

		Model Version									
Model Arm	Variable	Base Case	Modified Study Population	Modified Adverse Event Costs		Modified Medication Costs			Modified Treatment Efficacies		
				2005 Actual Hospitalization Costs	Fixed Hospital Cost per Day	Median Medication Usage	25th Percentile Medication Costs	85th Percentile Medication Costs	Median Treatment Efficacy	Treatment Efficacy - 1 Standard Deviation	Treatment Efficacy + 1 Standard Deviation
Iron and Epoetin	Cost of Iron	$499.13	$499.82	$499.13	$499.13	$457.92	$1,151.04	$1,988.16	$499.13	$499.13	$499.13
	Cost of Epoetin	$4,031.78	$4,144.26	$4,031.78	$4,031.78	$3,554.73	$7,346.23	$12,963.93	$4,031.78	$4,031.78	$4,031.78
	Cost of Adverse Events	$6,455.66	$6,742.66	$7,335.16	$10,042.69	$6,455.66	$6,456.66	$6,457.66	$6,455.66	$6,455.66	$6,455.66
	Probability of Adverse Events	26.60%	25.90%	26.60%	26.60%	26.60%	26.60%	26.60%	26.60%	26.60%	26.60%
	Treatment Efficacy	1.7g/dL	1.8	1.7g/dL	1.7g/dL	1.7g/dL	1.7g/dL	1.7g/dL	1.5	0.3	3.1
Epoetin Alone	Cost of Iron	$50.28	$48.20	$50.28	$50.28	$0.00	$115.96	$200.29	$50.28	$50.28	$50.28
	Cost of Epoetin	$4,248.92	$4,331.55	$4,248.92	$4,248.92	$3,892.94	$7,741.54	$13,662.12	$4,248.92	$4,248.92	$4,248.92
	Cost of Adverse Events	$6,858.47	$6,980.93	$7,314.61	$14,346.70	$6,858.47	$6,859.47	$6,860.47	$6,858.47	$6,858.47	$6,858.47
	Probability of Adverse Events	33.80%	33.30%	33.80%	33.80%	33.80%	33.80%	33.80%	33.80%	33.80%	33.80%
	Treatment Efficacy	1.3g/dL	1.4	1.3g/dL	1.3g/dL	1.3g/dL	1.3g/dL	1.3g/dL	1.3	-0.3	2.9

*Highlighted cells indicate the values that are different from the base case in each of the univariate sensitivity analyses

Table 3: Results from the univariate sensitivity analyses

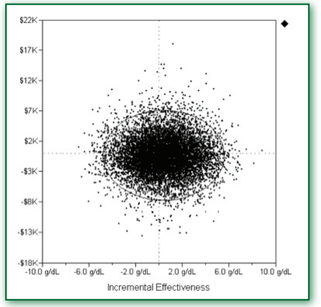
Model Version	Cost Effectiveness Ratio		ICER*
	SFGC and Epoetin Arm (cost per g/dL increase in Hb)	Epoetin Alone Arm (cost per g/dL increase in Hb)	
Base Case	$3,675.36	$5,064.68	SFGC and Epoetin Dominates Epoetin Alone
Modified Study Population (Using DRIVE II Safety Population vs. the DRIVE I ITT population)	$3,523.46	$5,064.67	SFGC and Epoetin Dominates Epoetin Alone
Modified Hospitalization Costs (used 2005 Actual reimbursements)	$3,812.98	$5,183.27	SFGC and Epoetin Dominates Epoetin Alone
Employed Fixed Hospital Cost per Day	$4,236.63	$7,011.61	SFGC and Epoetin Dominates Epoetin Alone
Employed Median Medication Usage	$3,370.50	$4,777.77	SFGC and Epoetin Dominates Epoetin Alone
Applied 25th Percentile Medication Costs	$7,768.38	$6,008.52	$288.95 per additional g/dL increase in Hb
Applied 85th Percentile Medication Costs	$12,344.60	$9,805.47	$1553.29 per additional g/dL increase in Hb
Used Median Treatment Efficacy	$4,165.41	$5,064.67	SFGC and Epoetin Dominates Epoetin Alone
Treatment Efficacy - 1 Standard Deviation	$20,827.05	-$21946.92**	SFGC and Epoetin Dominates Epoetin Alone
Treatment Efficacy + 1 Standard Deviation	$2,015.52	$2,270.37	SFGC and Epoetin Dominates Epoetin Alone

*If one treatment option is both less costly, and more effective, the ICER will be calculated as a negative number. When this happens, it is most appropriate to simply report that one treatment option dominates the other.

**Because epoetin alone actually had negative efficacy in this analysis, the cost effectiveness ratio was also negative.

Figure 3

Results of the Probabilistic Sensitivity Analysis, showing the incremental cost effectiveness scatterplot of SFGC and epoetin versus epoetin alone based on 1 million random iterations of the cost-effectiveness model (Monte Carlo simulation)



Results

Base Case Model Outcomes:

- SFGC and epoetin costs $3675.36 per g/dL increase in Hb.
- Epoetin alone costs $5064.68 per g/dL increase in Hb.
- Adding SFGC to epoetin provided a savings of $1389.32 for each g/dL increase in Hgb.
- The rolled back model with calculations is presented in Figure 2.

Univariate Sensitivity Analysis:

- The model was robust to sensitivity analyses which included modifications to:
  - Study population
  - Adverse event costs
  - Treatment efficacies
  - Medication costs, with one exception:
    - When the magnitude of the additional medication costs exceeded the savings associated with decreased adverse events, the cost of SFGC and epoetin combined was greater than that of epoetin alone. This was the case when the national reimbursement rates (at the 25th or 85th percentile) were used instead of Medicare reimbursement rates.

Probabilistic Sensitivity Analysis:

- Results of the probabilistic sensitivity analysis demonstrate that the combination of SFGC and epoetin tended to be the more cost effective than epoetin alone.
- The scatterplot in Figure 3 illustrates the extent of the variability in the model determined using the Monte Carlo simulation. The origin represents the relative cost and efficacy of epoetin alone and each point represents the comparative cost effectiveness of epoetin and SFGC in combination.
  - The 95% confidence interval includes the origin, so we cannot say with certainty that SFGC and epoetin dominates epoetin alone.
  - 32.53% of the points are in the lower left hand portion of the graph, representing the dominance of SFGC and epoetin in combination
  - 18.49% of points in the upper left corner representing the dominance of epoetin alone
  - 48.98% of points are in the two quadrants where a decision has to be made regarding an increased cost for increased efficacy.

Discussion

We believe this is a conservative model for the following reasons:

- Epoetin doses were flexible only during DRIVE II (the last 6 weeks of our model's time horizon), which limited the opportunity to observe a long-term difference in epoetin usage.
- Data on epoetin dosing were not available during patient hospitalizations. Since the rate and duration of hospitalizations were slightly higher in the epoetin only group and patients dropped out of the study if hospitalized because of a serious adverse event (the rate of which was significantly higher for the epoetin only group), it is likely that the true amount of epoetin administered to both groups exceeds our available data and is higher for the epoetin alone than the SFGC and epoetin group.

Study limitations:

- Because this model is based on protocol-driven clinical trial data, it does not accurately depict actual clinical practice. Future studies using observational data are essential to confirm these findings.
- The model considered only costs associated with serious adverse events.

Conclusions

This cost-effectiveness analysis of the DRIVE studies data suggests that administering 1 gram of SFGC to patients with high ferritin and TSAT of 25% or less results in cost savings when the Medicare perspective is employed.

When incorporated into a decision-analytic model, SFGC and epoetin treatment was estimated to result in a savings of $1389 per gram/dL of hemoglobin increase, which we believe to be conservative due to the fixed doses of epoetin required during the first 6 weeks of DRIVE.

Though there is uncertainty surrounding any economic analysis, our findings suggest that administering SFGC to this subset of anemia patients represents one potential strategy for reducing treatment costs in Medicare patients.

Application of our model to a population-level database is worthwhile to determine if findings hold true in actual practice.

References

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