

Human Recombinant Erythropoietin in the Medicare Patient Population

SUMMARY NOTES

(TAC RECOMMENDATIONS IN ITALICS)

Sixteenth Meeting of the
Medical Technology and Practice Patterns Institute's
Technical Advisory Committee (TAC)
Wednesday, November 16, 2005

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Issue 15N: Estimation of effect of epoetin on patient survival

TAC ACTION REQUIRED

1. Which of the following ways of coding (or estimating) the effect of epoetin is most useful to examine?

According to the TAC, MTPPI should prioritize the modeling as follows:

1. *average cumulative dose of epoetin during 2-year follow-up period*
2. *average dose for 3 – 6 month period*
3. *peak high dose of epoetin at any point in the study (e.g., >100,000 units/week)*
4. *percentage above a threshold dose (e.g., 30,000 units/week)*

Conclusion is to consider a variety of models

Regarding continuous versus quartile epoetin measures, TAC recommended:

- *quartiles*

Regarding which epoetin dose measure to use, TAC recommends both:

- ▶ *monthly average*
- ▶ *dose/administration*
- ▶ *do not consider weight*

2. What is the scientific/molecular/speculative basis for assuming any of these definitions of epoetin use will have short- or long-term effects on patient survival?

Not entirely clear based on the literature at this point.

Misc. Notes

To the extent possible, examine patients without (or with significantly less epoetin) compared to others.

Issue 16N: Understanding large changes in epoetin dosing

TAC ACTION REQUIRED

MTPPI would like to understand this process in greater detail, assuming there is some uniformity in the determinants and adjustment of epoetin dose. Addressing the following questions would be helpful:

1. What guidelines are used by practitioners to monitor and adjust epoetin dosing and outcomes? K/DOOI guidelines? Corporate protocols? Other standard of care documents?

Corporate protocols are in wide use, particularly nurse-driven protocols used by large chains.

2. What are the primary clinical determinants of altering dose (e.g., patient complaints of headaches, fatigue, other symptoms such as exacerbated hypertension, seizures, etc.)? Do clinical events influence epoetin dosing or are they addressed by increasing antihypertensive medications, for example.

No clinical determinants used to alter dose; driven almost exclusively by patient hematocrit.

3. Hematocrit appears to be the primary determinant of epoetin dose. Is there a general protocol to handle hematocrit values below, in the range of, or above the recommended (and reimbursed) K/DOQI guidelines?

Reimbursement rules are the primary determinant of dosing.

4. What reasons would cause a provider to change a patient's epoetin dose from the highest quartile to the lowest quartile or from the lowest to the highest quartile?

Besides changes in patient hematocrit, changes in physicians with different practice patterns for hospital-based facilities, noncompliance issues, and hospitalization.

Issue 17N: Withdrawal of epoetin for a month or longer

TAC ACTION REQUIRED

In attempting to model withdrawal of epoetin:

- a. Are there other reasons besides a high hematocrit to withdraw epoetin?

No. Although epoetin may be inadvertently stopped when a person is hospitalized.

- b. Is it clinically interesting to examine outcomes among patients who regularly stop and start epoetin treatment in contrast to patients who dose is more 'carefully regulated' not requiring stopping?

No. This has been forth largely by Amgen and there is no science base to support this theory. The TAC is interested in estimating the effect of several months without epoetin, however.

- c. Does zero dose indicate missed treatment (in contrast to incomplete claims data)?

Yes. Especially in view of the strong incentive to be reimbursed for an expensive drug.

Issue 18N: Modeling epoetin dosing based on hematocrit/dose history

TAC ACTION REQUIRED

We would like TAC input on the following issues:

1. Do the answers to the survey based on our convenience sample seem reasonable?

Yes.

2. Please give us your answers to the survey.

TAC members would have answered similarly.

3. Can we conclude therefore that a prior 2 month hematocrit history (possibly as a result of the 3-month rolling average for reimbursement purposes) is what is used, most often, to adjust the current epoetin dose?

Yes, especially in light of reimbursement incentives (3 month rolling average). Corporate protocols contain 2 - 3 month review of hematocrit in prescribing current dose. Nurse-driven protocol results have more variation than physician-driven, wherein more clinical judgement is utilized.

4. Can we assume that previous epoetin dose is not a factor in subsequent dosing?

Yes, according to most TAC members.

Issue N19: Modeling epoetin and adjunctive iron therapy

TAC ACTION REQUIRED

- How are iron and epo prescribed concomitantly?

Guidelines exist as to how to prescribe iron and epo.

- Why do we find some facilities/chains with very low iron and high epo and others just the opposite? What is the role of financial incentives?

It is surprising that such fluctuation exists. In 2001 both IV iron and IV epo were profitable.

- How do we measure different iron regimens with different concentrations? Two approaches have been put forth:

1. To "sum-up" different forms of iron, it is important to convert to the elemental stage. Iron is measured as elemental iron or Fe. Each salt can be measured in terms of elemental iron. For example:

Iron Dextran contains 50mg elemental Fe/ml

Iron Sucrose contains 20mg elemental Fe/ml

Sodium Ferric Gluconate contains 12.5mg elemental Fe/ml

The TAC recommends using approach 1 above. We may want to separate iron dextran since it is prescribed in high doses (>1,000 units/month).

2. Collapse all 3 iron products into 1 category (IV Iron) with the same unit (mg/month).

- Is iron overload a predominant problem among anemic ESRD patients?

No, it is not a problem. Rather, high iron usage is a marker of inflammation, just as high epoetin is. A patient with both high epo dose and high IV iron would be expected to be very sick.

- If so, should we control for the amount of iron consumed or just use categorical variable for iron use (Yes/No) as used in USRDS studies?

It is important to measure iron as a continuous variable not categorical. However, iron should be measured quarterly (not monthly) and categorized into quartiles or high/low doses.

Misc.

Iron is NOT used as a determinant in epoetin dosing. Iron influences hematocrit levels, and it is the hematocrit level (not the value of TSAT) that is used as the primary determinant of epoetin dosing. In this way, the influence of iron is absorbed by the hct value.

Issue 20N: Modeling other injectable drugs

TAC ACTION REQUIRED

In addition to iron, which injectable drugs might play an important role in anemia management to model in conjunction with epoetin use and patient outcomes?

- ▶ vitamin D
- ▶ Levocarnitine
- ▶ others?

None of the above injectable drugs have any direct relationship with anemia management or epoetin dosing. Do not therefore need to include in our model.

Issue 21N: Missing treatment-to-treatment data on epoetin dosing

TAC ACTION REQUIRED

Can the TAC suggest different strategies or approaches to mitigate these limitations?

We need to characterize the absences (e.g., noncompliance, hospitalizations, withdrawal from dialysis, etc.)

Misc.

Use networks versus large chains to examine effect of route of administration on study findings. Dr. Saddler will try to enlist DCI dialysis chains, comprising 190 facilities, to help in this effort to obtain treatment-to-treatment data.

Issue 22N: Censoring for missing claims data¹

TAC ACTION REQUIRED

- Is 30 days an appropriate time span for censoring on a gap?

It is a reasonable censoring gap, but the TAC recommends that we do a sensitivity analysis examining the patients that have such a gap and subsequently have additional information after this 30-day period. The TAC feels that this is informative censoring and that this population does differ in significant ways from the population that is not censored for such a large gap.

The reason that the USRDS uses 365 days for lost to followup is 1) patients move in and out of insurance coverage; and 2) avoid error on the side of losing patients.

- What are possible reasons for such a gap?

Possible reasons include: HMOs, recovery of temporary renal function, other individual reasons that are difficult to model (e.g., patient's feel better and stop dialysis or think they are healed from an herbal medicine.)

- How can we identify withdrawal from dialysis patients?

According to Paul Eggers, 20% of all death records indicate withdrawal from dialysis which is recorded as one of two causes of death: 1) failure to thrive; and 2).....[need to identify]

¹ Defined as a period of time in which there was no evidence of dialysis bills or other Medicare-reimbursed ESRD services including inpatient services, hospice or skilled nursing home care.

Issue 23N: Importance of including facility characteristics

TAC ACTION REQUIRED

We would like the TAC's guidance on the following issues:

1. How important are facilities characteristics in terms of the following:
 - a) understanding epoetin dosing, and
 - b) predicting survival.

Generally, the TAC did not think that facility characteristics would be predictive of epoetin dosing since this was an issue of physiology, not practice patterns. The TAC especially did not recommend use of SMR since they felt that SMRs were no 'longer in favor,' and that SMR did not adequately adjust for varying case-mix. The TAC suggested other ways of adjusting for quality of care such as a facility-wide adequacy of dialysis measure or other KDOQI guideline not including anemia management however. Furthermore, the TAC stipulated that SMR would be the result of appropriate epoetin use, but not to be placed on the other side of the equation and used to predict epoetin use. Finally, either network or geographic region was recommended but not both.

2. Which of the above-listed facility variables are most crucial?

None are critical, but the TAC recommended adding any facility variables in the model that are hypothesized would affect outcomes.

3. Are any variables not included that should be?

Mentioned above under question #1, possible other measures of quality of care.

Issue 24N: Patient selection criterion: removal of disabled ESRD patients

TAC ACTION REQUIRED

1. Are 20% of all under 65 ESRD patients disabled? In other words, does 20% seem like a reasonable proportion of nonelderly patients who were disabled first, allowing them to obtain Medicare eligibility, and subsequently having ESRD?

Given that diabetes is a cause of being 'disabled,' 20% seems very reasonable.

2. Is there a better way to identify disabled patients? Is there a flag in the administrative database?

Yes, there is a better way to identify a disabled patient; there is a flag called "Medicare Status Code" that should identify a patient as disabled.

3. Should we remove <65 year old 'disabled' patients, given that we do not remove >65 year old disabled patients? In other words, is the <65 year old disabled population representative or not representative of the nonelderly ESRD population at-large.

These under 65 disabled patients – predominately blind, amputees and stroke patients – are not representative of the general <65 ESRD population and therefore should not be included in our principal analysis.

Issue 25N: Defining epoetin resistance

TAC ACTION REQUIRED

The new draft 2005 KDOQI guidelines redefine *patient resistant to epoetin therapy* by increasing threshold from 450 units/kg/week to 500 units/kg/week despite a lack of studies supporting tangible clinical benefits. Given that the European clinical guidelines define epoetin resistance as greater than 300 units/kg.week, and given our results above which demonstrate that this new KDOQI recommendation may have serious potential mortality consequences of high epoetin requirements – for example, the highest quartile of epoetin use in the Zhang et al. (2004) study was only using greater than about 315 units/kg/week (22,068/70 kg); resulting in an unadjusted mortality rate in patients even at the target goal (11-12 Hb) was twice that of the lowest quartile.

What is the TAC recommendation on the optimal definition of epoetin resistance?

First, the TAC made it clear that weight is not an issue in defining resistance since there is total weight and muscle mass. Second, defining resistance is very arbitrary and is usually done based on the distribution of the data rather than a specific clinical endpoint or process. Third, there was a general consensus that any patient who required approximately 40,000 units/week, irrespective of his/her weight would be deemed resistant to epoetin therapy.