Trends-in-Medicine

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by Lynne Peterson

SUMMARY

The new KDOQI guidelines give doctors a little "wiggle" room to allow hemoglobin over 12 (but not over 13), which is more generous than the FDA guidelines warning that Hgb >12 has been associated with cardiac events and death. Most doctors still plan to take the cautious approach and stop or reduce the ESA dose at 12 because of fear of lawsuits. ♦ Doctors also may be a bit more cautious about pushing the ESA dose to hyporesponsive patients, but no government mandate on this is expected soon. ♦ The FDA is tightening requirements for clinical trials, reportedly demanding large superiority trials that show a ***clinical*** benefit. ♦ Thus, ESA use is predicted to go down 20%-25% year-to-year. ♦ Nephrologists are looking forward to newer ESAs, particularly Roche's Mircera and Fibrogen's oral FG-2216. ♦ Experts are urging doctors to use more IV iron to boost hemoglobin and reduce the ESA dose, but long infusions have been a barrier, so there is a buzz about Advanced Magnetics' fast push IV iron, ferumoxytol. Phase III efficacy and safety data for ferumoxytol looked good.

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NATIONAL KIDNEY FOUNDATION (NKF) SPRING CLINICAL MEETING (CM.07)

Orlando, FL
April 10-13, 2007

Nearly 20 million Americans have chronic kidney disease (CKD). Between 6-7 million of these are moderate-to-severe (Stage 3-4), and about 500,000 are currently being treated for end-stage renal disease (ESRD). Experts estimate the prevalence of CKD will double by 2010. Studies have found that primary care physicians are prescribing anemia treatment for only about 30% of their CKD patients with anemia. NKF CM.07 was dominated by two issues: new guidelines for anemia treatment and a call for more use of intravenous (IV) iron.

With only about 4,800 nephrologists in the U.S., speakers emphasized the importance of non-nephrologists identifying CKD and appropriately managing or co-managing those patients. In a national cross-sectional survey, physicians were given a hypothetical patient scenario, and the correct identification of CKD was made by only 59% of primary care physicians (PCPs), 78% of general internal medicine doctors, and 97% of nephrologists. Primary care physicians were less likely to recommend referral of patients with Stage 3-4 CKD to nephrologists, and both PCPs and internal medicine doctors wanted PCPs to maintain primary "control" over patient care.

Dr. L. Ebony Boulware of Johns Hopkins called for collaborative, multi-disciplinary care between nephrologists and PCPs, saying that could improve patient outcomes. Dr. Anton Schoolwerth of Dartmouth-Hitchcock Medical Center suggested one answer is CKD clinics. The advantages of these clinics, he said, are:

- Earlier detection of CKD.
- Earlier consultations with nephrologists, cardiovascular specialists, or dieticians.
- Guideline-based utilization of interventions to treat anemia, mineral metabolism and bone disease, hypertension, cardiovascular disease, diabetes, and malnutrition.
- Patient education and empowerment targeted towards CKD.
- An integrated approach to managing patients involving PCPs.

ERYTHROPOIESIS-STIMULATING AGENTS (ESAS)

The environment

At the American Society of Nephrology (ASN) meeting in November 2006, the CHOIR and CREATE trials were presented, and those trials suggested – but didn't definitely prove – that there is increased mortality with ESAs when hemoglobin

(Hgb) is targeted >12 g/dL in CKD patients. The conclusion from CHOIR, which was halted before its completion when the data safety monitoring board (DSMB) found more deaths in patients with higher Hgb targets, was that targeting Hgb >13 increased the risk of heart attack, death, and stroke. CREATE investigators found that a higher Hgb target did not reduce cardiovascular events (the primary endpoint) or all-cause mortality, but the time to dialysis and quality of life were significantly shorter in the higher target hemoglobin arm. The risk of congestive heart failure (CHF) also was higher in the higher target Hgb arm in CREATE.

Also in November 2006, the FDA issued a public advisory on the use of ESAs in CKD patients, warning that "patients treated with an ESA and dosed to a target Hgb of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a Hgb of 11.3 g/dL." The FDA urged doctors to follow currently approved prescribing information for Johnson & Johnson's Procrit (epoetin alfa), Amgen's Epogen (epoetin alfa), and Amgen's Aranesp (darbepoetin alfa), including a recommendation that the target Hgb not exceed 12 g/dL.

Then, on March 9, 2007, the FDA added a black box warning to all approved ESAs after other studies found more rapid tumor growth in patients with head and neck cancer who received high ESA doses. The Agency advised doctors to use the lowest dose of ESA that will ***gradually*** increase Hgb concentrations to the ***lowest*** level sufficient to avoid blood transfusions. The FDA also warned that ESAs increase the risk for death and serious cardiovascular events when administered to a target Hgb >12 g/dL.

A week later, the Centers for Medicare and Medicaid Services (CMS) announced it was opening a National Coverage Analysis (NCA) on the use of ESAs for conditions other than ESRD –i.e., use in cancer patients. This is the first step toward issuing a National Coverage Determination (NCD). Currently, CMS pays for ESAs needed to maintain a target Hgb level of 10-12 g/dL and reduces payment if Hgb is >13 g/dL unless the dose is reduced.

On May 10, 2007, the FDA's Oncologic Drugs Advisory Committee (ODAC) will meet to discuss recommendations for ESA use in cancer patients. A meeting of the FDA's Cardio-Renal Advisory Committee is also expected but has not been formally announced yet. An expert described the FDA as "very pressured, very distracted, and very, very vigilant" right now, making it difficult for companies with new ESAs in development. For instance, a source said Roche has two Phase IIIb trials that were supposed to have started but have been delayed until the target Hgb is revised, "The entry criteria would have been ≤13 g/dL and treat to 13.5, and that will now shift downward."

Dr. Anatole Besarab of Henry Ford Hospital in Detroit said, "The FDA wants more safety. New drugs have to be as safe or safer, with the emphasis on safer, than what we have. It isn't just equivalence any more, they have to show added value. They can no longer be non-inferior or equivalent, they need superiority…The FDA won't approve any trial overshooting 12, and the FDA is requiring dose reductions when a patient overshoots 12 with a single value, though it is possible that in hemodialysis patients they may allow a second measure before a dose reduction." What is added value? He said, "Something in Phase III that is clinically meaningful to the patient, the staff, or economically…Less cycling (fewer hemoglobin fluctuations) could be, but there are no studies to address that."

On April 18, 2007, an article came out in the ***Journal of the American Medical Association*** on for-profit dialysis units and how they use ESAs, accompanied by a very, very tough editorial. An expert at NKF predicted these pieces will "get the attention of Congress, of Rep. Pete Stark, and CMS." In the article, researchers – Mae Thamer PhD et al – reported on their study of the association between dialysis facility ownership and the dose of epoetin administered, looking at U.S. Renal Data System (USRDS) Medicare claims data.

They found: "Large for-profit chains administered higher epoetin doses, used higher dose increases, and had higher achieved hematocrit levels, as well as a larger proportion of patients above the upper limit of hematocrit level…The differences in epoetin dose levels among dialysis chains are not explained by differences in patient characteristics or responsiveness to epoetin therapy."

- Patients in large for-profit dialysis chain facilities were consistently given the highest doses of epoetin regardless of anemia status.
- Compared with nonprofit facilities, for-profit facilities administered, on average, an additional 3306 U/week of epoetin.
- Epoetin doses at large chains ranged from 17,832 U/week at one chain to 24,986 U/week at another.
- On average, compared with non-profit facilities, for-profit facilities increased epoetin doses 3-fold for patients with hematocrit levels <33% and also increased the doses among patients with hematocrit levels in the recommended target of 33%-36%, especially in the largest for-profit chain facilities.
- The greatest difference in dosing practice patterns between facilities was found among patients with hematocrit levels <33%.

The researchers concluded: "These findings suggest that reimbursement policy and clinical performance measures may provide incentives for dialysis facilities, in particular for-profit facilities, to target hematocrit levels exceeding those recommended by the clinical guidelines. As existing guidelines are reevaluated, it will be important for policy makers to design an epoetin reimbursement policy that provides an incentive to achieve desired clinical outcomes while optimizing epoetin usage."

In his ***JAMA*** editorial, Dr. Daniel Coyne of Washington University School of Medicine was critical not only of for-profit dialysis centers but also the National Kidney Foundation. Among his comments were:

- "Increasing the mean hemoglobin level in the U.S. dialysis population from 10 g/dL in 1993 to approximately 12 g/dL in 2004 certainly did not reduce mortality by [the predicted] 50%. The adjusted mortality rate for prevalent dialysis patients was 231 deaths (per 1000 patient-years at risk) in 1993 and 230 deaths (per 1000 patient-years at risk) in 2004."
- "The beneficial survival effect predicted by observational studies also was not observed in RCTs of higher vs. lower target hemoglobin levels in patients with chronic kidney disease. Indeed, it is possible that mortality rates in dialysis patients may not have decreased because higher hemoglobin levels, higher doses of an ESA, or both, increase cardiovascular events and death."
- *Why would nephrologists prescribe so much epoetin at certain for-profit chains?* Dr. Coyne suggested, "Some nephrologists may not even know they are making these prescribing decisions. Nephrologists frequently sign multipage standing orders for treatment of long-term dialysis patients that include an anemia protocol that may subtly increase epoetin and hemoglobin levels. Nephrologists often turn over management to anemia managers (dialysis chain employees)…In addition, many nephrologists may have been convinced that it is in the interest of patients to always maintain hemoglobin levels higher than 11 g/dL, and that exceeding a hemoglobin level of 12 g/dL is acceptable based on observational data."
- *Why would for-profit dialysis chains facilities permit or encourage such anemia management strategies?* Dr. Coyne pointed out, "Epoetin is profitable for dialysis facilities…The significant dependence of dialysis providers on epoetin for income, and the ease at which a higher hemoglobin target affords greater epoetin use, creates a tempting situation for all involved."
- "Physicians…should not wait for the NKF opinions (new guidelines), nor necessarily trust or follow them." Dr. Coyne pointed out that several potential conflicts of interest exist that raise questions about the independence of the NKF and the anemia work group.
- "Maintaining hemoglobin levels between 10.5 and 11.5 g/dL will reduce transfusion requirements in patients with chronic kidney disease who are receiving dialysis. This means rarely initiating an ESA if hemoglobin level is above 10 g/dL, and changing the ESA dose by approximately 25% monthly whenever the hemoglobin level is above or below this range in a patient treated with an ESA. The ESA dose should be reduced by approximately 50% or stopped when the hemoglobin level exceeds 12.5 g/dL."

New KDOQI guidelines on anemia

Following the release of the CREATE and CHOIR trials at the ASN last fall and the March 2007 FDA black box warning added to ESAs, doctors had been anticipating new guidelines from the National Kidney Foundation on ESA use, and a draft update of those guidelines was announced at the NKF meeting. The KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guidelines on Anemia and CKD will be published in the fall.

The KDOQI work group is recommending the target hemoglobin should generally be in the range 11.0 to 12.0 g/dL, but not above 13.0 g/dL. The document does note, though, that "because of natural fluctuations actual Hgb results will vary widely from Hgb targets." KDOQI vice chair Dr. Michael Rocco of Wake Forest University said, "The work group clearly felt that the evidence is even stronger now that their initial recommendation to choose Hgb targets below 13.0 g/dL is very appropriate for CKD patients." Dr. David Van Wyck of the University of Arizona College of Medicine, Co-Chair of the KDOQI work group, stressed the importance of these words in the guidelines: "generally in the range."

The new guidelines make four points:

1. The Hgb target is the intended aim of ESA therapy for the individual CKD patient. In clinical practice, achieved Hgb results vary considerably from the Hgb target. A target Hgb can be viewed two ways: either as a range from 11-12, or as discrete Hgb value (11.0, 11.5, 12.0).
2. Selection of the Hgb target and the level at which ESA therapy is initiated in the individual patient should include considerations of potential benefits (including improvement in quality of life and avoidance of transfusion) and potential harms (life-threatening adverse events). (*Clinical practice recommendation*.)
3. In dialysis and non-dialysis CKD patients receiving ESA therapy, the selected Hgb target should generally be in the range of 11.0 to 12.0 g/dL. Dr. Van Wyck said, "The wording explicitly excludes any reference to achieved Hgb. We fashioned the statement this way to balance the potential benefits of ESA therapy against the potential harm of targets >13." (*Clinical practice recommendation.*)
4. In dialysis and non-dialysis CKD patients receiving ESA therapy, the Hgb target should not be above 13.0 g/dL. (*Moderately strong clinical practice recommendation*.)

KDOQI Work Group Estimate of Relative Risk with Hgb Target >13

Relative risk	Non-dialysis CKD patients	Dialysis CKD patients
CV events	1.24	1.14
Mortality	N/A	1.12

Dr. Van Wyck said, "The statement about Hgb targets above the 13.0 g/dL threshold reflects our judgment that greater weight should be given to potential harm than to uncertain benefit…It was the agreement of the work group that the harm signals which were consistent for both dialysis and non-dialysis CKD patients, whether that achieved statistical significance or not, were sufficient to designate that as an evidence-based guidelines statement against targets >13…It was not sufficient enough to say 'strong evidence,' but it was sufficient to say 'moderate evidence'…and (the guidelines) should be applied to all CKD patients."

Reaction to new KDOQI anemia guidelines

The KDOQI guidelines themselves are expected to do little to change clinical practice with respect to ESA use, noting that they are somewhat less restrictive than the FDA guidance. Several sources suggested that the KDOQI guidelines are a political move, offering a bit of a "shield" from lawsuits for nephrologists who exceed Hgb 12 g/dL but who don't go over 13. An expert said, "Anything in the KDOQI guidelines that is not as cautious as the FDA guidelines will immediately raise conflict of interest issues, but I think most objective people will feel the guidelines are a really reasonable approach – even though they are not as strict as the FDA guidelines." Another expert said, "Doctors can always follow clinical practice guidelines, but you need to cover yourself more carefully when you vary from the package insert, especially when there is a black box warning."

However, another expert wasn't sure this will be much help against a lawsuit, "What do you think the lawyers will follow – KDOQI or the FDA? The FDA!" Dr. Richard Lafayette of Stanford warned, "We need to be careful not to regress to the pre-1980s where patients were suffering from severe complications of CKD…The benefits of ESAs are primarily improved quality of life, and that is incredibly important…We must be cautious and defend this population from the regression that could occur from adopting unreasonably low Hgb targets…We have to continue fighting for our patients' rights to get appropriate therapy."

Amgen issued a statement, saying, "Amgen always recommends that physicians and other prescribers carefully follow FDA-approved prescribing instructions for our products… Like others in the nephrology community, we just received the new draft guidelines and are reviewing them now. It is premature for Amgen to comment on the specifics of the draft guidelines at this time, but we continue to support the creation and updating of robust, independent, and evidence-based clinical practice guidelines."

Among other comments about the new guidelines were:

- Dr. Van Wyck called on investigators in recent major trials, including CHOIR and CREATE, to further analyze their data, "Let me propose we take this time to challenge those who have the data to analyze the data for rate of rise (of hemoglobin), for hemoglobin variability, and relate that to outcomes, if any.
- Dr. Anil Agarwal of Ohio State University said that, regardless of the new KDOQI guidelines, he will "keep Hgb <12 g/dL and follow the FDA recommendations for now."
- "Is there a way these guidelines could somehow have an influence over things such as the FDA's black box warning (on ESAs)?...Lawyers are already advertising for patients on an ESA with high hemoglobin...I think the FDA needs to take another look at the black box warning."
- "It is not clear that we will be able to keep patients in a narrow (Hgb 11-12 g/dL) interval. We well may have a bias of low or high dosing to keep patients in the interval. The goal is to find the sweet spot."

Dr. Robert Toto of the University of Texas Southwestern Medical School offered a defense to the CREATE and CHOIR trials. He said those trials are "important," but he also urged doctors to "look at the limitations" of those trials, especially the small size of the trials, "CREATE was woefully underpowered to detect significant differences in the outcome, even though there was a trend to a worse outcome in the higher-target group…CHOIR also had issues." CHOIR issues included:

- Baseline differences in CABG – 17% in the high Hgb group vs. 14% in the low Hgb group ($p<.03$).
- Baseline difference in hypertension – 95% in the high Hgb group vs. 92% in the low Hgb group ($p<.02$).
- >50% lost to follow-up, with dialysis started in about half, and the remainder withdrawn for various reasons.
- Higher doses of ESA were given than in CREATE.

Dr. Toto also pointed out that, even taken together, CREATE and CHOIR studied a very small segment of the overall CKD population. He said, "In the CREATE study, there are 600 patients. CHOIR had 1,400 patients. So, 2,000 patients total were randomized to controlled trials looking at different Hgb levels and looking at cardiovascular outcomes. That's it. That's the extent of CV outcome trials in patients with CKD not yet on dialysis…We have two studies that are outcomes trials in pre-CKD patients…But, to conclude on the basis of these two studies, with their limitations, that the game is over and that we know what Hgb levels should be, and that is the end for CV outcomes, I think is a little premature…(Those studies) actually had to be right-sized to fit the journal (***New England Journal of Medicine***). There is a lot of data never looked at. It may be we had some people at (Hgb) 14-15… Maybe it is the distribution of the vehicle – the drug – that we are giving them is inappropriately high for some patients."

Some doctors have been surprised that the TREAT trial, which compares a target Hgb of 13 g/dL to a target of Hgb <9, is being allowed to continue. TREAT is a randomized trial comparing Aranesp to placebo in 4,000 CKD patients. A California doctor said, "It is amazing the TREAT design was not changed to a lower Hgb than 13.5. I'm flabbergasted that

they are able to continue TREAT as designed, whether the DSMB is concerned or not. I'm not sure my local IRB (institutional review board) would approve TREAT participation today."

Dr. Toto, who is on the executive committee for TREAT, believes it will be fully enrolled by the end of 3Q07 or, at the latest, by the end of 2007. He said, "I think the TREAT trial will help by adding information to that. If TREAT shows more events happening, then I'm sure the study would be stopped by the DSMB…I'm not sure what TREAT will ultimately end up…I don't know if 13 will be achieved or slightly higher…And if it is higher and the event rate is higher, that probably would support the idea that a higher Hgb does increase cardiovascular risk…The TREAT DSMB met after CHOIR, CREATE, and the FDA warning (about ESAs)…and looked at all the available data and feels the study warrants continuing."

Outlook for ESA use going forward

On average, doctors at the NKF meeting estimated that their ESA usage in November 2007 will be 20%-25% below what they were using in October 2006. A few doctors predicted larger drops, and some chain doctors predicted smaller drops (in the range of 10%). Several sources noted that some of the ESA decreases will be offset by new patients coming into treatment. A California doctor said, "I predict a 50% cut in our EPO (erythropoietin) use in actively treated patients compared to last year. You need half the dose to get to 12 than you do to get to 13. But there will be more patients started on an ESA, so the market will grow."

The CHOIR and CREATE trials had some impact on ESA usage, the FDA warning and black box also affected use, but the fear of lawsuits is expected to be the real factor driving a decline in ESA use. Nephrologists are starting to worry that they will get sued if they give an ESA to a patient with an Hgb >12 and that patient has an event or dies. This fear factor will make doctors much more conservative in their use of ESAs, sources agreed. Dr. Toto said, "I think we are kind of stuck. We need to stay at a Hgb <12 g/dL because if a patient is over 12 g/dL and has an event, there could be legal exposure…I used to go closer to 13, and now I aim for 12." Another expert said, "Very few of the 4,800 nephrologists in the U.S., if surveyed, would be conscious of what the FDA label change actually says. What will get nephrologists engaged is the medico-legal issue – when they hear about lawsuits, etc. – because nephrologists are very risk averse."

Dr. Steven Fishbane of Winthrop University Hospital in New York said his hospital had a staff meeting about ESA usage after the CHOIR and CREATE results were announced, and there was "100% consensus" that the protocol should be changed to the "most conservative approach and follow the FDA guidelines strictly until the dust settles." The doctors there had been reducing the ESA dose by 25% when a patient reached Hgb 13, and now they are holding the ESA dose at Hgb 12. Under the old protocol, about 5% of outpatients had their ESA on hold at any given time; recently, a check found that 62.5% of outpatients had their ESA on hold. Dr. Fishbane said, "We are not representative, and independent dialysis centers are not that strict. And as our patients' hemoglobin drifts down, there will be fewer patients on hold."

Comments on the outlook for ESA use included:

- "Law firms are already advertising for patients who have had a cardiovascular event on an ESA."
- "Managed care organizations (MCOs) ***could*** reasonably say you can't initiate an ESA unless the patient is <10 and not unless <9 in patients with cardiovascular disease." But he didn't know of any MCOs that have done this yet.
- *Pennsylvania (academic center):* "At Hgb 12.2 or 12.5, I would hold the ESA dose in dialysis patients and lower the dose in CKD patients…Quality of life is still the biggest driver at the low Hgb end, so we will trade some risk at the end for this, and we don't know if Hgb <10 is worse than Hgb >12."
- "I heard a couple of big managed care organizations are not paying for ESA at a Hgb >10."
- *Florida #1:* "Our Hgb target was 13, and now it is 11-12, but we are getting more new patients, so I only expect our EPO use to go down 5%-10%...Over 12, I'll lower the dose because if you hold it, the patient can drop too far. For outpatients, I'll stretch the interval ***and*** lower the dose."
- *Florida #2:* "The KDOQI guidelines won't change what I'm doing because I already lowered my target, but EPO use will drop 20%...I won't change my high dose use of EPO, but I may start new patients more conservatively and not push as much, go slower. Slightly above 12, I won't do anything, but at 12.6, I'll lower the EPO dose by 20%."
- *Florida #3:* "The new KDOQI guidelines will reduce EPO use."
- *Illinois:* "I'll probably stop EPO at 12 now, but EPO improves quality of life."
- *Tennessee:* "Our median Hgb will fall. At 12.3, I won't change anything for dialysis patients. I hardly ever hold EPO. 12.2-12.3 is a gray area, but perhaps I'll decrease a little…Over the next 2-3 years, I expect EPO use will dip 10%-20%."
- *California:* "We will not stop at 12, but we will lower the dose…We have been targeting 11-12, and that means patients will go >12. Above 12 we will reduce the dose 25% if Hgb is rising slowly and reduce it 50% if it is rising rapidly. And if the trajectory is steep, we will see the patient sooner (in a couple of weeks)…But I'm not uncomfortable with a Hgb >12…If your target is >13, you could have a liability issue. Otherwise, going over 12 is an issue but completely unavoidable."

- *Fresenius official:* "We sent a directive to medical directors that 'we expect' – but don't mandate – a 25% EPO reduction when a patient goes over Hgb 12."

Asked if the government (FDA or CMS) is likely to give recommendations on the amount of ESA that can be given to an individual patient (maximum dosing) or to set a per-patient dose ceiling above which CMS will not reimburse for an ESA, experts offered differing opinions:

- *Tennessee:* "High dose patients probably are the issue (with ESA mortality at high Hgb targets), and there are likely to be limits on the dose, but not for a couple of years."
- *Ohio:* "CMS already has a limit in a given patient, but it is outrageously high. I think CMS will leave it to clinicians. They may suggest but not mandate a ceiling. It is too early for that."
- *Pennsylvania:* "I would not be surprised to see the government limit the (total) dose."
- *New York:* "Why does CMS reimburse for ESA at a Hgb >12 when the FDA says >12 is associated with increased CV events and death? That is an impossible position for CMS. So, the FDA has to change its language. I think the FDA will separate oncology and nephrology (recommendations on the use of ESA). There is some feeling at FDA that the Agency went too far with the current language."
- *Texas:* "I don't know if there will be limitations on the total EPO dose…You might speculate that (patients) requiring a higher dose means…that the patients selected were sicker, more inflamed, hyporesponsive, and therefore needed higher doses, or (you might speculate that) the drug didn't work as well…but that is speculation. I think that would be important information, but I don't think we know yet."
- *Michigan #1:* "I expect there will be a cap in CKD of total units a month for non-dialysis patients or in weekly units per kilogram for dialysis patients."
- *Michigan #2:* "I don't see CMS capping the total EPO dose."

Asked if ESAs are likely to get bundled in the composite rate that dialysis centers get, a doctor said, "We give insulin at home, so I see no reason not to do that with ESAs…ESAs in hemodialysis are all IV. We tried subcutaneous (SC) and found the nurses got confused with what people were doing. We will go to SC when EPO is bundled."

Dr. Robert Provenzano of St. John Hospital and Medical Center in Detroit, the immediate past president of the Renal Physicians Association, warned that government intervention is likely to increase, not decrease. He said that pressure on ESRD costs is continuing to increase, "We all have to be sensitive to the fact that cost is going up. The total amount spent on ESRD continues to increase, so a very small Medicare population (~0.6%) are consuming a disproportionate amount of Medicare dollars (6%-7%)…And employee group health plans have had the burden shifted more and more to them (for ESRD). When the government starts shifting Medicare responsibilities to the 'big boys,' I can guarantee pressure is coming down from everywhere. What do you do? It's sort of like stopping a riot; you shoot the first guy in the front line – and ESAs are a huge part of the (Medicare ESRD) spending."

Dr. Provenzano said the government is trying to micro-manage the ESA war, and he argued that this is not an effective approach. He described the ASP+6% that Medicare pays for ESRD drugs as "almost laughable," adding, "The essential concern was that (with ASP+6%) there would be no treatment for patients with anemia, and so far there is evidence that this is occurring...The ability to care for at-risk, highly co-morbid patients continues to decrease…CKD care is a money loser (for doctors), so the patients go on dialysis, and then there is no reimbursement problem. That (dialysis) is not a money loser…ASP+6% has been here only a year, but it certainly seems more and more physicians are telling patients to go to the hospital or the oncologist or the patients are not being treated. Is all this talk about dosing impacting that? I think so."

ESA hyporesponsiveness

Several experts estimated that ≤10% of non-dialysis CKD patients and 10%-30% of hemodialysis patients are hyporesponsive, requiring boosted doses of an ESA. However, Dr. Toto noted that there isn't a good definition of hyporesponsiveness. Dr. Jerry Yee of Henry Ford Hospital cited several causes of hyporesponsiveness to ESAs, aside from iron deficiency:

1. **Practice pattern-related:** protocol design, protocol compliance, lab monitoring, patient adherence, narrow target Hgb range, low KT/V, and payment restrictions.
2. **Patient factors and comorbidities:** ESA sensitivity, red blood cell (RBC) lifespan, inflammation, secondary hyperparathyroidism (SHPT), diabetes-related, cancer/ malignancies, hematologic disorders, malnutrition, and vitamin deficiency.
3. **Intercurrent events:** iron deficiency, infection, transient inflammation, hospitalization, bleeding/hemolysis, PRCA (pure red cell aplasia), medications, and interdialytic weight gain.

Dosing intervals and Hgb control

A 5-year retrospective chart review at the Cleveland Clinic, sponsored by Roche, looked at ESA usage patterns and Hgb control in 111 CKD patients not receiving dialysis. Researchers found:

- The majority of Epogen patients (67%) were started on QW dosing, and the dominant dosing interval was Q2W, but the most common final dosing reverted to QW.

- The majority of Aranesp patients (90.5%) were started on Q2W dosing, and the dominant dosing interval was Q3W, but the most common final dosing interval reverted to Q2W.
- Hgb variability outside the target range (11-12) was common, regardless of the dominant dosing interval.

Dosing Intervals and Hgb Control in CKD Patients

Measurement	Epogen	Aranesp
Injection-related time per month	10.73 hours	3.10 hours
Injection-related travel per month	76.28 miles	27.39 miles
Travel costs	$18.28	$7.66

Anemia management

Dr. Yee helped develop a computerized anemia management protocol (CAMP). It uses trend analyses, continuous quality initiatives, and algorithmic dosing of Aranesp and iron. So far, he said no other institutions have licensed CAMP from his hospital, but there has been interest in it.

CAMP Results as of February 2007

Hemoglobin level	% of patients achieving
<9.5	8.8%
9.5-11	16.2%
11-13	66.2%
>13	8.8%

Dr. David Spiegel of the University of Colorado Health Sciences Center has also developed a computerized dosing algorithm for anemia management. He said computers can learn what to watch for in individual patients and make adjustments in ESA dose before changes in hemoglobin are seen, and he noted that the cost of measuring the needed factors is offset by the improvement in quality of life. In a study of 9 patients, he found that EPO managed by a computerized anemia program lowered EPO use and increased the number of patients in target.

Asked if he would add IV iron to his algorithm, Dr. Spiegel said, "No, the assumption is the patient is iron replete when you use an ESA…Maybe if that were built into the algorithm, it might cut down on cycling…We will have to look at that… but how much data do you have to input into the algorithm?"

Specific ESAs

The current controversy over ESA dosing adds to the appeal of new agents on the horizon. Dr. Rebecca Schmidt of West Virginia University School of Medicine said, "We have a lot of challenges facing us. Our challenges, particularly of late, being not so much which option but how to take what options we have and fit them in to our regulatory, legislative, and pharmacoeconomic realms and requirements…It is good to have multiple agents on the horizon…Patients faced with significant costs may be helped in that some of the new agents could be used at longer dosing intervals." Dr. Fishbane said, "Current treatments are not optimal. They require frequent injections and stray excessively from the normal biology of erythropoietin."

➢ **Affymax/Takeda's Hematide,** synthetic peptide-based ESA, or EPO-mimetic. Hematide has finished Phase II trials and will start a Phase III trial as soon as details can be worked out with the FDA. Sources insisted that Affymax does not have to do another Phase II trial before moving to Phase III, but they said the FDA has changed and expanded the Phase III requirements. One expert said, "The days of non-inferiority on Hgb are probably over. What companies need to show in Phase III is harder…That means more extensive Phase III trials, and I don't think Affymax expected that. The Hematide trial will have to be bigger and slower than what Affymax

Approved and Investigational ESAs

Company	Brand Name	Type	Mean half-life
Approved in the U.S.			
Amgen	Aranesp	Darbepoetin alfa	25.3 hours IV 69.6 hours SC
Amgen	Epogen	Epoetin alfa	6.8 hours IV 19.4 hours SC
Johnson & Johnson	Procrit	Epoetin alfa	6.8 hours IV 19.4 hours SC
ESAs approved only outside the U.S.			
Elanex Pharma	Epomax/Hemax (South America, central Europe, India)	Epoetin omega	N/A
Roche	NeoRecormon (Europe)	Epoetin beta	8.8 hours IV 24.2 hours SC
Various	(third world)	Bio-similar generic epoetins	N/A
ESAs in development			
Affymax/Takeda	Hematide	Pegylated synthetic peptide-based ESA	75 hours IV 80 hours SC
Amgen	---	AMG-114, a hyperglycosylated analog of Aranesp	N/A
Fibrogen	---	FG-2216, a selective HIF stabilizer	7-8 hours
Fibrogen	---	FG-4592	N/A
Roche	Mircera	CERA, methoxy polyethylene glycol-epoetin beta	130-134 hours IV 133-139 hours SC
Transkaryotic Therapies	Dynepo	Epoetin delta	N/A

expected." Dr. Besarab said Hematide is being required to show an added benefit in outcomes in Phase III. (***See again the FDA reference on page 2*).**

Another speaker said that in Phase I studies this agent has shown a dose-dependent increase in EPO activity >1 month and no cross reactivity with EPO, with a single IV dose increasing Hgb >1.0 g/dL in 6 of 7 patients after 28 days. He added, "It is once-monthly, with no patent issues, is stable at room temperature, and does not cross-react with anti-EPO antibodies. It should be less expensive to produce, but I worry a little about immunogenicity."

Data were presented in a poster from a Phase II multicenter, open-label, sequential, dose-finding study of 165 patients with stable Hgb on prior EPO. The results showed that:

- 485 doses were administered, with 21% of patients getting a dose increase, and 11% a dose decrease.
- 78% of the 1,954 Hgb values taken were in the 10-12.5 range (7% <10, 6% >13).
- Mean reticulocyte increases were observed after every Hematide injection, with peak increase at about two weeks post-injection.
- Mean Hgb levels across all cohorts were maintained within ±1 g/dL.
- Mean Hgb at 4 weeks was: 11.2 whether the patient received 4, 5, or 6 injections.
- There was only one drug-related serious adverse event – a Grade 2 infusion reaction.
- 7% of patients had a drug-related adverse event: 3 fatigue, 2 weakness, 2 rash, and 1 worsening hypertension.
- Five patients died during the study – 3 cardiac arrest, 1 respiratory failure/sepsis, and 1 pneumonia/sepsis – but none were deemed related to Hematide.

Researchers concluded that patients dose by either a conversion factor or a weight-based tiered dosing strategy with dose adjustment guidelines had mean Hgb levels maintained within 1 g/dL of baseline. They also found that Hematide may be dosed Q4W in hemodialysis patients, and that it is well-tolerated and pharmacodynamically active.

➢ **AMGEN'S Aranesp (darbepoetin alfa).** An expert said there is "some data that Aranesp is not as good as Procrit in cancer patients."

➢ **FIBROGEN'S FG-2216.** There was no new information at the meeting on this Hypoxia Inducible Factor (HIF) stabilizer, which is in Phase IIb trials in both dialysis and non-dialysis CKD patients as well as a Phase II trial in myelodysplastic syndrome. A Fibrogen official said the Phase III trial will include iron therapy.

The FG-2216 program has seemed to move slowly, though a Fibrogen official claimed it is on schedule. A source said, "It is a slow program," suggesting some of the blame may be the fault of the CRO (contract research organization). He added, "Roche put incredible resources into the CERA program. Roche made it profitable (for doctors/hospitals) to do the studies, which caused incredible enrollment. That's what other companies need to do in their Phase III programs." Another doctor said, "FG-2216 has appeal because it is an oral drug, so I think they will be able to enroll patients quickly."

Several speakers described FG-2216 as "very promising," noting that it may have an advantage as a non-EPO given the mortality issue that has come up with ESAs. One speaker said, "In the few studies available, there were no drug-related adverse events noted, and the results look very promising. Response is quite significant at Day 42." Another expert said, "FG-2216 may have an advantage in patients with a cardio-vascular risk." A Michigan doctor said, "Clinically, it would be like from heaven, but it won't be available for years." Another speaker dubbed it a "hepatopoiesis" agent.

A Fibrogen official made these points about FG-2216:

- A 20 mg/kg dose induced doubling in baseline EPO.
- There is greater potency in anemic rats than in normal rats.
- No safety signals have been observed in any clinical studies.
- Low levels of circulating endogenous EPO are sufficient to induce erythropoiesis.
- EPO levels induced by FG-2216 are modest and signif-icantly lower than those associated with recombinant erythropoietin treatment.

➢ **FIBROGEN'S FG-4592.** There also were no new data at the meeting on FG-4592, which is in Phase II trials.

➢ **BIOGENIDEC/SYNTONIX'S EPO-Fc,** a pulmonary deliv-ery approach in which a single EPO molecule is conjugated to the Fc domain of IgG1. Very preliminary studies have indicated much higher reticulocytes with this drug than with control.

➢ **ROCHE'S Mircera (CERA, methoxy polyethylene glycol-epoetin beta).** In December 2006, Roche submitted additional information to the FDA on Mircera, and that extended the PDUFA to May 19, 2007. However, an expert said Mircera will be delayed until fall, explaining that the FDA is looking back at data on Hgb responsiveness.

Several speakers – even at events sponsored by Roche – described Mircera as a Peg-EPO. An investigator predicted Mircera will get the same black box warning as currently approved ESAs.

Mircera has some attractive advantages, and doctors appeared interested in having it available. One speaker commented, "I don't see any problem with CERA on titration." Another said the pharmacokinetics are "somewhat more 'natural'…If you think of other pegylated drugs, this is more integrated and stays whole during serum availability. It (the pegylated part) doesn't fall off."

- **Gradual hemoglobin rise.** While this might have been a negative a couple of years ago, sources speculated that the slower rise than with Epogen may enable doctors to target Hgb 11-12 easier, with less overshooting.

Mircera in Dialysis Patients With and Without CHF

Measurement	CHF			No CHF		
	Mircera Q2W n=90	Mircera Q4W n=85	Epoetin n=83	Mircera Q2W n=323	Mircera Q4W n=330	Epoetin n=334
Average Hgb						
Baseline	11.8 g/dL	11.7 g/dL	11.9 g/dL	11.9 g/dL	11.8 g/dL	11.8 g/dL
During titration (26 weeks)	11.9 g/dL	11.6 g/dL	11.8 g/dL	12.1 g/dL	11.6 g/dL	11.7 g/dL
Evaluation (8 weeks)	11.8 g/dL	11.5 g/dL	11.6 g/dL	11.7 g/dL	11.6 g/dL	11.6 g/dL
Adverse events						
Any adverse event	97.8%	90.5%	96.4%	89.1%	92.9%	90.4%
Adverse events related to treatment	4.4%	6.0%	2.4%	5.0%	4.9%	1.8%
Serious adverse events related to treatment	2.2%	2.4%	0	0.3%	0.9%	0.6%
Study withdrawals	23.3%	29.8%	27.7%	20.9%	21.2%	16.2%

- **IV efficacy = SC efficacy.** Because the half-life is relatively comparable whether administered IV or subcutaneously, a speaker said, "There is probably equal efficacy whether it is given IV or SC."
- **Switching is easy.** Switching studies indicate it is easy to move patients from another ESA to Mircera.
- **Once-monthly dosing.** While Amgen may claim Aranesp can be used once-a-month as well, Roche is preparing to counter that. It has started a head-to-head ***superiority*** trial of Mircera (QM) vs. Aranesp (Q2W and QM), and 61 patients are already enrolled. Asked how Mircera compares to Aranesp with respect to monthly dosing, an expert said, "I'm a little concerned with giving short half-life drugs (i.e., Aranesp) once-monthly…because of the spikes (in Hgb)…It might, from an erythropoietic standpoint, not be the most effective way to treat…There may be a penalty for giving short half-life drugs…can achieve normal Hgb giving once-monthly darbepoetin, but I have some theoretical concerns."

Asked if ESAs with a longer half-life decrease or increase cycling, Dr. Spiegel said, "We don't know that yet. There was a study suggesting the more frequently you measure Hgb, the more people you have in target…Presumably, our body adjusts to epoetin on a minute-to-minute basis…So, the verdict is still out on whether the long-acting agents give us better, worse, or the same control."

Roche released some new analyses at the NKF meeting from the CERA development program:

1. **Congestive heart failure (CHF).** A retrospective analysis of two Phase III trials found that dialysis patients could be converted from either epoetin alfa or epoetin beta to Mircera (IV and SC), administered Q2W or Q4W, and stable Hgb maintained, regardless of whether or not they had CHF.
2. **Activity-based cost analysis of in-center anemia treatment in dialysis patients.** A 5-center, prospective, observational study funded by Roche looked at 533 patients treated with Epogen TIW. The annual time and costs per center were estimated to be 539 hours and $35,120 for observed tasks and more when non-observed tasks were included. The single most time-consuming task was related to injections and record-keeping. The most costly expense was supplies for drug administration, with saline to flush infusion lines after ESA injection the single largest supply cost. Researchers estimated that a once-monthly ESA (Mircera) could reduce time per patient per year by 79% (481 minutes) and costs per patient per year by 81% ($444). The largest single cost-saving was in supplies, followed by savings in injections times and record-keeping.
3. **CKD and renal anemia.** A pooled analysis of 2,399 patients from six open-label, multicenter, parallel-group trials found that:
   - Hgb rose slightly slower but more steadily than with Aranesp.
   - The peak Hgb level was greater with Mircera than either Epogen or Aranesp.
   - The adverse event profile was similar to Epogen and Aranesp.
   - Patients formerly on Epogen or Aranesp maintained steady Hgb control when switched to Mircera, whether IV or SC.
4. **Pooled safety and tolerability from 10 Phase II-III trials in CKD patients.** This data analysis showed that the incidence of adverse events was similar between Mircera and the comparators ESAs.

IRON THERAPY

One of the key themes at this year's NKF meeting was: ***Give more IV iron.*** Speakers pointed out that iron deficiency anemia is:

- **Common among CKD patients.** Dr. Besarab estimated that 40% of his CKD patient population is iron deficient.
- **A frequent cause of inadequate response to ESA therapy** – in non-dialysis as well as dialysis patients.
- **A way to lower the ESA dose.** An expert said the DRIVE trial found that the ESA dose can be cut ~25% in patients who get 1 g IV iron. Another expert said, "You can get very substantial – 20%-75% – ESA dose reductions with IV iron." A third doctor said, "ESA use can go down 25%-50% with IV iron."
- **Frequently undertreated.** Experts claimed that most patients with CKD Stage 5 (CKD-5) have iron deficiency anemia, and supplemental iron is required in most of these patients, especially those on an ESA. Other experts estimated that ≥20% of all CKD patients would benefit from IV iron – if it didn't require an extended infusion.

Experts cited multiple reasons for iron deficiency in CKD, including:

- Poor intake/malnutrition, poor absorption.
- Blood loss in phlebotomy.
- Loss in dialysis.
- GI blood loss.
- Increased demand from ESA therapy.

The DRIVE trial and the DRIVE-II trial (which is about to be published) are part of the reason for the emphasis on increasing IV iron usage. The DRIVE study looked at dialysis patients in the "gray zone" with respect to current KDOQI iron guidelines, and it found better efficacy when IV iron (ferric gluconate) was added to EPO. The DRIVE-II study was a six-week observational study that showed patients who got IV iron gluconate + an ESA had a higher Hgb than patients who got Epogen alone – and the Epogen requirements fell substantially (almost 10,000 units a week) – so patients got a higher Hgb with less ESA.

Current KDOQI guidelines recommend iron therapy for CKD patients who don't meet these iron levels:

- **In dialysis patients** – TSAT >20% ***and*** serum ferritin >200 ng/mL. Iron therapy should be IV.
- **In patients not on dialysis** – TSAT >20% ***and*** serum ferritin >100 ng/mL. Iron therapy can be oral or IV.

However, speakers pointed out that there are patients with a TSAT >20% who can respond to iron therapy. Dr. Rajiv Agarwal of Indiana University School of Medicine said it is very difficult to diagnose iron deficiency with certainty, "Iron status test results reflect either the level of iron in tissue stores or the adequacy of iron for erythropoiesis. Serum ferritin is the only available blood marker of storage iron...Iron status testing (serum ferritin, TSAT) is poorly suited for predicting responsiveness to iron therapy…So, a diagnosis of iron deficiency in CKD patients can be made with reasonable confidence…but the tests are not absolute. Patients with higher serum ferritin or TSAT may still respond to IV iron therapy."

FDA-Approved IV Irons

Company	Brand	Type
American Regent	Venofer	Iron sucrose
Watson Pharma	Ferrlecit	Iron gluconate
American Regent	Dexferrum	Iron dextran
Watson Pharma	InFeD	Iron dextran

Dr. Agarwal discussed the comparative safety of the various types of iron, claiming iron sucrose and iron gluconate are much safer than iron dextran, with a lower risk of anaphylactic reactions and death. However, he said high doses of iron sucrose and iron gluconate should be avoided due to an unacceptably high rate of side effects. He concluded, "It appears the benefits of IV iron outweigh many of the side effects. Theoretical long-term risks have not been examined in large randomized trials, and we probably need to do that…Oral iron may be adequate in many non-dialysis and peritoneal dialysis CKD patients."

Asked what he would prescribe for Stage 3-4 CKD patients, Dr. Agarwal said, "Probably oral iron sulfate…and in eight weeks, if the response is suboptimal…I'd probably start EPO and possibly IV iron…I would use IV iron if the TSAT, after eight weeks, hasn't improved, and the patient is still anemic – and if the patient requires an ESA to fix the anemia…If the serum ferritin has not changed, and you have demonstrated that anemia is progressing, you will probably use IV iron…Today, we are sort of cost conscious…So, probably four weekly visits and a total of 1 g would be sufficient."

Among other comments on iron therapy included:

- *Dr. Besarab:* "I'm convinced that anaphylactic reactions are overstated in terms of frequency in some of the studies. Most of the reactions are anaphylactoid (not anaphylactic). We use IV iron dextran exclusively in 5 mg/minute infusions. That is 4 hours for 1 g. We've done several thousand infusions, and we've had only one bad case…Fresenius looked at the reaction rates in their database, and they found iron dextran was lower than iron sucrose and iron gluconate…but the preparation by American Regent had a much higher rate, so there may be differences among the dextrans."
- *Dr. Bradley Warady, professor of Pediatrics at the University of Missouri in Kansas City*, said even pediatric CKD patients don't get enough IV iron, "I agree with the adult (KDOQI) recommendation that the preferred route for iron therapy is IV in hemodialysis patients. Younger children are especially undertreated with IV iron."

- "I recently convinced our hospital to take iron dextran off our formulary because of anaphylactic reactions."
- *Michigan:* "IV iron is not reimbursed when administered in the office, and our hospital has refused to do IV iron because we sent too many patients to them for it."
- *Florida #1:* "We already use a lot of IV iron, but we could still use more. It is the administration (infusion) that holds us back."
- *Florida #2:* "We use all the IV iron necessary now, and we use Venofer exclusively. I don't think iron is under-used. Less than 5% of non-dialysis CKD patients get IV iron."
- *Florida #3:* "I'll consider using more IV iron. Only about 20% of non-dialysis CKD patients are on IV iron."
- *Tennessee:* "IV iron is underutilized. We need to reassess IV iron in the context of the DRIVE studies. We need to re-think it. I will re-think it."

Audience Iron Therapy Preference for ESA Hyporesponsive CKD Patients

Iron therapy	% of doctors choosing this
Oral iron	32%
IV iron 250 mg over 1-2 hours x 4	29%
IV iron 250 mg IV push x 4	21%
IV iron dextran 1000 mg over 4 hours	4%
Further evaluation before therapy	14% *

* Speaker's preference.

Oral iron therapies

There are a variety of oral irons, but several doctors had positive comments about a new oral iron – **COLORADO BIOLABS' Proferrin,** a heme iron polypeptide (HIP) extracted from bovine hemoglobin. Dosing is 3-4 tablets per day. Dr. Anil Agarwal described Proferrin as having "much better" (>10 times) absorption than ionic iron and said it "seems to be a reasonable drug to use in hemodialysis patients." Dr. Rajiv Agarwal said he likes this iron, but it is not on his formulary.

New iron agents in development

➢ **AMERICAN REGENTS' Ferniject (VIT-45).** This poly-nuclear iron carbohydrate complex is in Phase III trials, with a launch expected in 2008. It can be given as a 1 g infusion over 15 minutes. Dr. Anil Agarwal said, "This may be a rational therapy during dialysis."

➢ **ROCKWELL MEDICAL TECHNOLOGIES' Soluble Ferric Pyrophosphate (SFP).** Dr. Anil Agarwal pointed out that this has efficient transfer across dialyzer membranes, has hardly any free iron when it is given either IV or during dialysis, and does not cause oxidative stress. In fact, he said it has been suggested that SFP has some antioxidant properties as well. In Phase I/II, it was shown to be safe and effective in maintaining iron levels over six months, with an acceptable adverse event profile. A Phase III trial is planned in hemodialysis patients.

➢ **ADVANCED MAGNETICS' ferumoxytol.** New data were presented on the efficacy and safety of ferumoxytol, and it looked good. The only real questions related to adverse events.

There were numerically fewer drug-related adverse events in the first Phase III trial (presented at the ASN meeting last fall) than in the second Phase III trial presented at NKF, but this might actually be reassuring, suggesting that drug-related adverse events overall are comparable between ferumoxytol and oral iron. Asked to explain why the two trials had such different drug-related adverse event results, Dr. Bruce Spinowitz of New York Hospital Medical Center, the lead author on the second Phase III trial, said the discordance was probably due to "different sites and different centers."

Drug-Related Adverse Events in Ferumoxytol Phase III Trials

Measurement	Drug-related adverse events	
	Ferumoxytol	Oral iron
1st Phase III (at ASN)	10.6%	24.0%
2nd Phase III (at NKF)	21.4%	16.2%
Phase III trials pooled	15.6%	20.0%

No p-values were provided for the safety data. A company statistician claimed, "P-values are meaningless…It's what's clinically meaningful that matters…The FDA doesn't look at adverse event p-values." Two experts said they would not accept data for publication without p-values, and both were suspicious of the lack of p-values in any trial. However, another non-company expert said there were no p-values in the ferumoxytol trial because the data are still preliminary, and he insisted there will be p-values for the final data.

Asked about the importance of p-values, a senior FDA official took a more middle road, saying that p-values aren't meaningless but also that they add little value: "The problem is that safety evaluations aren't really hypothesis testing activities; rather, you're usually looking to see if any difference stands out. It's very hard in such cases to assign a valid p-value, although calculated p-values are sometimes given to represent, in a rough way, the 'strength of the evidence.' [In a case like this] we'd look at the rates of adverse events for each drug [IV iron, oral iron, and saline]; we might calculate a confidence interval for the difference (or risk ratio) between drug and saline or between drug and drug for each of the ADRs [adverse drug reactions] of interest. It's very hard in such cases to determine whether you've ruled anything out because you really don't know if the study was one that could detect the problem of interest (the assay sensitivity problem). A finding of a 'safety problem' is not fatal to approval. It depends on the nature of the problem…To say we would never look at p-values in those situations is overstated, and it's not unusual to provide them, but it is true that they don't have the same meaning as they do in describing the results of hypothesis-testing. For one thing, there are a

great many comparisons, so that correction for multiplicity would render most findings 'non-significant.' So, what we look for is consistency across studies, pharmacologic plausibility, etc. Also, some adverse events are so rare that you don't expect to see ***any*** in a database. In that setting, even two (maybe one) events can be of considerable interest…It sounds like all of the ADRs are pretty similar for the two treatments. In that case, running p-values would add very little."

The second Phase III trial, presented at NKF, was an open label, randomized, controlled, multicenter study of the safety and efficacy of two doses 510 mg of ferumoxytol administered within one week as an IV push vs. oral iron in 300 CKD patients. The median time for ferumoxytol administration was 25 seconds, and most patients received the two doses. Researchers reported:

- Greater increase in hemoglobin at Day 21 and Day 35 with ferumoxytol than oral iron. "In fact, the Hgb change with ferumoxytol alone was similar to what was observed with an ESA plus oral iron."
- Hgb levels did not rise excessively with ferumoxytol.
- The incidence of adverse events was similar, and there were no drug-related serious adverse events with ferumoxytol.

Results of Second Phase III Trial of Ferumoxytol

Measurement	Ferumoxytol n=226	Oral iron n=77	p-value
Lost to follow-up	0.4%	0	---
Baseline Hgb	9.85 g/dL	9.94 g/dL	---
Median dose received	1.02 g	4.1 g	---
Mean Hgb on Day 35	11.16 g/dL	10.51 g/dL	---
Primary endpoint: Mean change in Hgb from baseline to Day 35	+ 1.24 g/dL	+ 0.50 g/dL	<.0001
Secondary endpoint #1: Proportion of patients with a ≥1 g/dL increase in Hgb at Day 35	52.9%	18.2%	<.0001
Secondary endpoint #2: Mean change from baseline in serum ferritin at Day 21	+ 303.7 ng/mL	+ 3.0 ng/mL	<.0001
Safety			
Adverse events	55.5%	59.5%	N/A
Drug-related adverse events	21.4%	16.2%	N/A
Serious adverse events	7.7%	13.5%	N/A
Drug-related serious adverse events	0	1.4%	N/A
Adverse events in pooled analysis of both Phase III trials			
Constipation	1.8%	6.0%	N/A
Diarrhea	1.8%	4.7%	N/A
Infusion/injection site conditions	2.7%	0	N/A
Nausea	1.4%	2.7%	N/A
Dizziness	2.1%	0	N/A
Blood pressure decreased	1.6%	0	N/A
Vomiting	0.2%	2.0%	N/A

Another poster reported on the safety of IV ferumoxytol for iron replacement therapy in CKD. This was a Phase III double-blind, crossover design, multicenter study vs. placebo (normal saline) in 750 patients. Ferumoxytol was given as a rapid IV push over 17 seconds. Only rash, constipation, and skin bruising were reported more frequently with ferumoxytol, but the rates were very low. One patient had two serious adverse events that were considered by the blinded investigators to be related to ferumoxytol – an anaphylactoid reaction (hot flashes, itching) a few minutes after dosing and severe hypotension. This was an 85-year-old male not on dialysis, with a history of hypertension, coronary artery disease, stroke, and multiple drug allergies. He had no respiratory compromise and recovered promptly with SC epinephrine. He recovered without sequelae.

Phase III Safety Analysis of Ferumoxytol

Measurement	Ferumoxytol n=360	Saline control n=362
Baseline Hgb	11.3 g/dL	11.3 g/dL
Baseline serum ferritin	217.0 ng/mL	208.8 ng/mL
Baseline TSAT	15.1%	15.1%
Safety		
Adverse events	21.3%	16.3%
Drug-related adverse events	5.2%	4.2%
Serious adverse events	2.9%	1.8%
Drug-related serious adverse events	0.1%	0.1%
Temporary discontinuation of drug	0.1%	0
Permanent discontinuation of drug	0.7%	0.8%
Blood pressure increased	0.3%	0.1%
Blood pressure decreased	0.3%	0.1%

Doctors appeared impressed with ferumoxytol, and most predicted it could find a role in dialysis as well as non-dialysis CKD patients. Dr. Anil Agarwal, who participated in a ferumoxytol trial, praised the 17-second push delivery and the fact that it is not removed by the dialyzer during dialysis. Dr. Lafayette said, "The good thing is the safety data suggest you can give at least half a gram dose, and there is no large free radical release as there is with other IV irons." Another speaker called ferumoxytol a "small deal but a real deal," adding, "It will be an important drug in outpatient practices, less important in hemodialysis." He said he has had trouble convincing his infusion center to give 200 mg iron sucrose over 10 minutes because the center makes money on the longer infusion, noting, "They claim it is a safety issue." He is hopeful that when ferumoxytol is approved, he can force the infusion units to use it because the FDA approval will be for a short IV push, which should eliminate the safety argument his infusion center has been citing.

Asked how nephrologists and dialysis centers will choose among the various iron options once all of these agents are approved, an expert said the dialysis chains will probably base their choice on price, but he predicted all of them will find a place:

- "HIP has fewer side effects, and it is good for non-dialysis and CKD patients, but also for dialysis patients."
- "Ferumoxytol could be used in dialysis or non-dialysis patients. It will have the 17-second push advantage."
- "SFP – if the Phase III data are good – could become universal in hemodialysis, but injectables have reimbursement, and I don't know if SFP will be paid."
- "In CKD, I would try an oral iron first, and then if that doesn't work, go to ferumoxytol."

Asked if iron supplementation has anything to do with the increased mortality or negative effects of ESA use, Dr. Besarab said, "If you look at the DaVita database and adjust for demographics and metabolic/inflammatory complex issues, you don't see that. I think the problem is how you use your iron…I think you should give more frequent, lower dose (IV iron)…I think repeated boluses can be a problem."

Asked if IV iron is being underutilized clinically in the CKD outpatient clinic setting, a speaker said, "Having an infusion pump and a nurse watch a patient for four hours interferes with the flow of what happens in an office…We decided to do that because we couldn't manage anemia adequately with oral iron…(But) I need something more user-friendly than iron dextran – something we can give safer and faster."

MISCELLANEOUS

Home dialysis

Experts agreed that home dialysis is growing, but even if it doubled, the numbers would still be small. An expert explained, "Home dialysis is definitely an increasing trend, but it is for smarter patients. Half my patients can't do home dialysis."

♦