Trends-in-Medicine

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by Lynne Peterson

Quick Pulse

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AMERICAN SOCIETY OF NEPHROLOGY'S RENAL WEEK

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An important focus of Renal Week was on the management of conditions such as anemia, hyperphosphatemia, fibrosis, and hypertension in chronic kidney disease (CKD) and end-stage renal disease (ESRD). Overall, many of the results presented at Renal Week did not look favorable for the risk:benefit profile of erythropoiesis-stimulating agent (ESA) use in CKD patients.

ANEMIA

The negative safety news from the long-awaited TREAT trial may cause a significant reduction in the use of ESAs in CKD patients, and it could even have some small impact on use in dialysis patients.

AMGEN's Aranesp (darbepoetin alfa)

The final results of the TREAT trial were presented at Renal Week and simultaneously published in the ***New England Journal of Medicine (NEJM)***. TREAT found that intensive treatment with Aranesp was no more effective – and far less safe – than placebo in CKD patients with anemia and Type 2 diabetes. The researchers, led by Dr. Marc Pfeffer of Brigham & Women's Hospital, concluded: "It is our view that, in many patients with diabetes, CKD, and moderate anemia who are not undergoing dialysis, the increased risk of stroke and possibly death among patients with a history of a malignant condition will outweigh any potential benefit of an ESA." Another study found that not only did ESAs **not** reduce transfusion rates (as expected), ESAs were associated with an increased risk of venous thromboembolic events (VTEs). These findings combined with the new (composite rate) reimbursement policy of Centers for Medicare & Medicaid Services (CMS) may compel physicians to use iron supplementation and other alternatives instead.

TREAT was a 4,038-patient, randomized, double-blind, placebo-controlled trial at 623 sites in 24 countries (but ~57% of patients were in the U.S.), evaluating the effect of Aranesp vs. placebo. The combination of diabetes, CKD, and anemia is associated with a high risk of death, and the hypothesis in the trial was that Aranesp would reduce cardiovascular (CV) events in "patients with this triple whammy." Amgen, which sponsored the trial, hoped it would demonstrate that, with a hemoglobin (Hgb) target of 13 g/dL, this ESA would lower the risk of death and non-fatal CV events [non-fatal myocardial ischemia (MI), congestive heart failure, stroke, or hospitalization for MI]. It did not.

The trial was very disappointing. Dr. Pfeffer said, "Although darbepoetin had some benefits in the patients we studied, it also had important risks…In my view, for many patients the increased risk of stroke that was uncovered and possibly deaths in those with prior malignancy outweigh the potential benefits of ESA use."

The key findings, at a median follow-up of 29.1 months, were:

- **Hemoglobin** – ***positive:*** Aranesp significantly improved hemoglobin levels and did so significantly better than placebo.
- **Stroke** – ***negative:*** The risk of stroke was significantly higher with Aranesp. Dr. Pfeffer said the stroke rate was ~1% per year with conventional therapy but ~2% per year in Aranesp patients – "almost doubling the risk of stroke." The strokes that occurred were described as "predominantly ischemic," and the imbalance was not in one type of stroke. Asked if there is a mechanism of action or reason to think ESAs would increase stroke, Dr. Pfeffer said, "The history of this class is that VTEs are increased. That is long-term, and we saw that, too (in TREAT) – more VTEs with darbepoetin."

24-Month TREAT Trial Results

Measurement	Aranesp n=2,012	Placebo n=2,026	p-value	Hazard ratio
Median achieved hemoglobin level	12.5 g/dL	10.6 g/dL	**<0.001**	---
Patients switched to monthly dosing	84.6%	86.9%	---	---
Oral iron	66.8%	68.6%	Nss, 0.25	---
IV iron	14.8%	20.4%	**<0.001**	---
Median dose of Aranesp	225 µg	0	---	---
Mean dose of Aranesp	225 µg	5 µg	---	---
Primary cardiovascular endpoint: Composite of death or cardiovascular event	31.4% 632 patients	29.7% 602 patients	Nss, 0.41	1.05
Primary renal endpoint: Composite of death or end-stage renal disease (ESRD)	32.4% 652 patients	30.5% 618 patients	Nss, 0.29	1.06
Death from any cause	20.5%	19.5%	Nss, 0.48	1.05
MI	6.2%	6.4%	Nss, 0.73	0.96
Fatal or non-fatal stroke	5.0% 101 patients	2.6% 53 patients	**<0.001**	**1.92**
Heart failure (fatal and non-fatal)	10.2%	11.3%	Nss, 0.24	0.89
ESRD	16.8%	16.3%	Nss, 0.83	1.02
Death from cardiovascular causes	12.9%	12.3%	Nss, 0.61	1.05
Cardiac revascularization	4.2% 84 patients	5.8% 117 patients	**0.02**	0.71
Red blood cell transfusions	14.8% 297 patients	24.5% 496 patients	**<0.001**	1.05
Patient reported outcome (PRO): Improvement in patient-reported fatigue	+ 4.2 Modest improvement	+ 2.8	**<0.001**	---
Clinically meaningful improvement in fatigue by PRO	54.7%	49.5%	**0.002**	---
SF-36 energy score	+ 2.6	+ 2.1	Nss, 0.20	---
SF-36 physical functioning score	+ 1.3	+ 1.1	Nss, 0.51	---
Blood pressure				
Median systolic pressure over time	134 mmHg	134 mmHg	---	---
Median diastolic pressure over time	73 mmHg	71 mmHg	**<0.001**	---
Pre-specified categories of adverse events				
Hypertension	491 patients	446 patients	Nss, 0.07	---
Convulsions	9 patients	4 patients	---	---
Pure red cell aplasia (PRCA)	0	0	---	---
Venous thromboembolic events	2.0% 41 patients	1.0% 23 patients	**0.02**	---
Arterial thromboembolic events	8.9% 178 patients	7.1% 144 patients	**0.04**	---
Cancer				
Cancer-related adverse event	6.9% 139 patients	6.4% 130 patients	Nss, 0.53	---
Deaths attributable to cancer	39	25	Nss, 0.08	---
Deaths in patients with a history of cancer at baseline	60 deaths in 188 patients	37 deaths in 160 patients	**0.002**	---

- **Primary endpoint – *neutral:*** There was no significant difference in either the cardiovascular endpoint or the renal primary endpoint.

The TREAT researchers concluded that the stroke risk will, for many doctors, "outweigh the potential benefits." They added, "This study provides support for an adverse relationship between ESAs and stroke…It is possible that other dosing strategies could be developed to mitigate the risk of stroke while conserving the modest benefits of treatment."

- **Cancer – *negative:*** Aranesp was associated with significantly more deaths in patients with a history of cancer at baseline. Dr. Pfeffer said, "We can say with confidence that cancer-related adverse events were not more commonly seen in patients on darbepoetin. On the other hand, deaths attributed to cancer were numerically greater, not statistically, but numerically greater. In the patients with a history of malignancy – less than one-tenth of our patients – they were more likely to have higher all-cause mortality, and there were more deaths attributed to cancer (with Aranesp). So, we think this follows other data that there is a possible problem with cancer with ESAs."

  Dr. Pfeffer said that there is no additional information on the types of cancers involved because patients entering the trial simply checked a box indicating they did or didn't have a prior malignancy, not what type of malignancy, how it was treated, etc., "We did some preliminary looks and couldn't see a particular form (of cancer) that was consistent. My concern is that (this cancer finding) supports what has been going on in the cancer field (with ESAs)."

- **Transfusions – *positive:*** Aranesp significantly reduced the need for blood transfusions and cardiac revascularizations. Dr. Pfeffer said, "We can't say if the transfusions are from auto accidents, procedures, etc., but it is a clear message that those at higher Hgb are less likely to get transfusions, and much of that comes from when the blood banks weren't what they are today…But if you are on the transplant list, you don't want transfusions that can cause sensitivity."

  Dr. Robert Toto, another TREAT researcher from the University of Texas Southwestern Medical Center, said, "The transfusions were likely given at different points, and that decision was up to the physician…There is evidence that transfusing patients before transplant can sensitize them, and that could prolong the time to kidney transplant, which is already pretty prolonged."

- **Death – *neutral:*** The greatest excess risk for death (EDR) was in non-white, non-African Americans.

- **Patient-reported fatigue – *small positive:*** A "modest" but statistically significant improvement with Aranesp vs. placebo. There was a statistically greater improvement in fatigue with Aranesp, but Dr. Pfeffer questioned the clinical significance of that, "We delved into this with an exploratory analysis, asking experts what the numbers mean. Most said a change of three points is clinically meaningful, and we saw that 54.7% of the darbepoetin group had this (3-point) change that is considered clinical improvement…but almost half of the placebo patients – 49.5% – had this (same) clinically significant improvement…So, we looked at other scales (within SF-36, such as energy and physical function), and on those we didn't see a difference…They were not significantly altered between the groups…Placebo also improved. It is a real lesson about the placebo."

Often, the devil is in the details, but in this case, there were no surprises hidden in the trial. There was just very little positive to say about Aranesp. The Kaplan-Meier curves for CV events, death, heart failure, and MI were all virtually identical. Stroke showed a separation, beginning at about 12 months and continuing to diverge out to 48 months, with Aranesp becoming significantly worse than placebo over time. On the primary renal endpoint, the curves began to diverge at about 24 months, with Aranesp patients trending worse over time.

Other interesting findings in TREAT included:

- The findings differ from the CHOIR trial in CKD patients, which found a higher CV risk in epoetin alfa (Amgen's Epogen) patients targeted Hgb 13.5 g/dL vs. patients with a lower target (11.3 g/dL). That risk was led by deaths and heart-failure events, not stroke. However, in TREAT, it was stroke and not heart failure or deaths that were increased with the ESA. The TREAT researchers warned, "The final results of our study demonstrate the importance of completing the planned follow-up of trials and the potential to draw misleading conclusions when premature discontinuation results in an insufficient number of events to allow for a reliable estimate of the effect of treatment."

- 46% of placebo patients got at least one dose of Aranesp as rescue therapy for low hemoglobin (<9 g/dL).

Malignancy in TREAT

Measurement	Aranesp	Placebo	p-value
Overall			
Cancer-related adverse events	6.9% 139/2,012 patients	6.4% 130/2,026 patients	Nss, 0.63
Deaths attributed to cancer	1.9% 29/2,012 patients	1.2% 25/2,026 patients	Nss, 0.08
Subgroup of patients with baseline history of malignancy (n=348)			
All-cause mortality	31.9% 60/188 patients	23.1% 37/160 patients	Nss, 0.13
Deaths attributed to cancer	7.4% 14/188 patients	0.6% 1/160 patients	0.002

- The two arms were well matched, except that more patients on placebo had a history of CV disease, heart failure, and/or a pacemaker. Medication use was comparable.
- The FDA's warning that ESAs should not be used in patients with "anemia of cancer" appear to have been on the mark. The TREAT protocol was amended to discontinue Aranesp in patients who developed cancer, but mortality was higher in patients taking Aranesp who had a history of cancer at baseline.

Dr. Pfeffer said that the results of TREAT were shared with the Data Safety Monitoring Board (DSMB) for the RED-HF trial of Aranesp in heart failure, and that trial is continuing, "About one-third of our patients had heart failure…When we knew of our results, the data were transmitted to the RED-HAT DSMB, and that trial is continuing...They had the knowledge of our findings…and that trial is ongoing."

In an accompanying editorial in the ***New England Journal of Medicine***, Dr. Philip Marsden of the University of Toronto predicted, "The results of…TREAT will influence practice guidelines and inform physicians, patients, and policymakers. In many of these stakeholders, the risk of stroke will outweigh the potential benefits of darbepoetin alfa." He called the improvement in quality of life with Aranesp "a humble improvement at best."

However, Dr. Marsden pointed out that the trial gives ammunition to the "naysayers" as well, "The TREAT data may not be applicable to other populations, especially patients who are undergoing dialysis. Alternative dosing strategies…may alleviate the risk of stroke yet consider the modest benefits observed in quality of life." Among the issues in TREAT on which the pro-Aranesp people may hang their hats – and make their arguments are:

- Patient baseline differences, for example in heart failure, prior ESA use, or prior transfusions.
- Differences in iron supplementation.

Impact of TREAT on ESA use

Dr. Pfeffer predicted that ESA use in CKD patients will go down further than it already has as doctors who were continuing to use it and pushing it to boost the hemoglobin level respond to these findings. He said, "No trial can answer all the situations the doctor and patient face, but we provide some pretty definitive data for that decision to be made...You have to ask yourself what benefit you are trying to achieve, with the knowledge of the risk…It is our view that this will change the risk:benefit profile, and there will be less use."

Nephrologists generally were not aware of the TREAT findings before they were presented at Renal Week, and most of those who had heard the top-line data were waiting for the formal presentation and publication before changing practice.

About two-thirds of the nephrologists questioned at the meeting about the TREAT results predicted that TREAT will cause a ***significant*** drop in use of all ESAs in CKD and could have some small fallout effect on ESA use in dialysis patients. Even though ESA use has decreased significantly in the past three years, these doctors insisted that TREAT will make it fall even further. Most experts also predicted that the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines will be changed to reflect the TREAT (and other) safety findings.

The other nephrologists questioned insisted that their ESA use has already bottomed and did not expect it would fall even further. However, remember that nephrologists have repeatedly underestimated the impact of negative safety news on the use of ESAs.

Comments included:

- *Texas #1:* "For many patients with CKD, anemia, and diabetes, the overall risks detected for stroke and the possible risk for higher cancer have to be balanced against quality of life and the fact that fewer transfusions are a quality of life issue. It points me, as a nephrologist, to individualizing treatment, and one does have to weigh these things."
- *Virginia:* "TREAT will not look good for ESAs, so treating anemia may mean an increase in the use of iron …I think ESAs will almost disappear in CKD, and the target will be 10 g/dL when they are used…In dialysis, the risk of cancer was 0.9% before ESAs were introduced, and now it is 1.4%. I'm asking if ESA is causing clinically insignificant cancer to become clinically significant and possibly cause death."
- *New Jersey, speaking before the results were released:* "If TREAT is higher on any safety endpoint – if the trial shows anything negative − ESAs will be dead. How could you use it? The market will collapse. The class – the whole class − is dead if there is a cancer risk. I wish I were a product liability lawyer; they will take advantage of this."
- *Maryland:* "Per the package insert, Aranesp is underused based on transfusions. Empirically, people say they feel better on Aranesp. TREAT will have some impact, but doctors are not all evidence-based. If their anecdotal experience is positive, they will struggle with TREAT. But bottom line ESA use will get hit even more. Medicare will not want to pay for it, and CMS will use any excuse not to pay."
- *Germany:* "I'll wait for the sub-analysis. The problem in TREAT is when patients get a high dose. Aranesp is best if you give patients a low dose. The dose matters, not just the hemoglobin. TREAT won't impact my Aranesp use."
- *Arkansas:* "We have already cut our ESA use, and it won't go down any further. It would be hard to go down further."

- *New York:* "My use has already gone down. TREAT will change the target but not the number of patients on an ESA. My threshold for starting an ESA is lower now. And I will inform patients about the TREAT results, but there is no alternative to an ESA."
- *Sweden:* "TREAT will decrease ESA use. There will probably be more reluctance to increase hemoglobin too much. With no benefit on cardiovascular outcomes but an increase in stroke, it is very scary. Now 25%-30% of my CKD patients are on an ESA. In a year, it will probably be 15%-20%."
- *Texas #2:* "TREAT won't change anything right away because we have outcomes (standards) that the dialysis centers hold us to in terms of hemoglobin, but use will go down if those outcomes change."
- *Florida:* "TREAT won't change things because their treatment goals are not what we do in clinical practice. But it is sobering."
- *Jamaica:* "I don't believe it as yet. It won't change what I do tomorrow. I'll wait for more information, definitely. All it means to me is to be cautious with that drug (Aranesp)."

ESAs and VTEs – more negative news for ESAs

A new study published in the ***Journal of the National Cancer Institute*** on November 10, 2009, reported that ESAs are associated with an increased risk of VTEs and do not reduce transfusions as expected.

ESAs stimulate red blood cell production and, therefore, were approved to reduce the number of blood transfusions required during chemotherapy, but Dr. Dawn Hershman of Columbia University Medical Center in New York and her colleagues found that ESA use does not appear to have reduced blood transfusions. The researchers analyzed 56,210 chemotherapy patients ≥age 65 diagnosed with diffuse large B-cell lymphoma or colon, non-small cell lung, or breast cancer from the Medicare SEER (Surveillance, Epidemiology, and End Results) database from 1991-2002. Among these patients:

- 4.8% received an ESA in 1991 vs. 45.9% in 2002 ($p<0.001$), an almost 10-fold increase in ESA use.
- In a subset of patients with ≥2 claims for anemia, ESA use increased from 8.5% to 60.5%. In these anemic patients, ESA recipients had a ***higher*** transfusion rate than those who did not get an ESA. About 30% of ESA users had a transfusion in the year before getting the ESA, and ~50% had a transfusion in the year after getting an ESA.
- ESA use was highest in women, patients with higher socioeconomic status, comorbid patients, and metastatic cancer patients. Of the cancers studied, colon cancer patients were the least likely to get an ESA.
- The rate of blood transfusions per year remained constant at 22%. The primary reason for giving ESAs was supposed to be prevention of transfusions, which occurred in the clinical trials on which FDA approval was based, but that benefit was not the case in this analysis.
- Overall survival was similar with or without an ESA.
- 14.3% of the 12,522 ESA patients developed a VTE vs. 9.8% of the 34,820 patients who did not get an ESA ($p<0.001$, HR 1.93).

Factors Associated with Increased Risk of VTE

Demographic factor	Thrombosis	Hazard ratio (multivariate)
ESA use	14.3%	1.93
Age 70-74	11.6%	1.16
Age 75-79	11.3%	1.21
Age ≥80	9.7%	1.18
African American	13.8%	1.20
Radiation therapy	12.0%	1.22
Increased comorbid conditions (>1)	12.1%	1.32
≥5 ESA claims	---	1.55
<5 ESA claims	---	1.31
≥5 ESA claims in patients with non-metastatic cancer	---	1.72
<5 ESA claims in patients with non-metastatic cancer	---	1.36
Recurrent or metastatic cancer	11.6%	1.53
Lung cancer	9.8%	1.14
Colon cancer	11.0%	1.00
Breast cancer	12.0%	0.83

The researchers pointed out, "Total U.S. sales of ESAs increased from $6.2 billion in 2002 to $10 billion in 2006, accounting for a greater Medicare Part B expenditure than any other drug. We speculate that this use was fueled by aggressive marketing to patients and physicians that focused on a promise of increased energy during chemotherapy treatment …(However,) a substantial reduction in the use of blood transfusion was not observed…(But there was an) increased risk of VTE that was associated with the use of an ESA."

The researchers warned, "Further efforts at monitoring use and long-term toxicity of expensive oncology drugs should be put in place to ensure that for any drug the benefits outweigh the risks in community practice."

Bundling and ESAs

While the negative news from the TREAT trial of Aranesp in CKD is likely to have a dampening effect on the use of all ESAs (not just Aranesp), mostly in CKD but perhaps even a little in ESRD, the biggest impact on ESRD use of ESAs is likely to come from Medicare bundling, combining dialysis payments and drugs under one reimbursement (called a composite rate).

Currently, Medicare pays separately for drugs at 6% over the manufacturers' average sales price (ASP), so dialysis centers generally make money on administration of ESAs. CMS is required by Congress to move to a bundled system, starting in January 2011.

Every nephrologist questioned at the meeting predicted that when bundling goes into effect, the use of ESAs in ESRD patients by dialysis centers will go down. One way they plan to do this is by increasing the use of intravenous (IV) iron, but that most likely means low-cost IV iron, not AMAG Pharmaceuticals' Feraheme (ferumoxytol) both because of cost and because it is not approved for ESRD use yet. Nephrologists said that they plan to get even more conservative on hemoglobin targets, aiming just above 10 g/dL rather than 11-12 g/dL.

Bundling also may spur a shift to subcutaneous ESAs. Nephrologists said that dialysis patients might not like it, but subcutaneous ESAs may be less expensive, and that is what will drive the choice.

Physician comments on the implications of bundling included:

- *Florida:* "I'll have to use more iron. ESA dose will decrease, or the (dialysis) companies won't be able to survive. It will also make subcutaneous ESAs more attractive – if patients will accept them, and if they are once a week but not three times a week. If you dialyze shorter, you need more ESA, so patients also may be dialyzed longer."
- *Colorado:* "I don't think the hemoglobin target will change, but there may be caps on how much ESA we can give…I also think we will be under big pressure to decrease the dose. Various doses are given around the country with the same results. Why? I think people will increase iron to decrease ESA use…Subcutaneous ESA is a question. The data are not real clear. There are some data that a dose reduction doesn't last, that it trickles up over time. Subcutaneous use will be driven by total dose and cost."
- *Ohio:* "The hemoglobin target won't change, but the way we treat anemia will. I still think that in most U.S. dialysis units, anemia management lacks an iron protocol. At this point, it is in the centers' financial interest to push ESA use. But iron use will increase, and they will start looking at other parameters that affect ESA resistance. I firmly believe the ESA dose will come down…There is a huge possibility that the cumulative dose might go down. Some units may try subcutaneous ESA, including possibly me, but it is difficult to convince patients."
- *Arkansas:* "Bundling will mean less ESA use and more IV iron use…The ESA dose will come down, and subcutaneous ESA use will increase…Subcutaneous ESA will be an issue with patients who are used to an IV. I don't think a (dialysis) patient would change (dialysis) centers because a center initiates subcutaneous ESA."
- *Georgia:* "I will start doing more IV iron because I want to cut my ESA use."
- *Missouri:* "In dialysis patients I prefer maintenance iron (2-3 g/year or 50-60 mg/week). I will use less ESA over a year with this strategy…The dialysis centers do want use of ESAs to decrease, and the only way to do that is either subcutaneous ESA, a lower hemoglobin, or IV iron… TREAT will not look good for ESAs, so treating anemia may mean increased use of iron. Bundling also will increase IV iron use."

A Medicare Evidence Development & Coverage Advisory Committee (MedCAC) meeting is scheduled for March 24, 2010, to review ESA use to treat anemia in CKD patients, and the results of the TREAT trial are expected to be a key topic at that meeting. The panel is being convened to provide CMS with guidance in developing national coverage policies for this use of ESAs. CMS estimates that 26 million Americans have been diagnosed with CKD, with anemia affecting 27% of those in the early stage and 87% of those in later stages. An expert said, "CMS wants to know why it should pay for ESAs. The cancer signal in TREAT will drive ESA use down in CKD and down more (than has already occurred) in dialysis."

The TREAT results also are likely to have implications for other hemoglobin-raising agents, including Affymax's Hematide and FibroGen's FG-2216. Experts expect the FDA to require more information on outcomes, in particular more data on stroke and cancer, which could delay approvals.

Early vs. delayed ESA initiation

A retrospective study of non-dialysis CKD patients in the national VA database was presented at Renal Week by University of Maryland researchers. The study, sponsored by Amgen, looked at the value of early ESA initiation (outpatient hemoglobin 10-11 g/dL) or delayed ESA initiation (Hgb 6-9.9 g/dL) and found:

- Overall mortality was less with early ESA initiation vs. late initiation − 13.3 vs. 16.3 per 100 person-years (p=0.07, HR 0.84).
- Blood transfusions were significantly lower with early ESA administration.

Hemoglobin target

A study by German researchers found it is very hard to keep patients in the 10-12 g/dL hemoglobin range. They concluded, "There is probably nothing wrong with overshooting, and that is much less worse than undershooting." They also reported that there is a discussion going on in Germany of imposing an upper limit on hemoglobin with ESA use, but a researcher said that if regulators try to do that, they will increase the number of people with Hgb <10 g/dL and will increase cycling.

A Korean study found high dose erythropoietin (EPO), 10,000 U, given subcutaneously every 2 weeks (instead of weekly) is as effective as Q2W subcutaneous dosing with Aranesp in CKD patients.

AFFYMAX's Hematide

This once-monthly, synthetic peptide-based ESA is unrelated to erythropoietin, and it doesn't have the potential to cause pure red cell aplasia (PRCA).

Preliminary Analysis of Phase II Trial of Hematide in Dialysis Patients

Measurement	Hematide 0.4 mg/kg Q4W n=39	Hematide 0.8 mg/kg Q4W n=37	EPO TIW n=38
Treatment-related adverse events	15%	3%	8%
Hypertension	8%	3%	8%
Transfusion	1 patient	0	0
Therapeutic phlebotomy	0	1 patient	0
Serious adverse events	13%	14%	8%
Arteriovenous thrombosis	2 patients	1 patient	1 patient
Vitreous hemorrhage	2 patients	0	0
Treatment-related serious adverse event	1 patient (fistula thrombosis)	0	0

A French nephrologist explained that the advantages of Hematide vs. Aranesp are only in CKD: it is peptide-based rather than protein-based, it is new, and it is given monthly. In dialysis, he said there is no advantage, "but ambulatory patients who come monthly like monthly injections." Another researcher said, "I heard the company plans to submit it by the end of 2010. I don't expect any PRCA with this, but the cancer and stroke risk are the same. There will be similar label warnings as with other ESAs, but there will be an appetite for this…There are three Phase II outcomes studies: EMERALD-1, EMERALD-2, and PEARL, with results due in 2010." Another doctor said, "The studies are done, but we need to see the safety vs. ESAs." A third said, "Hematide may get the same label as the ESAs – a class label, and it may have its use limited in CKD. FibroGen may have a bigger problem because it has other issues to overcome as well."

A poster by Dr. Andrey Gurevich of the Russian Federation *et al* presented the preliminary analysis of data from a 28-week, Phase III, randomized, active-controlled, open-label study of once-monthly Hematide in dialysis patients. The study found:

- The 0.8 mg/kg dose of Hematide – but not the lower 0.4 mg/kg Hematide dose − increased hemoglobin levels as much as EPO 50 U/kg three times a week.
- The Kaplan-Meier analysis of Hematide efficacy showed that both doses had similar curves to EPO, with the high Hematide dose peaking a little higher, and the low dose peaking a little lower.

Another poster, presented by Dr. Marc Froissart of France, suggested that a treatment may finally be near for PRCA caused by EPO (Ab+PRCA) − Hematide. The researchers reported the interim results from an ongoing, 14-patient, efficacy and safety study of Hematide in patients with Ab+ PRCA. Patients with Ab+PRCA have a virtual absence of erythropoiesis and are dependent on chronic blood transfusions, so Hematide could be a real hope for these patients.

FIBROGEN

➢ FG-2216 is an oral Hypoxia Inducible Factor (HIF) stabilizer. A FibroGen official said that they just started a Phase II trial in diabetic nephropathy because "of available data that it could reverse fibrosis." The trial includes a cardio-vascular substudy that will be expanded. FG-2216 also is in Phase IIb trials in both dialysis and non-dialysis CKD patients and in a Phase II trial in myelodysplastic syndrome. The FibroGen official stated that the Phase III trial will include iron therapy.

➢ FG-3019 is a connective tissue growth factor monoclonal antibody. A poster presented the results of a 37-patient, randomized, double-blind, placebo-controlled, multicenter, Phase I study of FG-3019 in Type 1 and Type 2 diabetics with diabetic kidney disease who were on background therapy with an ACE inhibitor or an ARB. The study showed that FG-3019 was well tolerated for 10 weeks, blood pressure was stable, C_{max} and area under curve (AUC) values were comparable to levels in a previous study of patients with microalbuminuria. A 150-patient, 6-month, multicenter, randomized, double-blind, placebo-controlled Phase II study is underway in patients with diabetic kidney disease, testing 2 doses, looking at changes in levels of albuminuria. There will also be a cardiovascular substudy in this trial.

Phase I Results with FG-3019

Measurement	FG-3019 3 mg/kg		FG-3019 10 mg/kg	
	First dose	Last dose	First dose	Last dose
C_{max}	73 µg/mL	76 µg/mL	420 µg/mL	511 µg/mL
T_{max}	2.25 hours	4.12 hours	3.04 hours	6.00 hours
Adverse events				
Hypoglycemia	13.5%			
Edema peripheral	13.5%			
Fatigue	8.1%			
Edema	8.1%			
Back pain	8.1%			
Hyperglycemia	5.4%			

PROMETIC BIOSCIENCES' PBI-1402

This is an oral compound with erythropoiesis-stimulating activity distinct from erythropoietin. At Renal Week, Canadian researchers reported on a rat study which showed that PBI-1402 improved glomerular filtration rate (GMR) and suggested that it is a potential new therapy for preventing and/or reducing fibrosis and sclerosis. They concluded that PBI-1402 preserved renal function, as shown by an improvement in GMR, a decrease in histological damage, and a decrease in fibrosis and sclerosis.

IRON SUPPLEMENTATION

At a symposium sponsored by AMAG Pharmaceuticals (formerly known as Advanced Magnetics), Dr. Csaba Kovesdy of the Veterans Administration Medical Center in Salem VA pointed out that mortality doubles when iron is low in patients on maintenance dialysis, but mortality also increases if iron is too high in both ESRD and CKD patients. The problem is that there is no agreement on the way to most accurately measure iron. The four leading markers are:

- Ferritin
- Transferrin saturation
- Serum iron
- Hepcidin

Dr. Daniel Coyne, director of the hemodialysis center at Washington University in St. Louis, discussed optimizing iron therapy in CKD outpatients. He warned, "In certain populations it takes patients a while to respond to IV iron therapy… and it may be that responses to oral iron therapy are also delayed…Short-term use of oral iron is not a fair test of that product. If we commit to oral iron, we should give it for an extended period of time – months at least…The differences in the IV iron labels reflect a change in the FDA more than differences in the products. The FDA goal now is very practical advice."

A poster that was a collaborative effort by researchers in the U.S., Europe, and Japan found that both ESA and IV iron dose requirements were lower in hepatitis C (HCV) patients. In addition, the odds of requiring no ESA or no IV iron were greater for HCV patients. However, hepatitis B (HBV) infection conferred no advantage in terms of the need for an ESA or IV iron. Interestingly, hemodialysis patients with HCV were almost never treated with antiviral medication. The researchers speculated that HCV infection "may stimulate hepatic erythropoietin production and/or may improve iron availability by altering the hepcidin axis."

AMAG PHARMACEUTICALS' Feraheme (ferumoxytol)

On June 30, 2009, the FDA approved Feraheme, an IV iron, to treat anemia in CKD patients. Few nephrologists questioned have used it yet, mostly because it is not on most formularies but also out of some concern about cost. Unless and until it is on formularies, doctors are extremely unlikely to use it. Thus, it is clear that the company needs to put some additional effort into convincing managed care companies to include it in their formularies.

Asked about the safety of Feraheme vs. oral iron, Dr. Coyne said, "(In a trial) three patients had serious hypersensitivity, and three had serious hypotensive reactions…So, as with any IV iron, we need to beware there may be serious adverse events. Patients need to be monitored for symptoms for at least 30 minutes after each injection."

Physician comments on Feraheme included:

- *Florida:* "Feraheme is a good product. I don't push it with patients, but I use it sometimes. Reimbursement is an issue. Approval of Ferrlecit (Watson Pharma, sodium ferric gluconate) is faster."
- *Colorado:* "I don't use it. It's not on the formularies, and there is no real benefit in dialysis patients to give iron faster."
- *Ohio:* "I haven't used it yet because of cost and because it is not on the formulary yet. My iron use may increase, but we may go back to iron dextran (Schein's INFeD) because it is cheap. Feraheme may have an advantage in CKD, but I need to see it first."
- *Arkansas:* "I haven't used it yet, but it is interesting. However, it is not on the formulary…IV iron use is limited by inflammation and side effects."
- *New York:* "It is not on the formulary, so I haven't used it yet. Nephrologists are slower to jump on new drugs than cardiologists."
- *Missouri:* "Given the risks of ESAs, there is increased interest in IV iron, and Feraheme is the most convenient at this time…We've given a dose or two of Feraheme. It is in the hospitals, and it is approved for outpatient use. But there is no urgency to getting Feraheme on the formulary except for peritoneal dialysis…For CKD, we've just started stocking it, and use is up to our doctors. I don't know if there is reimbursement, but only one managed care plan has given me a hassle. However, there is doctor pushback on laying out the money for Feraheme until the reimbursement is assured. So, only a handful of CKD patients are on it so far…Most nephrologists don't give any iron in their office; it's usually given at academic centers or infusion centers. Some doctors recognize the need but don't do it because it is inconvenient, or they don't want to lay out the money up-front…We break even on IV iron; it is not a money maker…I use Feraheme when it is inconvenient to use total dose infusions, which is the case with most CKD patients, in peritoneal dialysis patients (who are typically seen monthly anyway), and home hemodialysis patients…In CKD, I most often use INFeD because it is the least expensive, and some formularies require it."

- *Maryland:* "I haven't used Feraheme yet, and the real reason is that I don't like IV iron in CKD patients, but it also isn't on the formulary. I use Venofer (Luitpold Pharmaceuticals/American Regent, iron sucrose) in the hospital and Ferrlecit at the VA."
- *Georgia:* "I haven't used it yet, but I'm learning about it. I'm nervous about hypotension, but I'm getting more comfortable with it."

LUITPOLD's Ferinject/Injectafer (ferric carboxymaltose)

This IV iron was turned down by the FDA but is approved in Europe as Ferinject. Swiss researchers reported in a poster at Renal Week on an analysis, which found that, from the perspective of the Swiss healthcare system, the use of this IV iron in CKD patients would reduce ESA use and costs, reducing overall treatment costs for these patients.

SERUM PHOSPHORUS AND CALCIUM

Now that a generic version of Nabi Biopharmaceuticals' PhosLo (calcium acetate) is available, doctors are starting to use it, and it appears that use of other agents may decline somewhat.

GENZYME's Renagel (sevelamer HCl) / Renvela (sevelamer carbonate)

Renagel has had surprisingly strong legs. Despite the pill form which many had considered burdensome, most nephrologists said they are continuing to use it.

An analysis by Canadian researchers of the cost-effectiveness of Renagel in the U.K. found that it "offers good value for the money" in treating hyperphosphatemia in dialysis patients vs. calcium-based phosphate binders. They estimated the cost per quality-adjusted life year (QALY) gained was £28,959 over 10 years. Post hoc subgroup analyses found that the cost-effectiveness was most favorable for patients >age 65 but was within accepted levels for all age groups >45.

Cost-Effectiveness of Renagel in the U.K.

Age group	Incremental cost per QALY
≥45	£18,164
≥50	£17,517
≥55	£17,224
≥65	£16,304

SHIRE's Fosrenol (lanthanum carbonate)

This still has a very small share of the market, according to doctors. One commented that use is low because "the binding is not as strong, it is expensive, and there is a limit on how much we can give."

KERYX's Zerenex (ferric citrate)

This potential hyperphosphatemia treatment (phosphate binder) could reduce the pill burden for patients. Original studies were done using ten 375 mg pills, but now it has been formulated as a 1 g capsule, so patients might need only 2 capsules per meal. In a 55-patient, 7-center, 6-month, Phase II study, compliance was 75% with 19 capsules/day, but six patients required titration up to 11 g/day. Adverse events include change in stool color (62%), constipation (15%), bloating (7%), diarrhea (7%), and nausea (5%). There was no significant difference between prior phosphate binder use and Zerenex, showing equivalent efficacy but the potential for a reduction in pill burden. Of the patients enrolled, 57% were on PhosLo, 43% on Renagel, and 6% on Fosrenol. A Phase III trial is expected to start in January 2010.

AMGEN's Sensipar (cinacalcet)

The EVOLVE trial, a cardiovascular mortality study, will report results in 2010. Doctors are aware of the trial but not particularly excited about finding out the results. A New England doctor said, "It depends on the type of patients recruited. It will probably be an influential trial since there have been studies in both directions, but we are not all on the edge of our seats waiting for the results." Doctors said Sensipar may have boosted the use of PhosLo.

AMGEN's AMG-223

An Amgen researcher said this polymer-based phosphate binder is "on hold for business reasons." Astellas, which has the rights outside the U.S., reportedly has a 240-patient, safety study ongoing in Japan, and it is fully enrolled. The results are expected in fall 2010.

HYPERTENSION

CVRx's Rheos

Rheos is an implantable device that electrically activates the baroreflex nerve, which sends a message to the brain, which, in turn, tells the kidneys to reduce fluid in the body, causing a drop in blood pressure of up to 30 mmHg. The system has three components: the implantable generator, two lead wires that run from the device to the baroreceptors on the carotid arteries, and an external programmer. It is being tested in refractory hypertension patients who are not well controlled on at least three medications, one of which must be a diuretic.

At Renal Week, Dr. Domenic Sica of Virginia Commonwealth University provided an overview of Rheos. He pointed out that it not only reduces blood pressure, but it also has been shown to reduce left ventricular mass. However, he also noted several negative aspects to the system:

- The surgical time is 3-6 hours, and a specific anesthesia has to be used. What takes the time is mapping the baroreflex nerve, "searching for the sweet spot to get the best blood pressure reduction."

- The battery has to be "routinely replaced."
- It currently is a bilateral procedure. "Typically one side gives better blood pressure reduction than the other, and we can't adjust the different sides differently…I believe there will be a modification…Maybe one-sided leads are in the offing, which will lead to shorter surgical times."

Asked if Rheos goes beyond simple blood pressure reduction, Dr. Sica said, "I can't answer that at this point…There may be additive effects beyond blood pressure (e.g., reduction in left ventricular mass, improvement in pulsatile flow, etc.)…But that is speculative on my part…The preservation of the estimated glomerular filtration rate (eGFR) in CKD patients on maximum medical therapy suggests that Rheos therapy may be renoprotective."

Asked about complications implanting the device, Dr. Sica said, "Complications have been quite minimal. The technology is much advanced from the 1960s (when a similar device failed), so complications are surgical if any, and wound infection has been rare."

Asked if Rheos is like a beta blocker, Dr. Sica said, "I think it is different than a beta blocker in its activity based on the influence on the sympathetic nervous system…It will be positioned along with other therapies for resistant hypertension. It is going to become a crowded market…but also a fairly lucrative market for those who get there quickest with a (safe and effective product)."

Asked about his personal experience with adjusting the device, Dr. Sica said, "There is considerable intricacy to programming and optimizing the response. The typical session is about three hours…This is a rudimentary field. Each person has a very specific set point to what gets them lowest, and we are trying to find that, and we are trying to figure out what drugs to pull away from patients."

This last comment is a little confusing since the drug is positioned as a therapy for patients who have high blood pressure despite maximum medical therapy, not as a replacement for medications. Furthermore, most patients – at least so far – have continued to have blood pressure above normal despite the device, so removing medications doesn't appear either to make good sense or to be something regulators are likely to consider appropriate. However, Dr. Sica said the current protocol includes patients with a systolic blood pressure ≥135 mmHg on three medications (including a diuretic), so it is possible that some patients would get normalized. Dr. Sica said, "There are some medications that don't work…If I'm seeing someone at 172 mmHg on (multiple medications), and the patient is getting side effects from one, I stop it and see if the pressure goes up. On the device, when the pressure comes down, there is an attempt to wean them off the drugs and see if the pressure goes up."

Asked if patients really would get the device with a systolic blood pressure of 135 mmHg, Dr. Sica said, "I can't say how many people would do it at that."

Asked how he would use Rheos if it were approved, Dr. Sica said, "In people with difficult-to-treat hypertension where they have exhausted most of the avenues…Patients with anxiety, pain, fear, depression, changes in sleep architecture, neurohormonal parameters, medication tolerance…and after 24-hour blood pressure monitoring…and whether patients want to (get off) multiple drug therapy…Some people wouldn't be suitable…due to family dynamics, fear of surgery, etc."

A 300-patient, blinded, pivotal trial in hypertension is almost fully enrolled, with the results expected at perhaps the American College of Cardiology 2011 or the American Society for Headache 2011. In early October 2009, CVRx announced that enrollment also had begun in its 500-patient, pivotal, Phase III HOPE4HF trial of Rheos vs. standard of care to treat symptomatic (diastolic) heart failure in patients with preserved ejection fraction.

ARDIAN's catheter-based radiofrequency (RF) kidney denervation system for resistant hypertension

There was no news on this, but there were a couple of posters on the denervation in general that appeared to support the concept. Dr. Sica (a CVRx Rheos researcher) said, "I don't know the durability (of denervation). If it is durable, then it has some legs…(If it works out), it will be marketed widely, and a lot of people will want it because it is a technically simple procedure…but at the end of the day when you distribute the procedure into the hands of people not routinely dealing with hypertensive patients, then you run the risk of over or under using it. We need to see who is the best patient for renal denervation. It has a solid future…but it is hard to predict the future…I have no experience with renal denervation. Very few centers have it yet. Ardian is the only one doing it right now. People like me need to vet the procedure …It would have a role, but we have to figure out where the positioning is, who at the institution would do the procedures, what the complication rate is – because it, too, has a complication rate. Then, figure where you position it head-to-head (with Rheos)…They (Ardian and Rheos) are not mutually exclusive, but I hesitate to think one would do both, they are not necessarily additive…If Rheos didn't work, I'd be surprised if Ardian worked, and possibly vice versa…Rheos works even with renal denervation…If you do renal denervation in a dog model and then put Rheos in, the pressure still comes down."

MISCELLANEOUS

There were a number of interesting posters and presentations at Renal Week on new therapies in development, including:

DAIICHI SANKYO's Olmetec (olmesartan), an ARB

The randomized, double-blind, placebo-controlled ROAD-MAP trial showed that olmesartan delayed time to first onset of microalbuminuria (a 23% risk reduction). Although there was no overall effect on cardiovascular events, cardiovascular death was reduced, but the numbers were too small to make definitive conclusions on cardiovascular mortality.

FIBROTECH's FT-011

Australian and Canadian researchers reported on a cell line study of this anti-fibrotic. They found it attenuates albuminuria and renal fibrosis and attenuates functional and structural manifestations of diabetic nephropathy. The method of action is uncertain. The company is going into clinical development for treatment of progressive kidney disease.

Homocysteine

The 4,110-patient, randomized FAVORIT trial, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), showed that lowering homocysteine with a regimen of high dose folic acid, B6, and B12 vitamins does not reduce cardiovascular outcomes or total mortality in chronic, stable, renal transplant recipients.

NOVARTIS's Tasigna (nilotinib)

A poster by Japanese researchers found that this tyrosine kinase inhibitor which is approved to treat chronic myeloid leukemia (CML) "significantly attenuates renal injury following subtotal renal ablation in rats, suggesting that nilotinib may prove useful in limiting the progression of chronic renal disease to end-stage renal failure."

ONO PHARMACEUTICALS' ONO-1301

Japanese researchers looked at the therapeutic effect of this oral prostacyclin PGI_2 in preventing glomerular and tubulointestinal alterations in a rat model of progressive glomerulonephritis. They found it ameliorated both histological alterations and proteinuria.

PFIZER's PF-002

A Pfizer researcher presented a poster on PF-002, a potent, selective, chemokine (C-C motif) receptor 2 (CCR2) agonist in diabetic nephropathy. This drug is not being developed; it is just a tool for other studies looking at CCR2 expression, which the researcher said Pfizer wants to understand better. This was the first report of increased plasma monocyte chemotactic protein-3 (MCP-3) in the presence of CCR2 antagonism, but that is just an observation; the researcher didn't know what it means except to say it isn't a negative finding, "We were trying to determine that there is a positive effect in diabetic nephropathy with a CCR2 comparable to losartan (Merck's Cozaar), and there is. So, there is an intriguing potential for this (CCR2) in nephropathy."

PFIZER/WYETH's Rapamune (sirolimus)

Long Island Jewish Medical Center researchers suggested that sirolimus has a possible role to reduce the severity of lesions caused by HIV in HIV-associated nephropathy.

STRYKER's OP-1 (BMP-7)

A Stryker poster on a mouse study suggested that BMP-7 shows promise for the treatment of renal disease and increased the lifespan of mice with lupus. Studies are underway to see if the effect would be consistent if treatment was initiated after the onset of ***clinical*** renal disease. The researchers speculated that systemic administration of BMP-7 may inhibit tubular inflammation and tubular interstitial fibrosis, thus slowing the progression of renal disease.

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