Trends-in-Medicine

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SUMMARY

Nephrologists are starting to prescribe Amgen's Aranesp for pre-dialysis patients, and the outlook is for use to continue to ramp up, but reimbursement remains a problem. ♦ Use of Genzyme's Renagel is expected to continue to increase, limited only by patients' ability to pay for it, but doctors are anxious for a cheaper alternative. ♦ Doctors are willing to try Shire's Fosrenol (lanthanum) if it gets FDA approval, but they remain nervous about long-term safety. ♦ Amgen's oral calcimimetic, AMG-073, is not widely known, but doctors who are aware of it are very excited about it.

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RENAL RESEARCH INSTITUTE
INTERNATIONAL CONFERENCE ON DIALYSIS:
ADVANCES IN ESRD 2003
Miami, Florida
January 30-31, 2003

This report focuses only on the last two days of this meeting and on selected topics. In addition to the lectures, sixteen nephrologists were interviewed on a variety of topics.

DIALYSIS OUTLOOK

A speaker offered some interesting statistics on ESRD:

- The number of diabetics in the U.S. is increasing by 4.25% a year.
- In 1999-2000, 18.3% of Medicare patients were diagnosed with diabetes.
- 275,000 people are on dialysis.
- 5.8% of all Medicare spending in 2000 was for ESRD.
- The probability of new cardiovascular disease developing after two years of dialysis is 24%.
- 11% of CKD patients have a new diagnosis of congestive heart failure in one year.

Sources generally agreed that the number of patients on hemodialysis is likely to increase, but peritoneal dialysis (PD) is flat to slightly down. The demographics of patients continue to change – more diabetics, more older patients, and more co-morbidities.

Daily Dialysis Costs

Increased	Neutral	Decreased
Nursing – up 23%	Administrative	Dialysis center revenue – down 16.7%
Waste management – up 100%	Epogen	Blood pressure medications – down 43%
Med/Surgical supplies – up 89%	Lab measures	
Overall cost – up 31%		
Hospitalizations for pulmonary access-related infections		

Two key topics of discussion at the meeting were the ADEMEX and HEMO studies. AMEDEX was multi-center, prospective, randomized, controlled trial of 965 continuous ambulatory PD patients in Mexico who were followed for a minimum of two years. The trial was designed to examine the effect of increasing PD small solute clearances (Kt/V, a common measure of toxin removal and kidney function) on mortality outcomes in patients with ESRD. The HEMO trial, which has not yet been published but was presented in April 2002, casts doubts on the advantages of achieving higher than recommended small solute clearance targets.

A speaker offered this "reality check" on both those studies. In the U.S., she said, 60%-65% of PD patients are reaching DOQI guidelines – which means 35%-40% are not getting to goal. Canada is doing only slightly better, with about 30% not reaching target, "Do I believe 30% of PD patients are under-dialyzed and suffering from it? No. But I also believe some patients are getting inadequate dialysis…We need to broaden and encourage transplantation; patients do better with a transplant."

- "AMEDEX challenges the DOQI guidelines as they are currently presented – both the process and the generalizability -- so they are not the holy grail."
- "HEMO says we are giving our patients adequate care/dialysis...but USRDA data indicates 14% of patients are below target, and the mortality rate is 16.6% per 100 patient years. HEMO tells us nothing about alternative hemodialysis methodologies, but it does show that proposed targets can be reached and not achieving them is not acceptable. About 14%-15% of patients are not reaching target and in any given network from 8%-17% of patients did not achieve target."

The message, doctors said, was that asymptomatic patients who are slightly below target may not need additional dialysis, leaving them where they are may be fine. Currently, doctors and dialysis centers "push" these patients with additional dialysis trying to get them to goal, but that may be unnecessary. Is this good news for the dialysis companies? Doctors doubted it; while they generally accepted the finding, they were not sure they would actually change any practices or that, if they did, it would have any significant impact on dialysis center margins.

DIALYSIS CENTERS

The five major dialysis chains – Davita, DCI, Fresenius, Gambro, and Renal Care Group – are relatively similar in terms of quality, sources agreed. However, doctors did offer some comments that help differentiate these companies.

- **Davita**. A doctor said, "Davita does more lower-end and Medicaid patients." Another source said, "Davita's quality of care is better than the others. It has extensive staff education, the staff are very happy, and there is low turnover. It's a highly ethical company."
- **DCI**. A doctor said, "We had DCI, but the care was substandard, so we helped bring in another firm. We felt the quality of DCI nursing was not sufficient. It was big and understaffed**."**
- **Fresenius**. The company claims to be the largest chain and touts its technology and field-based quality teams. It is doing a pilot project of scheduled dialysis rather than shift-scheduling. A Texas doctor said, "Fresenius is higher end." Another source said, "Fresenius has very high staff turnover. There is a constant push for more, more, more. There is no encouragement, and little staff education. Their attitude is, 'If it can be billed, bill it.' And they do what's best for the company."
- **Gambro**. A Florida doctor said, "We've had infection problems with a Gambro center." Another source said, "Gambro is the McDonald's of dialysis. They've taken cross-training too far. They expect everyone to do everything, so they are a jack of all trades but master of none. And, like Renal Care Group, salaries are low."
- **Renal Care Group.** A doctor praised the company for "paying its medical director based on outcomes." Another source said, "Salaries are poor, benefits are limited, and there is less staff advancement, but the corporate ethics are better than either Fresenius or Gambro."

The choice of a dialysis center generally is dictated by geography. Patients usually go to the closest center with which their doctor is affiliated. A few doctors said they dictated the center, but most said the decision is made more by managed care, social workers, and patients. A Texas doctor said, "Most doctors refer to units they are involved with, but there is a lot of patient preference."

The big risk for dialysis centers is a potential change in Medicare reimbursement for Amgen's Epogen. A source said, "Amgen has a stranglehold on the industry. If Medicare lowers the reimbursement for Epogen without increasing the composite rate, it would bankrupt the dialysis centers." An Amgen source said, "Without medications, dialysis centers lose 7% a year.

ANEMIA:
Amgen's Epogen (epoetin alfa) and Aranesp (darbepoetin alpha)

An Israeli researcher offered these statistics:

- Half of CHF patients are anemic
- Half of CHF patients have CKD
- Half of CKD patients are anemic

Does anemia cause CHF? The link is there but not proven. Diabetes – but not CHF – is a contributing factor to renal failure. A speaker speculated that anemia and CHF could have an additive effect leading to progression of the CHF and kidney failure, "It looks like CHF is just another cause of the anemia of chronic disease." He noted that American Heart Association guidelines on heart failure have not mentioned anemia, but said that the concept is beginning to be discussed by cardiologists, and he urged nephrologists to talk to their cardiologists about the association of CHF, anemia and renal failure.

Nephrologists predicted that, as total number of ESRD (dialysis) patients goes up, Epogen use will go up as well. A Florida doctor said, "The outlook is for total Epogen use to go up, but the dose per patient is stable."

Aranesp is starting to catch on with nephrologists – but for CKD (chronic kidney disease, formerly called chronic renal insufficiency), not ESRD patients. Half these sources have started prescribing Aranesp. Most have prescribed it for only a few patients, but they generally predicted usage will grow. A Florida doctor said, "I'm using lots of Aranesp in CKD, and I expect usage to go up. I'm starting new patients on it, and switching some Procrit (Johnson & Johnson) patients to Aranesp, which I'm giving mostly once every four weeks. The barrier is getting primary care physicians to refer." A Maryland doctor said, "I recently started prescribing Aranesp, usually for CKD, and that will increase." A social worker commented, "Aranesp has been heavily advertised in ESRD publications."

Most of these nephrologists were totally unaware of the PRCA problem that has arisen with Eprex in Europe, and none are concerned about the safety of Procrit. Their interest in Aranesp is strictly related to dosing regimens.

Reimbursement and formularies remain a barrier to use. Several doctors complained that they are not yet able to get reimbursed for Aranesp – despite what Amgen and its sales reps claim. A Kentucky doctor said, "There is no J code yet, and my office manager says we can't get reimbursed. If it gets reimbursed, I may use it, but we've gotten along fine without it so far." A New Mexico doctor said, "My use is up but reimbursement is difficult. I don't have the time to spend an hour on the phone for each patient." Another source said, "I'm starting to use it in CKD, and I hope to break even on money."

An Amgen official admitted that reimbursement has been a slow process. He could only point to a few doctors who have mastered reimbursement and are getting paid within 14 days. Sources insisted the reimbursement has to improve for usage to increase substantially.

CALCIUM AND PHOSPHATE BINDERS: Genzyme's Renagel and Shire Pharmaceuticals' Fosrenol

A speaker urged better serum phosphorus control. He commented, "Elevated phosphorus levels are below the radar screen of the family MD…(but) as serum phosphorus increases so does the relative risk of death. Mineral metabolism abnormalities (are) an area where we can do something and maybe save some lives…In a paper coming out soon in *Hemodialysis International*, we described a small sample of patients where we found serum phosphorus and calcium were the only demonstrable lab tests that really mattered as residual renal function changed…I think we can accomplish better phosphorus control than we have."

GENZYME'S Renagel (sevelamer hydrochloride): Sources all prescribe Renagel, generally 800 mg TID, but a significant number of patients need even higher doses. On average, half their patients are taking Renagel, and doctors said they would have even more patients on Renagel if it were cheaper. Indeed, cost is not only a major barrier to broader use, but it has created significant ill-will for Genzyme. As a result, many doctors said they reserve Renagel for patients who aren't controlled with a calcium binder. A Kentucky doctor said, "I changed all my patients to Renagel, and then I found out not all of them could get it because of cost. Payment is a big problem. Patients without drug coverage don't get it. The company is generous with samples, but there are still a lot of patients who can't get it." A Florida doctor said, "I give it to every patient who can pay for it, but coverage has gotten worse recently." A social worker said, "Younger patients prefer Renagel, but it causes stomach problems in some patients."

Despite the price issue, most doctors predicted that Renagel usage would increase. A California doctor said, "Use will continue to increase until new products come along." The exception was a nephrologist who said, "My use is steady, but I'm using Renagel less in CKD because of the risk of Renagel-related acidosis. PhosLo (Braintree Labs, calcium acetate 667 mg gelcaps) may be better." Another source said, "Renagel use will increase because it makes a patient a better transplant candidate."

SHIRE PHARMACEUTICALS' Fosrenol (lanthanum), formerly Foznol: Shire had a booth at the meeting, but it was empty -- no display and no personnel – so perhaps it was not surprising that few doctors were aware of Fosrenol, and only one was excited about it. The others are worried about Fosrenol's safety because it is a metal, given their earlier experience with aluminum. An Ohio doctor said, "I will still be nervous about safety, even if the FDA approves it." A Florida doctor said, "I worry about long-term safety."

Fosrenol was submitted to the FDA in April 2002, so a decision is expected in the next couple of months. Thus, if Fosrenol gets FDA approval, most doctors are likely to try it, at least in a few patients to start, but it is not expected to catch on quickly. A Kentucky doctor said, "I'm willing to try it." A Florida doctor said, "If it's approved, use will depend on price. If it's cheaper than Renagel, I'll use it – unless the Renagel price comes down." A California doctor said, "I'll use it if it's cheaper than Renagel." Another nephrologist said, "If it is approved, I'll try it in a few patients, but I also want to hear the experiences of my colleagues with it."

Two factors could help boost Fosrenol use:

1. Doctors expressed considerable anger with Genzyme, and they are anxious for an alternative to Genzyme's Renagel.
2. If it is priced sufficiently lower than Renagel, doctors believe that would drive usage, but doctors also hope that competition will drive down the price of Renagel.

AMGEN'S (AMG-073, also known as NPS-1493, cinacalcet HCl): Only about a third of sources were familiar with this first-in-class oral calcimimetic, which is in Phase III development, but those who are aware of it are very excited about it. In fact, a Florida doctor's face lit up at the mention of AMG-073. A Texas doctor said, "It will be very, very good if it pans out." Another doctor said, "We are involved in the trial. It seems very good. It is promising and exciting." A Maryland doctor said, "It is very innovative and exciting. I'm looking forward to it."

Data presented at the Endocrine Society meeting last year found that daily dosing with AMG-073 over one year (compared to placebo) was associated with a decrease in plasma levels of PTH, which in turn were associated with a decrease in levels of circulating calcium. Phase II data on once-daily, oral AMG-073 has shown that, over 12 weeks, dialysis patients experienced a dose-dependent decrease in plasma levels of PTH which were maintained.

IRON: Several sources volunteered the information that iron use is going up. One commented, "Right now I'm splitting my use pretty evenly between Schein Pharmaceutical's Ferrlecit (sodium ferric gluconate complex in sucrose injection and American Regent Laboratories' Venofer (iron sucrose injection) may have advantages and may gain over Venofer."

NEW DOQI GUIDELINES (DISEASE OUTCOMES QUALITY INITIATIVE)

Asked how the new guidelines will change their practice, sources generally agreed they will use more statins and possibly more Renagel. One doctor said, "The guidelines won't cause any remarkable change; it's just fine tuning."
The latest cardiovascular guidelines are expected to be published in April 2003, but an exact date has not been set. The proposed guidelines recommend more lipid testing, lower lipid targets, and more liberal use of statins and bile acid sequestrants. Proposed guidelines include:

- All adults and adolescents with CKD should be evaluated for dyslipidemia, and the assessment should include a fasting lipid profile.
- For patients with Stage 5 CKD, dyslipidemias should be evaluated upon presentation and two to three months after any change in treatment or other conditions known to cause dyslipidemia, and at least annually thereafter.
- Hemodialysis patients should have lipids measured either before dialysis or on days they are not receiving dialysis.
- CKD patients with dyslipidemia should be evaluated for secondary causes.
- For adults with Stage 5 CKD and LDL>100, consider treatment to reduced LDL to <100.
- For Stage 5 CKD adults with LDL<100 but triglycerides ≥200, calculate the non-HDL cholesterol, and if that is >130, consider treatment to reduce non-HDL cholesterol.
- Give more satins and consider bile acid sequestrants.

Other sources said the new K/DOQI guidelines also will recommend:

- Stricter control of calcium-phosphate levels in dialysis patients. Reportedly, the new calcium-phosphate target will be 55 mg^2/dL^2, compared to historical limits of about 70 mg^2/dL^2.
- Not to use calcium-based phosphorus binders in patients with hypercalcemia.