Eculizumab Offers No Benefit in the Treatment of Hemolytic Uremic Syndrome Caused by E. coli, Preliminary Report Finds

When an outbreak of foodborne Shiga-toxin producing Escherichia coli O104:H4 (STEC) hit northern Germany beginning in May 2011, physicians had no established treatment regimen and therefore tried various therapies. By the time the outbreak ended in late July 2011, there were 52 deaths among the 3052 incidences of STEC and 733 confirmed cases of hemolytic uremic syndrome (HUS).

Within a week of the outbreak the German Society of Nephrology developed an online data collection form and registry to track cases of HUS and document the short-term effectiveness of best supportive care, therapeutic plasma exchange (TPE), and, for patients with HUS, TPE with eculizumab (TPE-Ecu). Best supportive care consisted of dialysis, mechanical ventilation, and active fluid management. Eculizumab is a monoclonal antibody that interferes with the terminal components in the activation of the complement cascade.

Jan Kielstein, MD, PhD, associate professor of medicine at the Medical School of Hannover in Germany, presented an analysis of the registry data at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris in May. He told Kidney News that the data suggest that the TPE-Ecu combination does not provide any further benefit in the treatment of HUS compared to TPE alone.

Of the 631 entries from 84 centers in the STEC-HUS registry, the investigators confirmed 491 STEC-HUS cases, of which 241 underwent TPE, 193 TPE-Ecu, and 57 best supportive care. The patients who received best supportive care alone were almost 10 years older on average (55 years) than the TPE and TPE-Ecu groups combined (45 years). Yet patients in the best supportive care group had less severe disease (including hemolysis), less need for dialysis, and a lower frequency of seizures. These patients also had lower serum creatinine at hospital discharge (1.1 mg/dL compared with 1.2 mg/dL and 1.4 mg/dL for the TPE and TPE-Ecu groups, respectively). Very few patients required dialysis at discharge, and there was no significant difference between groups.

However, mortality was significantly higher in the best supportive care group compared to the others: 10.5 percent compared with 3.7 percent and 2.6 percent in the TPE and TPE-Ecu groups, respectively.

Kielstein cautioned that one must examine the raw data from the best supportive care group, especially the mortality data, because the best supportive care group was older than the other groups “and age is an overriding risk factor for death in this patient population.” Also, of the six patients who died in the best supportive care group, two opted out of further treatment because they had advance directives, and one additional patient died from complications of insertion of the central venous catheter intended for TPE. “This very much illustrates the difficulty looking at those registry online data, and this I think is the main disadvantage from the bios, that we don’t have prospective controlled data,” Kielstein said.

Further complicating interpretation of the results, disease severity triggered different intensities in treatment, so the less severely ill patients received best supportive care. The most ill patients, especially those with neurological complications, received TPE-Ecu.

While acknowledging the “scarce evidence at best” to support the use of eculizumab, Kielstein explained the rationale for its use in patients with HUS. A few preliminary studies have shown upregulation of the complement system in the active phase of HUS. “But the main triggering event to use eculizumab in these patients was, number one, the safety profile of eculizumab,” he said, “number two, the fact that it was available on compassionate use [so] nobody had to pay for it, and number three, the fact that in the middle of the crisis there was a report in the New England Journal of Medicine (1) showing remarkable recovery of three pediatric patients that were suffering from severe neurological symptoms in the context of STEC-HUS.”

From the registry data, it can’t be determined if antibiotics were useful because data were lacking on the antibiotics used, their time course, and their dosages. Kielstein noted that a recent article in the Journal of the American Medical Association (2) showed that azithromycin can significantly decrease the shedding time of STEC from the gut, possibly prompting a rethinking of a previous recommendation not to use antibiotics in STEC-HUS lest the bacteria release more Shiga toxin as they are destroyed.

As with antibiotics, some hospitals used steroids with TPE and others did not, further complicating the retrospective analysis.

Kielstein suggested that the medical community establish systems now to collect data in a crisis situation and design a fast-track process to approve clinical trial protocols at the start of future crises since the present approval process is unable to react quickly enough.

The study had no commercial funding. Dr. Kielstein had no disclosures.

References

Blood Pressure Lowering With Olmesartan No Better at Preventing Negative Outcomes in Patients on Hemodialysis

Patients receiving olmesartan fared no better in terms of outcomes or blood pressure lowering than those receiving conventional antihypertensive therapy other than angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors in a recent study. The study looked at the effect of olmesartan in lowering blood pressure to decrease the risk of death and nonfatal cardiovascular (CV) outcomes in hypertensive hemodialysis patients.

Data indicate that hypertensive hemodialysis patients have a better prognosis compared to hemodialysis patients with normal or low blood pressure, but guidelines for treating hypertension in hemodialysis patients do not exist, said lead author Kunioshi Iseki, MD, of the University Hospital of the Ryukyus in Nishihara, Okinawa, Japan. On the other hand, a meta-analysis showed that survival in hemodialysis patients was better if they received antihypertensive drugs, regardless of their blood pressure, suggesting possible other effects of the drugs.

The Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS) was an open-label, parallel-group study with a 1-month trial with blinded outcome assessment to determine if an ARB would lower the risk of CV disease and death among hypertensive hemodialysis patients. In an interview with Kidney News at the 49th European Renal Association–European Dialysis and Transplant Association Congress in Paris, Iseki described OCTOPUS and its findings.

Eligible patients had a predialysis blood pressure of 140/90 mm Hg or 200/100 mm Hg and could not have used ACE inhibitors or ARBs in the previous month. The trial’s target was a predialysis blood pressure below 140/90 mm Hg. The mean age of the patients included in the study was 60 years (range 20–79 years), and they received hemodialysis three times a week. After a 1-month period using other conventional blood pressure medications, during which resistant hypertension was confirmed, patients were randomized to conventional therapy not directed at the renin-angiotensin system (234 patients) or to olmesartan 10 mg/day (235 patients). Doses could be escalated in either group to achieve the target blood pressure.

The groups were well matched at baseline for pre-hemodialysis blood pressure, hemodialysis duration (88 months), and hemodialysis dose (Kglv 1.15–1.16), as well as other characteristics. The primary end points were 1) all-cause mortality; and 2) the composite of death or nonfatal CV disease, including stroke, myo-

Findings
European Renal Association—European Dialysis and Transplant Association Congress
cardiovascular death risk in comparison with baseline. There were no blood pressure differences between the groups, Iskeli said. The blood pressure in both groups had dropped by approximately 7.2 mm Hg compared with baseline. The olmesartan group had a non-significant reduction in systolic blood pressure versus the conventional therapy control group (0.9 mm Hg, p = 0.45).

There was no difference in the degree of diastolic blood pressure reduction. Among the olmesartan patients, 28.9 percent reached the primary composite end point versus 28.6 percent of patients in the control arm (hazard ratio [HR], 1.00, p = 0.99). Similarly, 16.2 percent of patients in the olmesartan group died from any cause versus 16.7 percent in the control group (HR, 0.97, p = 0.91). Iskeli concluded that blood pressure reduction with olmesartan did not alter the risk for major CV events or death among chronic hemodialysis patients with hypertension compared with other drugs to lower blood pressure. Fewer than 20 percent of patients in either treatment group reached the target blood pressure of less than 140/90 mm Hg.

He said the annual incidence of the primary composite end point (9.1 percent) and overall mortality (4.7 percent) were lower than expected. Japanese hemodialysis patients typically experience annual mortality of about 6.5 percent, Iskeli noted. A limitation of the study was that olmesartan was compared with active blood pressure-lowering therapies and not with placebo, so the absolute effect of blood pressure reduction with olmesartan could not be determined. A second and important limitation was that adherence to olmesartan and to the other antihypertensive drugs was marginal.

The study population was about 60 years of age in each country. COSMOS essentially confirmed the relationship of phosphorus levels and mortality risk seen in previous studies, with the lowest risk of all-cause mortality occurring at a serum phosphorus level near 4.0 mg/dL. Below 3.0 mg/dL, the mortality risk doubled (hazard ratio [HR], 2.0). An elevated serum phosphorus level also conferred a higher mortality risk, increasing at a phosphorus level greater than 5.5 mg/dL. The mortality risk was about 50 percent higher (HR of about 1.5) when the serum phosphorus exceeded 6.5 mg/dL.

Similarly, for cardiovascular mortality the lowest risk was at about 4.0 mg/dL, with higher risks observed at both low and high serum phosphorus levels. The use of PBAs reduced the risk of all-cause and cardiovascular mortality, in many cases by as much as 50 percent. The findings held regardless of age, sex, history of diabetes or cardiovascular disease, time on hemodialysis, or baseline serum parathyroid hormone, calcium, or phosphorus levels.

The investigators developed three statistical models to study the association between mortality rates and the use of phosphate binders. The models took into account and adjusted for differences in the case mix, case mix plus therapies other than PBAs, and case mix plus other therapies plus blood chemistries.

For each model, all PBAs (except those containing aluminum) were associated with significantly lower risks of all-cause and cardiovascular mortality. A wide range of PBAs were included, encompassing those containing calcium or lanthanum, calcium and lanthanum, polyanionic gels, calcium or lanthanum plus polyanionic gels, polyanionic gels plus a lanthanum-containing PBA, a calcium plus aluminum-containing PBA, and polyanionic gels plus an aluminum-containing PBA. The greatest risk reduction (73 percent) occurred with the use of a polyanionic gel plus a lanthanum-containing PBA.

“The main message is that PBAs are ... related with a lower mortality,” Cannata-Andia concluded. “We can say that this effect is from the phosphate binder and not the effect of vitamin D or a calcium mimic.”

He emphasized that the combination of PBAs, which is a common practice, did better than agents used singly.

Cannata-Andia noted “huge differences in price” for PBAs, with the oldest and least expensive PBAs (those containing aluminum) having lesser efficacy in terms of mortality risk, and the newer and more expensive PBAs having more efficacy but also a higher cost. Still, he said it is “very reassuring” that combinations of calcium-containing and non–calcium-containing PBAs “did very well.”

The study was supported by Fundación Renal Iñigo Alvarez de Toledo and by Amgen. Dr. Cannata-Andia had no other disclosures.

Sevelamer Linked to Lower Cardiovascular Death Risk in Patients on Hemodialysis

In a trial comparing the phosphate-binding agents (PBAs) in patients on hemodialysis is associated with reduced mortality risk regardless of other factors, according to results from the large European Current Management of Secondary Hyperparathyroidism—a Multicenter Observational Study (COSMOS). The association applied to all types of PBAs except those containing aluminum, said trial chairman Jorge Cannata-Andia, MD, of the Hospital Universitario Central de Asturias in Oviedo, Spain.

The study, conducted at 220 centers across the European Union, investigated the association between treatments affecting bone metabolic parameters and clinical outcomes among patients on hemodialysis. Specifically, the researchers looked at the association between the use of a single PBA or a combination of PBAs and mortality. COSMOS was an observational study with 3 years of follow-up that enrolled patients from a wide geographic area in Europe in numbers approximately proportional to the number of patients on hemodialysis in each country.

COSMOS essentially confirmed the relationship of phosphorus levels and mortality risk seen in previous studies, with the lowest risk of all-cause mortality occurring at a serum phosphorus level near 4.0 mg/dL. Below 3.0 mg/dL, the mortality risk doubled (hazard ratio [HR], 2.0). An elevated serum phosphorus level also conferred a higher mortality risk, increasing at a phosphorus level greater than 5.5 mg/dL. The mortality risk was about 50 percent higher (HR of about 1.5) when the serum phosphorus exceeded 6.5 mg/dL.

Similarly, for cardiovascular mortality the lowest risk was at about 4.0 mg/dL, with higher risks observed at both low and high serum phosphorus levels. The use of PBAs reduced the risk of all-cause and cardiovascular mortality, in many cases by as much as 50 percent. The findings held regardless of age, sex, history of diabetes or cardiovascular disease, time on hemodialysis, or baseline serum parathyroid hormone, calcium, or phosphorus levels.

The investigators developed three statistical models to study the association between mortality rates and the use of phosphate binders. The models took into account and adjusted for differences in the case mix, case mix plus therapies other than PBAs, and case mix plus other therapies plus blood chemistries.

For each model, all PBAs (except those containing aluminum) were associated with significantly lower risks of all-cause and cardiovascular mortality. A wide range of PBAs were included, encompassing those containing calcium or lanthanum, calcium and lanthanum, polyanionic gels, calcium or lanthanum plus polyanionic gels, polyanionic gels plus a lanthanum-containing PBA, a calcium plus aluminum-containing PBA, and polyanionic gels plus an aluminum-containing PBA. The greatest risk reduction (73 percent) occurred with the use of a polyanionic gel plus a lanthanum-containing PBA.

“The main message is that PBAs are ... related with a lower mortality,” Cannata-Andia concluded. “We can say that this effect is from the phosphate binder and not the effect of vitamin D or a calcium mimic.”

He emphasized that the combination of PBAs, which is a common practice, did better than agents used singly.

Cannata-Andia noted “huge differences in price” for PBAs, with the oldest and least expensive PBAs (those containing aluminum) having lesser efficacy in terms of mortality risk, and the newer and more expensive PBAs having more efficacy but also a higher cost. Still, he said it is “very reassuring” that combinations of calcium-containing and non–calcium-containing PBAs “did very well.”

The study was supported by Fundación Renal Iñigo Alvarez de Toledo and by Amgen. Dr. Cannata-Andia had no other disclosures.

Sevelamer linked to benefits on many outcome measures

After 36 months of follow-up, the patients using sevelamer had an 89 percent lower risk of CV-related mortality than the patients taking the calcium-containing PBA (relative risk [RR], 0.11, p < 0.001). There were nine CV-related deaths in the sevelamer group versus 79 in the calcium PBA group. When adjusted in a multivariate analysis for possible contributing factors, the RR remained 0.11, indicating that sevelamer use was an independent predictor of the much lowered risk.

Similarly, the sevelamer group did much better in terms of all-cause survival, with a greater than 70 percent reduction in the risk of all-cause death regardless of whether the RR was unadjusted or adjusted for various possible confounding factors. There were 28 deaths from any cause in the sevelamer group at 36 months compared with 100 deaths in the calcium-containing PBA group.

Sevelamer was also linked to less progression of coronary artery calcification (CAC) when examined after 24 months of the study. At 12 months, half of the calcium PBA group had CAC progression whereas only one-fifth had progression in the sevelamer group (p < 0.001). At 24 months, CAC progression...