Adjuvant Sunitinib Improves Survival in High-Risk RCC

Adjuvant treatment with the oral antiangiogenic drug sunitinib increases disease-free survival but increases toxicity in patients with metastatic renal cell carcinoma (RCC) at high risk of recurrence, reports a trial in The New England Journal of Medicine.

The randomized, international, phase 3 trial included 615 patients with locoregionally advanced, high-risk clear-cell RCC who had undergone nephrectomy. Intervention patients received sunitinib, 50 mg/d, on a 4-weeks-on, 2-weeks-off schedule. Treatment continued for up to 1 year; controls received placebo. Disease-free survival was compared between groups, along with secondary outcomes.

Sunitinib was associated with significant improvement in disease-free survival: 6.8 months in the intervention group versus 4.8 months in controls. The 2-year disease-free survival rates were 38% and 20%, respectively.

The results support the use of sunitinib, 50 mg/d, for 1 year in high-risk patients who had undergone nephrectomy.

References:
8. Data on File 1, Keryx Biopharmaceuticals, Inc.

A NON-CALCIUM, NON-CHEWABLE, FILM-COATED TABLET

For the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

AURYXIA® (ferric citrate) IS THE FIRST AND ONLY ABSORBABLE-IRON–BASED PHOSPHATE BINDER

CLINICALLY PROVEN TO MANAGE HYPERPHOSPHATEMIA

• Proven control of serum phosphorus to 4.88 mg/dL at Week 56 (within KDOQI guidelines) 4, 8
• Demonstrated safety and tolerability profile over 52 weeks
• A starting dose of 6 tablets a day (2 tablets with each meal) with a maximum dose of 12 tablets a day

Drug Interactions: Doxycycline should be taken at least 1 hour before AURYXIA. Ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Consider separation of the timing of the administration of AURYXIA with drugs where a reduction in their bioavailability would have a clinically significant effect on safety or efficacy.

Please see Brief Summary on following page.

You may report side effects to Keryx at 1-844-44KERYX (844-445-3799)

References:
High-Risk RCC

Continued from page 7

versus 5.6 years, hazard ratio 0.76. Overall survival could not be assessed at the time of data cutoff; about 20% of patients had died in the groups. Sunitinib was associated with increased toxicity, including higher rates of grade 3 and 4 adverse events and adverse events requiring dose reductions, interruptions, or discontinuation. The overall rate of serious adverse events was 21.9% with sunitinib and 17.1% with placebo, with no toxicity-related deaths.

Previous studies have established that sunitinib, a vascular endothelial growth factor receptor pathway inhibitor, is an effective treatment for metastatic RCC. Two RCTs show that adjuvant sunitinib can increase survival in patients with loco-regional, high-risk clear-cell RCC. Sunitinib is associated with increased toxicity, leading to moderate declines in quality of life during active treatment [Ravaud A, et al. Adjuvant sunitinib in high-risk clear-cell carcinoma. N Engl J Med October 10, 2016 DOI: 10.1056/NEJMoa161406].

Angioplasty and Stenting for Renal Stenosis: Evidence Still Limited

Available evidence shows no consistent benefit of percutaneous angioplasty with stent replacement over medical therapy for patients with atherosclerotic renal artery stenosis (ARAS), concludes an updated systematic review in the Annals of Internal Medicine.

A comprehensive literature review identified 83 studies providing evidence on the benefits and harms of PTRAS versus medical therapy for ARAS. Thirty-three studies were newly identified since a 2007 review. The review was funded and followed a standard protocol by the Agency for Healthcare Research and Quality.

The review identified 15 comparative studies including a total of 4066 patients. Of these, 7 were randomized controlled trials (RCTs) including 2178 patients, most enrolled in two large trials (AS-TRAL and CORAL). Five of the RCTs reported similar blood pressure control with ARAS versus medical therapy. None found significant differences in kidney function, mortality, need for renal replacement therapy (RRT), cardiovascular events, or pulmonary edema.

There were 8 nonrandomized comparative studies including 1828 patients. The findings were variable, especially in terms of kidney function and blood pressure. Most of the studies reported no differences in mortality, RRT, or cardiovascular events.

There were few procedure-related adverse events, and no medication-related adverse events. Two RCTs reported no patient factors affecting clinical outcomes with either PTRAS or medical treatment. Some relevant patient characteristics were reported in single-group studies, but these were inconsistent. Some case reports suggested clinical benefits of PTRAS in patients with acute decompensation.

The updated review does not find strong evidence that PTRAS is superior to medical therapy alone for most patients with ARAS. Some observational studies suggest improvements in kidney function or blood pressure for certain groups of “high-risk” patients. The researchers write, “Future studies should focus on patients who are putatively most likely to benefit from PTRAS, namely those with proven hemodynamically significant ARAS or those who have signs of decompensation” [Raman G, et al. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. Ann Intern Med 2016; 165:635–649].

BRIEF SUMMARY

AURYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use.

INDICATIONS AND USAGE

AURYXIA® is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

AURYXIA® is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: When using AURYXIA® from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 52-week, single-arm trial in which concomitant use of AURYXIA and IV iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level ≥500 μg/L, as compared with 13 (9%) of patients treated with active control. Assess iron parameters (e.g. serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy. Patients receiving IV iron may require a reduction in dose or discontinuation of IV iron therapy.

Accidental Overdose of Iron: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 years of age. Keep this product out of the reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

Patients with Gastrointestinal Bleeding or Inflammation: Patients with inflammatory bowel disease or active, symptomatic gastrointestinal bleeding were excluded from clinical trials. Safety has not been established in these populations.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions to a drug are most readily ascertained by comparison with placebo, but there is little placebo-controlled experience with AURYXIA, so this section describes adverse events with AURYXIA, some of which may be disease-related, rather than treatment-related.

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (levosimendan carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA. In these trials, adverse events reported for AURYXIA were similar to those reported for the active control group.

Adverse events reported in more than 5% of patients treated with AURYXIA in these trials included diarrhoea (21%), nausea (11%), constipation (8%), vomiting (7%), and cough (6%).

During the 52-week active-control period, 60 patients (21%) on AURYXIA discontinued the drug because of an adverse event, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (levosimendan and levocarnitine carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA (14%). AURYXIA is associated with discolored feces (dark stools) related to the iron content, but this staining is not clinically relevant and does not affect laboratory tests for occult bleeding, which detect heme rather than non-heme iron in the stool.

Drug Interactions

Doxycycline is an oral drug that has to be taken at least 1 hour before AURYXIA. Ciprofloxacin, an oral drug, should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amiodipine, aspirin, atorvastatin, calcium, clopidogrel, digoxin, diltiazem, doxercalfexil, enalapril, fluvastatin, glimepiride, losartan, metoprolol, metformin, simvastatin, slagipril, and warfarin. There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are no adequate and well-controlled studies in pregnant women. It is not known whether AURYXIA can cause fetal harm when administered to a pregnant woman. Animal reproduction studies have not been conducted.

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation.

Labor and Delivery: The effects of AURYXIA on labor and delivery are unknown.

Nursing Mothers: Data from rat studies have shown the transfer of ferric citrate by divalent metal transporter 1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 106 subjects aged 65 years and older (33 subjects aged 75 years and older). Over all, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease on dialysis, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant IV iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient administered IV iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Inform patients to take AURYXIA as directed with meals and adhered to their prescribed diets. Instruct patients on concomitant medication that should be dosed apart from AURYXIA.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered not clinically relevant and does not affect laboratory tests for occult bleeding, which detect heme rather than non-heme iron in the stool.