



Medication Access Program Newsletter

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Inside this Issue

- 1 Inhibition of the RAS and Renal Outcomes
- 2 Effects of Losartan
- 3 BYETTA™

The Medication Access Program (MAP) is a statewide program for solid-organ transplant recipients in Georgia that offers information about medication assistance programs and helps with the enrollment into these programs.

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Inhibition of the RAS and Renal Outcomes

A systematic review and meta-analysis examined effects of renin-angiotensin system (RAS) inhibitors and other antihypertensive drugs on renal outcomes.¹ Randomized controlled trials assessing antihypertensive drugs and progression of renal disease published between 1960 and January 2005 were evaluated. National guidelines and recommendations from the American Diabetes Association and the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Blood Pressure endorse the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) to delay the progression of renal disease. ACEIs and ARBs are assumed to have renoprotective effects beyond those resulting from blood pressure lowering alone. The analysis was conducted to evaluate guidelines endorsing the use of ACEIs and ARBs as a result of placebo-controlled trials that fail to use clinically relevant endpoints.

Studies included in the analysis had to have adult participants, had to be randomized, controlled, and parallel-design, and had to examine the effect of any drug treatment with blood pressure lowering action on the progression of renal disease. Primary outcomes for progression of renal disease measurement included a doubling of serum creatinine and end-stage renal disease. Secondary continuous outcomes included glomerular filtration rate, serum creatinine, and urine albumin excretion. Investigators compared effects of RAS inhibition by use of ACEIs or ARBs to other antihypertensive agents.

The results showed that when compared to other antihypertensive drugs, ACEIs or ARBs yielded a statistically significant relative risk reduction for doubling of creatinine. The analysis also showed a small benefit on the development of end-stage renal disease. Use of ACEIs or ARBs in diabetic nephropathy patients showed no benefit

on the doubling of creatinine, end-stage renal disease, glomerular filtration rate, or creatinine amounts. Placebo-controlled trials of ACEIs or ARBs showed greater benefits than comparative trials on all renal outcomes, which may be attributed to a substantial reduction in blood pressure.

The authors suggest that benefits of ACEIs and ARBs are likely the result of blood pressure lowering and emphasize that blood pressure lowering remains more important than the drug classes used for management of hypertension. Until there are more definitive studies comparing various antihypertensive agents, clinicians should continue to base therapy recommendations on blood pressure lowering effect, comparative tolerability, and the cost of treatment.

Authored by Christy Norman

¹Casas J, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; 366: 2026-2033.



Effects of Losartan

A randomized, double-blind, placebo controlled trial compared the effects of the angiotensin receptor blocker (ARB) losartan (Diovan®) on albuminuria (the chief marker of glomerular damage in the kidney) with those of carvedilol (Coreg®, a beta-blocker) and placebo in 14 renal transplant patients.¹ Study inclusion criteria were as follows:

(a) transplantation period greater than 6 months, (b) a cyclosporine-based immunosuppressant regimen with stable trough levels in the last 6 months, (c) normal or slightly impaired renal function, (d) arterial hypertension treated with 1 or 2 antihypertensive agents, and (e) no proteinuria.

During the run-in phase, any angiotensin converting enzyme inhibitors (ACEIs) or ARBs being taken were discontinued. This phase lasted for 8 weeks to avoid skewing results with residual effects of ACEIs or

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ARBs. Patients on calcium channel blockers (CCBs) were allowed to continue taking them throughout the trial, and CCB therapy was initiated in any patient not taking a CCB. CCB doses were adjusted during this phase only. Target trough blood pressure (BP) was set as 130/85 mmHg or less. Doxazosin (Cardura®, an alpha adrenergic blocking agent) was added if needed to maintain target BP. Patients were then randomized into 1 of 2 treatment sequences, and doxazosin was replaced with losartan or carvedilol. Sequence 1 received 8 weeks of losartan, 8 weeks of placebo, and then 8 weeks of carvedilol. Sequence 2 received 8 weeks of carvedilol, then placebo, then losartan. Doses of carvedilol and losartan during the first week of treatment were 12.5mg and 50mg, respectively, but were doubled on a once weekly basis as necessary to maintain target BP. To achieve consistent BP control, doxazosin was administered to patients in the placebo phase as needed. Patients were asked to continue their normal patterns of sodium and protein intake. Blood pressure, albuminuria, serum creatinine, potassium, hemoglobin, cyclosporine levels, and creatinine clearance were measured at the end of each 8-week phase.

One patient required an increase from 50mg of losartan to 100mg, and 2 patients required an increase from 12.5mg of carvedilol to 25mg. Ten patients in the placebo phase required an average doxazosin dose of 3.0±0.53mg to maintain BP. All patients achieved a trough BP below target. Losartan treatment decreased albuminuria more effectively ($p<0.05$) than placebo or carvedilol. Ten patients received the greatest decrease in albuminuria from losartan, 3 from carvedilol, and 1 from placebo (doxazosin). No correlation was found between albuminuria changes and BP changes. Creatinine clearance and cyclosporine levels remained stable during the study period. Although the study treatments were well tolerated overall, hemoglobin levels dropped significantly ($p<0.01$) after losartan when compared to placebo. No

differences in potassium existed between the groups.

The authors concluded that ARBs may be more nephroprotective than other antihypertensive agents.

Authored by Julie Williamson

¹Tylicki, Biedunkiewicz, et al. Randomized Placebo-Controlled Study on the Effects of Losartan and Carvedilol on Albuminuria in Renal Transplant Recipients. *Transplantation* 2006;81: 52.

BYETTA™

BYETTA™ (exenatide injection), manufactured by Amylin Pharmaceuticals, is the first in a class of medicines for type 2 diabetes called incretin mimetics. Incretins enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions when released into the circulation from the gut. Exenatide mimics the enhancement of glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. It was approved by the Food and Drug Administration in April 2005 as adjunctive therapy to improve glycemic control in patients who are taking metformin, a sulfonylurea, or both. When added to sulfonylureas and/or metformin, it results in additional lowering of hemoglobin A_{1c} by approximately 0.5% to 1%.

BYETTA™ works to improve glycemic control by reducing fasting and postprandial glucose concentrations. It enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. In pre-marketing studies, the addition of BYETTA™ to metformin, a sulfonylurea, or both resulted in statistically significant reductions from baseline hemoglobin A_{1c} at week 30 compared with patients receiving placebo in three controlled trials. The studies also showed that BYETTA™ resulted in statistically significant reduction in fasting and postprandial plasma glucose concentrations.

BYETTA™ is not a substitute for insulin in insulin-requiring patients and should not be used in patients with

type 1 diabetes or for treatment of diabetic ketoacidosis. As of March 2005, BYETTA™ had not been studied in conjunction with insulin, thiazolidinediones, D-phenylalanine derivatives, meglitinides, or alpha-glucosidase inhibitors. BYETTA™ is not recommended for use in patients with end-stage renal disease or severe renal impairment. The drug should also be avoided in patients with severe gastrointestinal disease.

BYETTA™ should be initiated at 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals. It should not be administered after a meal. Dosage may be increased to 10 mcg twice daily after 1 month of therapy. Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

The most common adverse effects seen include hypoglycemia when added to a sulfonylurea (but not metformin), nausea which can be severe, and vomiting. Diarrhea may also occur. Because the drug slows gastric emptying, it may affect the efficacy of other drugs such as antibiotics and oral contraceptives. As a result, oral drugs should be taken at least one hour before exenatide.

For information about Amylin's patient assistance program, contact the pharmaceutical company at 1-800-330-7647 or the MAP office at (706) 721-0131.

Authored by Christy Norman

BYETTA™ Prescribing Information. Available at: <http://www.byetta.com>. Accessed March 2005.

The MAP newsletter is published quarterly to present topics of interest to the transplant community. If you would like to submit material to be considered for publication in the newsletter, please contact MAP at: Medication Access Program University of Georgia at the Medical College of Georgia Clinical Pharmacy Program CJ-1020 Augusta, Georgia 30912 706-721-0131 or 800-736-2273 ext. 0131 or e-mail us at: map@mapuga.com

