PERSPECTIVE

LESS IS MORE

Dual Therapy Difficulties in Angiotensin Blockade for Proteinuria
A Teachable Moment

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A man in his 60s with lymphoproliferative B-cell disorder, hypertension, and stage 3 chronic kidney disease (CKD) secondary to diabetic nephropathy presented for follow-up of his diabetic nephropathy.

Story From the Front Lines

The patient was initially referred to renal clinic in 2010 for elevated serum creatinine level and was found to have nephrotic range proteinuria at 3.7 g/d. He was prescribed losartan to control his proteinuria and blood pressure and observed subsequently by multiple nephrologists. His proteinuria gradually improved, but creatinine levels remained elevated while he was receiving losartan, and 3 years later lisinopril was added to his regimen in an effort to reduce proteinuria to less than 1 g/d. One month later, he developed acute kidney injury (AKI) and his losartan dose was decreased. At his next appointment (the one prior to his visit with us), proteinuria remained above goal despite combination therapy, so the lisinopril dose was increased. The patient subsequently developed progressive fatigue. At his first visit to us, he was hypotensive, with a blood pressure of 90/56 mm Hg, and we discontinued his lisinopril use. The patient reported feeling better, and his blood pressure returned to normal at his next primary care visit.

Teachable Moment

In the 1990s, several studies suggested that treatment with angiotensin-converting enzyme inhibitors (ACEIs) slowed progression of renal failure and decreased proteinuria independent of the effects on blood pressure. It was postulated that the renoprotective effects of ACEIs were due to reduced proteinuria. Thus, proteinuria reduction became synonymous with nephroprotection, and studies of ACEIs and angiotensin receptor blockers (ARBs) to reduce proteinuria were conducted.

Dual ACEI-ARB therapy arose from the concept that monotherapy resulted in incomplete blockade of the renin-angiotensin system. In 2003, the COOPERATE trial[1] found that compared with monotherapy, dual therapy decreased proteinuria and slowed progression of CKD. Several follow-up studies demonstrated that patients with the greatest reduction in proteinuria had the lowest rates of progression to end-stage renal disease and supported the idea that reducing proteinuria should be a target of treatment. In 2004, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease[2] recommended treating proteinuria to a target of less than 500 to 1000 mg/d with ACEIs, ARBs, or dual therapy. By 2010, more than 200 000 US patients were treated with dual renin-angiotensin system–blocking therapy, most commonly ACEI-ARB therapy.[1]

The COOPERATE findings were subsequently retracted for data validity concerns, and several studies showed adverse effects from dual therapy. The ONTARGET study[3] found that dual therapy was associated with decreased proteinuria but increased incidence of requirement of dialysis, doubling of serum creatinine levels, hypotensive symptoms, and syncope without any mortality benefit. However, the majority of ONTARGET participants had normal urinary protein excretion at baseline. To specifically assess the benefit of dual therapy in patients with proteinuric kidney diseases, the VA NEPHRON-D trial[4] was conducted in patients with proteinuric diabetic nephropathy and showed that dual therapy yielded no benefit in glomerular filtration rate, cardiovascular events, or mortality compared with monotherapy but was associated with higher rates of AKI and hyperkalemia (serum potassium level, >6 mEq/L [to convert to millimoles per liter, multiply by 1.0], or requiring hospitalization, dialysis, or emergency department visit).

Despite improvement in proteinuria, overwhelming evidence now demonstrates significant harm with dual therapy without any benefit in mortality or kidney function.[1] In fact, evidence from ONTARGET, VA NEPHRON-D, and other studies resulted in revision of national guidelines. The 2012 update of the KDOQI Clinical Practice Guideline for Diabetes and CKD[5] recommends against dual therapy because of increased risk for adverse events despite decreased proteinuria and urges caution when albuminuria is used as a surrogate for clinical outcomes. Because hyperkalemia, hypotension, or AKI may occur at any time, 1 agent should be discontinued in patients receiving dual therapy to prevent these complications.

Despite clear evidence of harm with dual ACEI-ARB therapy, some may believe that these studies do not apply to patients with heavier proteinuria. Thus, some practitioners might still consider instituting dual therapy with the goal of proteinuria reduction and presumed nephroprotection. However, caution must be exercised when one relies on surrogate markers to predict disease progression irrespective of clinical outcomes. There is neither clear evidence nor prospective randomized trial results showing that targeting proteinuria to a

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goal is beneficial in terms of long-term outcomes, but it is evident that targeting proteinuria with dual therapy is harmful. Our patient did not achieve the less than 1 g/d proteinuria goal with dual therapy yet experienced AKI and hypotension. When weighing risks and benefits of therapy, one should not institute therapy on the basis of a theoretical benefit when there is proven harm.

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