CLINICAL VIGNETTE

Chronic IgA Nephropathy with Nephrotic Range Proteinuria Successfully Controlled with Novel Combination Therapy

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Case

A middle-aged Caucasian male was first diagnosed with biopsy-proven IgA nephropathy in January 2020 after he was found to have proteinuria and hematuria. His renal biopsy revealed IgA nephropathy with one crescent and focal endocapillary hypercellularity with Oxford Classification: M0 E1 S0 T0 C1 without interstitial fibrosis or tubular atrophy.

The patient had not revealed any steroid based therapy since diagnosis due to phis concerns regarding potential side effects. He received conservative medical management with angiotensin converting enzyme (ACE) inhibitor, Ramipril, for blood pressure control and fish oil. His creatinine and proteinuria had slowly worsened in the three years since diagnosis. His 24-hour urine showed 5.5 g of protein and creatinine had increased to nearly 1.5 mg/dl at that time.

He was started on Sparsentan, an endothelin and angiotensin 2 receptor antagonist agent that recently received accelerated approval from FDA for treating IgA nephropathy. He also started Dapagliflozin, a SGLT2-Inhibitor and the ACE inhibitor, Ramipril, was discontinued. After starting this combination therapy, his proteinuria started to improve. After one month spot protein creatinine ratio normalized to less than 0.2 grams, and serum creatinine improved to 1.2 mg/dl from 1.5 mg/dl. He also reported no gross hematuria or lower extremity edema for 6 months. With FDA accelerated approval required monthly liver enzymes which remained within normal limits throughout treatment.

Discussion

IgA Nephropathy is the most common type of glomerulonephritis worldwide, found more in men and distinctly less in blacks. About 40 to 45% of patients, 35% to 40% present with macroscopic hematuria, microscopic hematuria, and proteinuria and with nephrotic syndrome or acute renal failure in the remainder. The diagnosis relies on the finding of dominant or codominant mesangial deposition of IgA on immune-histologic kidney biopsy.

While the pathogenesis remains unknown, increasing evidence suggests a pivotal role, for polyclonal stimulation of immunoglobulins, perhaps coupled with structural abnormalities of IgA. These defects may account for the variety of autoantibodies present in patients with both IgA Nephropathy and Henoch-Schoenlein Purpura (HSP). IgA Nephropathy generally has an indolent course, with about 30% of patients reaching ESRD after 20 years. Particularly in patients presenting with hypertension, heavy proteinuria, or renal insufficiency.

Patients with IgA Nephropathy and little or no proteinuria (<500 mg/day) have low risk of short term progression. Those with sustained proteinuria > 3 g/day have 25-fold faster decline in renal function.[1,2]

Treatment of IgA Nephropathy has been challenging and mostly involves use of steroids, which comes with significant side effects. Steroids are not continued long term due to risk of relapse.

The recent PROTECT clinical trial reported Sparsentan, a novel, non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist, significantly reduced proteinuria versus Irbesartan, an angiotensin II receptor blocker, for treatment of IgA Nephropathy. Over 110 weeks, treatment with once-daily Sparsentan versus maximally titrated Irbesartan in patients with IgA Nephropathy resulted in significant reductions in proteinuria and preservation of kidney function. The safety of Sparsentan was similar to Irbesartan.[3,4]

Conclusion

Although IgA Nephropathy was first described in 1968, treatment has remained challenging. To date most IgA nephropathy treatments are based on immune-suppressive medications such as steroids, with serious side effects. The introduction of Sparsentan, a non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist agent, brings new hopes for treatment. Our patient showed efficacy of this dual endothelin angiotensin receptor antagonist agent in treatment of chronic IgA nephropathy. He also showed the benefit of combination therapy of dual endothelin angiotensin receptor antagonist along with SGLT2-Inhibitor agent to successfully control severe proteinuria. This prognostic factor in IgA nephropathy, decreased to an acceptable range of less than 500 mg.

Additional data from upcoming clinical trials are needed to assess if this dual therapy will be helpful in other IgA Nephropathy cases.

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