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Review Article

THE EFFICACY OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEIS) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBS) ON PROTEINURIA IN MEMBRANOUS NEPHROPATHY

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ABSTRACT

Membranous Nephropathy (MN) is an autoimmune disease and the common cause of proteinuria. Renin-angiotensin aldosterone system (RAAS) plays a significant role in pathophysiologic changes leading to proteinuria in glomerular diseases like membranous nephropathy. Proteinuria is a strong indicator of progressive decline in renal function. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) blocks RAAS and reduces proteinuria. This review focuses on the efficacy of ACEIs and ARBs in reducing proteinuria in the treatment of membranous nephropathy.

Keywords: Membranous nephropathy; Angiotensin converting enzyme inhibitors; Angiotensin receptor blockers; Proteinuria

INTRODUCTION

Membranous nephropathy (MN) is a glomerular disease characterized by thickening of the glomerular basement membrane resulting from the deposition of subepithelial immune complexes. Deposition of Immunoglobulin G and C3 is seen mainly along the capillary wall in immunofluorescence. Electron microscope shows basement membrane thickening and epithelial foot process fusion [1,2]. MN occurs in about 75%-80% of cases with unknown causes and is known as primary MN and approximately 20%–25% of MN occurs secondarily due to other systemic illness [3-5]. In 1957 Membranous nephropathy was first described by David Jones [4,6]. A literature review showed incidence of MN of 1.2 per 100,000 per year worldwide with a 2:1 male predominance [7,8]. MN usually affects people of 40-50 years of age and is uncommon in people under 20 years of age [9,10]. MN is the most common cause of nephrotic syndrome in adults [11,12]. Cases of nephrotic syndrome in adults with MN is between 20-40% [9,12,13]. Nephrotic syndrome includes proteinuria >3.5 g/24h, edema, hypoalbuminemia and hyperlipidemia. About 70% of patient have severe proteinuria and high chance of progression to renal insufficiency [14,15]. Protein overabsorption by renal tubules induces inflammation ultimately resulting in tubulointerstitial injury [16]. In a study conducted by Yizhi et al, tubulointerstitial injury was an independent risk factor for 20% decline in renal function and 50 % progression to end stage renal disease [17]. A study showed the relapse or persistent proteinuria is associated with a poor renal survival rate in patients with nephrotic syndrome diagnosed as membranous nephropathy [18]. Risk for disease progression in membranous nephropathy can be classified into low, moderate and severe risk. In Low risk, proteinuria remains <4 g/day and normal creatinine clearance for 6 months. Here patients have a less than 8% risk of renal failure over 5 years and can be managed with conservative therapy. In Moderate risk, proteinuria range between 4 and 8 g/day and persists for more than 6 months. Creatinine clearance is normal or near normal over 6 months. Approximately 50% of these patients develop chronic renal insufficiency over 5 years. Patients should receive disease-specific therapy if not better with conservative therapy within 6 months. In high risk, proteinuria is > 8 g/day and persists for 3 months and/or below normal or decline in renal function during the observation period. Approximately 75% of such patients are treatment with ACEIs or angiotensin receptor blockers ARBs are at risk of progression to chronic renal insufficiency over 5 years. Patients should be treated with disease-specific therapy along with conservative therapy [19-22]. Renin-angiotensin aldosterone system (RAAS) plays a vital role in the genesis of glomerular lesions leading to proteinuria. Various studies done showed that RAAS blockade successfully reduced proteinuria. Thus, ACE inhibitors and ARBs are recommended as first line treatment for proteinuria. These drugs decrease glomerular pressure through vasodilatory effect on the glomerular efferent arteriole and has protective effect on the glomerular filtration barrier. It can also reduce proteinuria by 35% in early MN [19,23]. Kidney Disease Improving Global Outcomes (KDIGO) in 2012 published guidelines for the treatment of MN suggesting that all patients should receive conservative therapy like ACEIs and ARBs. These drugs effectively lower proteinuria than other antihypertensive drugs and improve outcome in patients with proteinuria in chronic kidney disease [24-27]. There are various adverse effects of ACE inhibitors and ARBs such as acute kidney injury, hyperkalemia, hypotension.

These medications should be used cautiously in nephrotic patients with renal impairment. Therefore, ACE inhibitors or ARBs should be decreased in dosage or even stopped to avoid above mentioned complications [28].

DISCUSSION

Recently several advances have been made in the treatment of membranous nephropathy. Patient with proteinuria in membranous nephropathy should be initially managed conservatively with ACEIs and ARBs as these patients are at the risk of progression to chronic renal failure. Studies done in past showed that the factors like proteinuria at the time of presentation and conservative therapy with ACEIs or ARBs affects the outcomes such as complete and partial remission [29]. Complete remission is achieved when proteinuria is ≤ 0.3 g/d and partial remission is achieved when there is reduction in proteinuria more than with proteinuria < 3.5 g/d [30]. Remission may occur in two years, with a mean of about one year [20,31]. Some studies stated that patients with mild proteinuria achieve higher spontaneous remission rates with ACEIs and ARBs [1,32]. In multicenter cohort study done in Korea demonstrated that the use of ACEIs/ARBs in about 83% of elderly patients with idiopathic membranous nephropathy had better renal outcome (HR 0.06, 95% CI 0.01–0.36, P = 0.003) [33]. A Spanish Group for the Study of Glomerular Disease (GLOSEN) included 328 patients diagnosed with nephrotic idiopathic membranous nephropathy between 1975 and 2007 and were followed up for approximately 6 years. Among two-thirds of patients receiving ACE inhibitors or ARBs, about 32% of patients achieved spontaneous remission in 2 years from the onset of disease [22,34-36]. Another study done by McQuarrie et al. analyzed patients with membranous nephropathy diagnosed between 1997 and 2008. About 95% of patients received ACE inhibitors and/or ARBs. This study showed that achieving complete or partial remission or ACE-I/ARB treatment-induced remission was independently associated with a reduced risk of requiring renal replacement therapy (hazard ratio, 0.02; 95% confidence interval 0.0–0.2; P=0.001) and reduced risk of death (hazard ratio, 0.07; 95%confidence interval 0.02–0.3 ;P=0.001) [34,37]. The combination therapy with ACE inhibitors plus ARBs is suggested by National Kidney Foundation in the reduction of proteinuria in patients with kidney disease but further larger studies are required [38].

CONCLUSION

Reduction of proteinuria is a key in the management of membranous nephropathy at the onset of disease in order to decrease the risk of progression of disease to renal failure. Thus, patients with membranous nephropathy should be initially managed with ACE inhibitors or ARB. Evidences and many studies support that ACE inhibitors and ARBs safely slow down progression of end stage renal disease by inhibiting RAAS. Therefore, ACE inhibitors and ARB are effective in the reduction of proteinuria in membranous nephropathy.

Conflict of interest: None

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