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## Contemporary immunosuppressive treatment for membranous nephropathy

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Membranous nephropathy (MN) is the leading cause of nephrotic syndrome in adults. Although its course includes spontaneous remission in about 30% of patients, nephrotic patients who do not achieve remission have a higher risk of progression to end-stage renal disease (ESRD). Recently, understanding of the pathogenesis of primary MN has progressed with the identification of M-type phospholipase A2 (PLA2) receptor and thrombospondin type-1 domain-containing 7A (THSD7A) as target antigens. However, treatment is still challenging and there remain controversies for management of patients with primary MN.

Conservative managements including controlling of proteinuria and blood pressure, reducing edema and hypercholesterolemia are recommended for at least 6 month, unless progressive loss of renal function or other severe complications of nephrotic syndrome. However, more specific treatment has been recommended for non-responders to conservative treatment. In patients with MN, cyclophosphamide, calcineurin inhibitors (CNIs), rituximab and ACTH are all available treatment options with different adverse effects. In this talk, the risk-benefit profile of contemporary immunosuppressive treatments for primary MN will be reviewed.

### ***Immunosuppressive treatment for MN***

Although, alkylating agents remain the only proven agent in preventing ESRD or death, cyclophosphamide-based regimens are associated with significant toxicity and long-term risk for malignancy. CNIs reduce proteinuria, but they are nephrotoxic and should be avoided in patients with abnormal renal function. Thus, there has been a desire for more targeted therapy with equal efficacy but less toxicity.

### ***Rituximab for the treatment of MN***

Rituximab (RTX), IgG1k chimeric monoclonal antibody directed against CD20 on B lymphocyte lead to depletion of peripheral and tissue B lymphocyte. RTX reduced proteinuria and achieved complete or partial remission in nephrotic patients with primary MN with a higher safety profile [1-3]. In the Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMIRITUX) study, RTX is more effective in inducing remission than placebo [4]. Anti-PLA2R antibody levels are valuable for monitoring treatment and predicting relapse. Previous reports have shown that a decrease of antibody levels precedes clinical remission, and anti-PLA2R Ab serial measurement may help to determine optimal timing and duration of immunosuppressive therapy. A new therapeutic algorithm composed of an individualized serology-based approach that refines the traditional proteinuria-based approach has been proposed in patients with MN. Further evidences to support RTX treatment in MN are expected from the ongoing RCTs (MENTOR and STARMEN trials).

### ***Adrenocorticotrophic hormone for the treatment of MN***

Adrenocorticotrophic hormone (ACTH), either as synthetic ACTH analog or natural ACTH gel formulation has been evaluated in patients with MN, and a growing body of evidence supports its efficacy in this condition. Earlier study using synthetic ACTH analog has revealed decreases in both urinary protein and serum creatinine in patients with primary MN [5]. A randomized pilot trial comparing cyclophosphamide plus methylprednisolone vs. synthetic ACTH for 6 month have shown similar efficacy in proteinuria reduction [6]. Recently, natural ACTH gel (80U s.c., twice weekly) reduced proteinuria in more than half of the patients with parallel or precedent reduction of anti-PLA2R Ab levels [7]. Further prospective studies with longer period of follow-up would be needed to assess the efficacy of this agent.

### ***Other potential therapies for MN***

Second-and third-generation anti-CD20 antibodies (obinutuzumab, ofatumumab) that bind to

different epitopes on the CD20 molecule may be a potential therapy. Belimumab targets soluble B lymphocyte stimulator and induces apoptosis of autoreactive B cells. In patients with anti-PLA2R-positive MN, belimumab significantly decreased anti-PLA2R Ab levels, decreased proteinuria, and normalized serum albumin levels. Proteasome inhibitors may be another option considered for the treatment of resistant MN.

In summary, available evidences have suggested that B-cell targeted therapy with RTX is safer and better tolerated. In addition, the new paradigm, a serology-based approach using anti-PLA2R Ab monitoring should be kept in mind to complement the proteinuria-based approach for better outcomes.

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