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Key Points in Managing PLA2R-Associated Membranous Nephropathy

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The therapeutic approach to primary membranous nephropathy (PMN) typically revolves around the optimization of antiproteinuric therapy and cyclophosphamide and corticosteroids (CYC/CS) or rituximab as first-line interventions in those at high risk of progressive disease.[1] Economic considerations, fertility preservation, the presence or predisposition to diabetes mellitus, degree of proteinuria and/or serum albumin levels, and the levels of anti-M-type phospholipase A2 receptor (PLA2R) antibodies principally influence the selection between these modalities. Guideline groups, such as the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 have provided recommendations on managing this population.[1] Despite the simplicity of these treatment strategies, persistent misconceptions cloud their utilization, underscoring the importance of attention to detail in PMN management. Drawing upon over 5 decades of collective experience, we proffer key insights essential for the optimal management of PMN.

Conservative Care in the Anti-PLA2R Era

The law of one-third governs the trajectory of PMN, wherein approximately one-third of individuals undergo spontaneous remission. Owing to the potential adverse effects of immunosuppressive regimens, clinical guidelines recommend limiting their use to patients at high risk of progressing to kidney failure, which is determined by the degree of proteinuria, kidney function, and anti-PLA2R titer.[1] In an analysis of 328 patients with PMN and nephrotic syndrome enrolled in the Spanish registry, 32% experienced spontaneous remission.[S16] Hofstra *et al.* documented a robust correlation between clinical activity and anti-PLA2R titers.[S17] Three recent publications have reported spontaneous remission among patients exhibiting anti-PLA2R levels below 100 RU/ml.[S18–S20] The study conducted by Porcine and colleagues revealed a spontaneous remission rate of 65% in patients with anti-PLA2R levels below 97 RU/ml. Decreasing levels of anti-PLA2R titers also strongly predict spontaneous remission of proteinuria.[S21]

Given the low likelihood of spontaneous remission in subjects with high levels of antibody, it makes sense to shorten the period of observation on nonspecific antiproteinuric therapies in those with high anti-PLA2R titers (>100 RU/ml) to minimize the period when the patient is at risk of developing complications of nephrotic syndrome. The updated KDIGO 2021 guidelines have embraced this approach.[1]

Utility of Anti-PLA2R in Managing PMN

Integrating anti-PLA2R testing marks a paradigm shift in diagnosing and managing patients with PMN.[S17,S22,S23] A positive anti-PLA2R test obviates the need for a kidney biopsy to diagnose PMN in nondiabetic patients with preserved kidney function.[S23] Although numerous investigations have explored the correlation between anti-PLA2R and disease course, a consensus is yet to be achieved regarding its use in monitoring a patient with PMN.[S17,S24,S25]

In clinical trials, antibody levels were assessed 3- and 6-months post-rituximab therapy.[2,3,S26] However, the optimal timing for anti-PLA2R testing remains to be determined. Recent *post hoc* analyses of the MENTOR cohort have revealed that anti-PLA2R titers exceeding 323 RU/ml and 14 RU/ml in the third and sixth months, respectively, portended resistance to treatment.[S27] Limited data exist regarding the temporal evolution

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of anti-PLA2R in patients undergoing CYC/CS therapy. Our previous investigation involving 30 patients with PLA2R-related PMN revealed that elevated anti-PLA2R levels correlated with ongoing disease activity at 6 months.[S25]

In terms of guiding therapeutic decisions, a recent study by Vink *et al*. underscores the utility of antibody-guided treatment with CYC/CS, yielding cumulative remission rates of 71% at 8 weeks and 89% at 12 months.[S28] Nonetheless, a subset experiencing clinical remission encountered relapses, necessitating additional interventions.

In summary, anti-PLA2R has emerged as a critical parameter in the management of PMN. As recommended by KDIGO 2021,[1] initial testing for anti-PLA2R should precede immunosuppressive therapy, with subsequent assessments recommended between the third and sixth month for patients undergoing rituximab therapy (primarily for dosing adjustments) and after the sixth month for those on cCYC/CS therapy (primarily for identifying resistant disease).

Anticoagulation in Membranous Nephropathy

Individuals afflicted with nephrotic syndrome face an elevated susceptibility to thromboembolic events.[S29,S30] Among primary glomerular diseases, membranous nephropathy has the highest risk of thrombotic complications.[S31,S32] Hypoalbuminemia in patients with PMN significantly increases the risk of thrombotic incidents, particularly venous thromboembolisms. Moreover, the risk of venous thromboembolisms and arterial thromboembolism is highest within the first 2 years of clinical presentation.[4,S32]

Despite evidence favoring anticoagulant therapy in PMN with hypoalbuminemia, its utilization remains suboptimal; this is chiefly attributable to the necessity for regular monitoring and apprehensions surrounding bleeding risks associated with vitamin K antagonists and lack of pharmacokinetics and pharmacodynamics of non-vitamin K antagonist oral anticoagulants in nephrotic syndrome.[4,S33] The arrival of non-vitamin K antagonist oral anticoagulants provides a hopeful solution to ease these monitoring worries without the heavy cost burden.

In conclusion, as per the KDIGO recommendation, nephrologists are strongly encouraged to contemplate the initiation of oral anticoagulation therapy for patients with PMN with severe hypoalbuminemia and a low predisposition to bleeding, whereas individuals at a heightened risk of bleeding are counselled to pursue aspirin monotherapy.[1]

Additional Dosing of Rituximab

An analysis focusing on patients with anti-PLA2R-associated PMN treated with rituximab (administered at 375 mg/m^2 daily on days 0 and 7) or CYC/CS unveiled rituximab's inefficacy in cases marked by anti-PLA2R levels residing in the third tertile (exceeding 150 RU/ml).[5] This finding has been widely cited as justification for favoring CYC/CS in individuals with very high anti-PLA2R titers.

Dahan and collaborators undertook a study wherein rituximab was readministered to patients displaying persistent positivity for anti-PLA2R antibodies after the third month.[S34] This intervention yielded remission rates of >85%, even among individuals with elevated anti-PLA2R titers. The observed shortcomings in achieving remission among one-third of rituximab-treated cases in diverse studies may partly be attributed to an inadequate dosing regimen.

In summary, patients undergoing rituximab therapy should undergo evaluation for anti-PLA2R antibodies after the third month, with retreatment warranted for those failing to attain immunological remission.

Malignancy-Overrated Complication With Cyclical Therapy

Treatment with cyclophosphamide is associated with secondary malignancies, which include cancer of the urinary tract and hematopoietic system.[S35,S36] However, the risk of these secondary malignancies depends on the cumulative dose of cyclophosphamide. In a study of 293 patients with granulomatosis with polyangiitis, the incidence of bladder cancer and acute myeloid leukemia was increased only in the subgroup of patients treated with cumulative cyclophosphamide doses >36 g.[S36,S37] In a study of 272 patients with membranous nephropathy, there was a 3-fold increase in cancer risk, and this translates to an annual risk from 0.3% to 1.0%.[6] The mean cumulative dose of cyclophosphamide was 37 g. Therefore, the incidence of malignancy will be low if the total cumulative dose of cyclophosphamide is less than 36 g while treating membranous nephropathy with the cyclophosphamide-based regimen.[6] None of the studies reporting the medium-term and long-term outcomes of patients treated with cyclical therapy report a heightened risk of malignancy.

Pneumocystis Jirovecii Pneumonia Prophylaxis

Due to drug-induced lymphopenia, patients undergoing rituximab or high-dose cyclophosphamide and corticosteroid treatments are at an elevated risk of contracting

Pneumocystis jirovecii pneumonia.[S38,S39]

The TESTING trial, which was examining methylprednisolone in IgA nephropathy, was prematurely halted due to safety concerns arising from breakthrough Pneumocystis jirovecii pneumonia and an uptick in fatalities within the Chinese cohort.[S40] Notably, the standard-dose TESTING trial omitted cotrimoxazole prophylaxis. However, in the ensuing low-dose TESTING trial, all participants received cotrimoxazole prophylaxis, resulting in zero incidences of Pneumocystis jiroveci pneumonia.[S41] Convincing evidence underscores the protective efficacy of cotrimoxazole against this pathogen, even in conjunction with rituximab treatment.[S42] Administering cotrimoxazole to rituximab-treated patients yields a number needed to harm of 101, juxtaposed with a number needed to prevent 1 infection of 32.[S43]

Despite the weight of evidence, cotrimoxazole prophylaxis is not uniformly prescribed to patients undergoing CYC/CS therapy. Consequently, we advocate for the universal administration of cotrimoxazole prophylaxis to all patients with PMN who are undergoing rituximab or CYC/CS treatment, aligning with the KDIGO 2021 guidelines.[1]

Corticosteroid Withdrawal With Cyclical CYC/CS

The KDIGO Glomerulonephritis 2021 guidelines advocate using cyclical CYC/CS in patients with high and very high risk PMN.[1] This treatment regimen involves the rapid withdrawal of high-dose corticosteroids (0.5 mg/kg/d of oral prednisolone) at the end of months 1, 3, and 5. This abrupt cessation often precipitates a spectrum of symptoms, as observed firsthand, attributed to corticosteroid withdrawal.

From our experience, we believe that the consequences of abrupt steroid withdrawal, especially symptoms such as weakness, loss of appetite, nausea, and joint pain, are among the most overlooked complications linked to the cyclical protocol for managing PMN. These adverse reactions often play a significant role in patients' reluctance to adhere to the prescribed treatment plan. In addition, research indicates that approximately one-fourth of individuals subjected to the cyclical protocol experience hypothalamic-pituitary axis suppression.[S44] In light of these considerations, it is imperative to promptly recognize symptoms and provide patients with appropriate reassurance, a measure that typically proves efficacious.

Vaccination Before Immunosuppressants

Patients with membranous nephropathy treated with immunosuppressive agents are at a high risk of infection[S45] Apart from cotrimoxazole prophylaxis for Pneumocystis jiroveci pneumonia, other precautions should be taken to avoid or reduce the risk of infection, including administering appropriate vaccines before initiating immunosuppressive agents. Vaccines for COVID-19, influenza, pneumococcal, zoster (Shingrix) and other nonlive vaccines should be administered before initiating immunosuppressant agents.[S46,S47] These vaccines could be administered while being treated with supportive therapy and being investigated for secondary causes of membranous nephropathy. Supplementary File 1 outlines further crucial aspects of PMN management.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Reference.

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