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ANTI-PLA2R ANTIBODY AND PRIMARY MEMBRANOUS NEPHROPATHY: A LITERATURE REVIEW

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Abstract: Membranous nephropathy is the most common cause of nephrotic syndrome in non-diabetic Caucasian adults over 40 years of age and a leading cause of nephrotic syndrome in adults. Classified into primary and secondary membranous nephropathy related to various conditions including infection (hepatitis B), systemic disease (SLE and sarcoidosis), medications (nonsteroidal anti-inflammatory drugs), thyroiditis, and malignancy. Evidence of the clinical utility of measuring PLA2R plasma levels has increased over the last 2 years and was the main focus of this review. The guiding question was: "What is the clinical applicability of the anti-PLA2R antibody in the management of primary membranous nephropathy, as reported in the literature?". The literature review was developed following the PICO search strategy. All patients with primary membranous nephropathy must be treated with supportive care from the time of diagnosis to minimize protein excretion. Patients with elevated anti-PLA2R levels and proteinuria >3.5 g/d at diagnosis and those who fail to reduce proteinuria to <3.5 g after 6 months of supportive care or have complications of nephrotic syndrome must be considered for immunosuppressive therapy. Accepted regimens include steroids/cyclophosphamide, calcineurin inhibitors, and B-cell depletion. The anti-PLA2R antibody is the first serological marker that has promising evidence to be used as a tool to predict the course of the disease. More importantly, therapeutic agents such as rituximab and adrenocorticotropic hormone analogues are new therapeutic options that must be considered in the therapy of primary MN.

Keywords: Membranous nephropathy; primary membranous nephropathy; anti-PLA2R antibody.

INTRODUCTION

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in non-diabetic Caucasian adults over 40 years of age. It has an estimated incidence of 8 to 10 cases per 1 million. Fifty percent of patients diagnosed with primary MN continue to have nephrotic syndrome and 30% of patients may progress to end-stage renal disease within 10 years. MN, one of the main causes of nephrotic syndrome in adults, is classified into primary membranous nephropathy (PMN) and secondary MN related to various conditions including infection (hepatitis B), d systemic disease (SLE and sarcoidosis), medications (non-steroidal anti-inflammatory drugs), thyroiditis and malignancy (LU PANG; DE VRIESE et al. 2017). About 80% of cases are renal limited (PMN) and 20% are associated with other diseases or systemic exposures (secondary MN) (COUSER W. et al, 2017). This review only focuses on PMN. PMN is a kidney-specific autoimmune glomerular disease that presents with increased protein in the urine associated with a pathognomonic pattern of damage to the glomeruli. Most PMNs are mediated by antibodies to the M-type phospholipase A2 receptor (anti-PLA2R) (85%), thrombospondin type 1 domain containing 7A (THSD7A) (3% to 5%) or by other yet unidentified mechanisms (10 %) (COUSER W. et al, 2017). Treatment is still challenging and controversial due to potential toxicity and lack of a reliable prognostic marker.

Traditionally, the differential diagnosis and management of MN is based on the integration of clinical and biopsy findings. In the past, several studies have shown that immunosuppressive therapies such as steroids and alkylating agents or cyclosporine could lead to remission of proteinuria and preservation of renal function (POURCINE et al, 2017). However, immunosuppressive therapies cause adverse events such as infections and malignancy.

The ideal treatment of patients with PMN is still a matter of debate. According to Dahan K. et al, 2017, 30% to 40% of affected patients will undergo spontaneous remission, usually partial, within a year after the onset of the disease[3]. In addition, kidney toxicity is a concern. The most recent guidelines for improving global outcomes in kidney disease (KDIGO) restricted the indication of alkylating agents to patients at high risk of progression and considered calcineurin inhibitors as an alternative therapy. Indeed, current challenges include identifying patients with a severe prognosis, treating them appropriately, and assessing the effectiveness of treatment as early as possible in order to adapt therapy to each patient and thus avoid side effects and unnecessary costs.

In this setting, subsequent research has focused on the clinical utility of anti-PLA2R antibodies. Several studies have shown that the prevalence of anti-PLA2R antibodies ranges from 52% to 69% in membranous nephropathy, as determined by standardized methods (LI X. et al, 2016). In this article, we will explore how the discovery of podocyte target antigens and the development of commercial assays for PLA2R can guide diagnosis and management and complement traditional algorithms. The following questions will be addressed. Can PLA2R be used to diagnose MN and thus avoid the need for a kidney biopsy? Can PLA2R adequately discriminate between primary and secondary MN and thus avoid the need to look for the presence of a secondary condition? Can PLA2R quantification guide prognosis and the decision to initiate, adapt, or withdraw immunosuppressive treatment for primary MN? Can PLA2R level help in predicting, detecting and treating post-transplant recurrence? Evidence of the clinical utility of

measuring PLA2R plasma levels has increased over the last 2 years and was the main focus of this review.

MATERIAL AND METHODS

A literature review was carried out, which is considered a unique tool in the field of health as it enables the synthesis of available evidence on a given topic and directs clinical practice based on scientific knowledge. The guiding question of the research was: "what is the clinical applicability of the anti-PLA2R antibody in the management of primary membranous nephropathy, as reported in the literature?".

The literature review was developed following the PICO search strategy, which is an acronym for Patient or problem, Intervention, Control or comparison and Result12 ("outcome" in English); defining the questions as follows: "P" - patients with primary membranous nephropathy; "I" - interventions carried out by health professionals; "C" - not applicable, as no intervention for comparison was established; and "O" – Management of primary membranous nephropathy.

The research took place in the following stages: establishment of the hypothesis and objective; establishment of inclusion and exclusion criteria for articles (sample selection); definition of the information to be extracted from the selected articles; results analysis; presentation and discussion of results; elaboration of the final text.

For the selection of articles, the Electronic Medicus Index database of the National Library of Medicine (MEDLINE) was consulted via PUBMED. Therefore, articles in English from 2014 to 2019 were selected.

Inclusion criteria were articles published in the last five years in humans with availability of abstracts for identification and free access to them in full whose themes were related to the clinical applicability of phospholipase A2 in primary membranous nephropathy, excluding those focusing merely on histopathological, genetic or laboratorial, in addition to those covering the secondary forms of the disease in question. Furthermore, studies covering the pediatric and obstetric populations were also excluded.

As recommended by Lopes et al, 2019, due to the specific characteristics of accessing each of the selected databases, the strategies used to locate the articles were adapted according to the research questions and inclusion criteria to maintain consistency in the search for articles and avoid possible biases. From this perspective, the keywords used in English were: "anti-PLA2R" and "primary membranous nephropathy" and "Immune response", "anti-PLA2R antibody" and "randomized controlled trial", "anti-PLA2R antibody", "severe adverse event" and "glomerular PLA2R deposition", "membranous nephropathy" and "Phospholipase A2", "Autoantibodies" and "class II histocompatibility", "nephrotic syndrome", "podocyte", "subepithelial deposits IgG4", "proteinuria", "polymorphisms", "glomerulonephritis".

The online search found 153 articles. Those that did not meet the aforementioned criteria were excluded, totaling 15 articles related to the proposed topic, as shown in Figure 1.

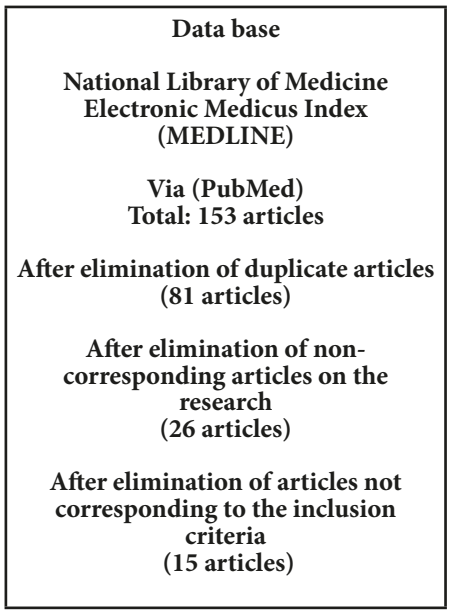

Figure 1: Flow diagram of the article inclusion process, Valença, Rio de Janeiro, Brazil, 2023.

Source: Lopes G. et al, 2019.

RESULTS

The study Couser et al, 2017, reveals that in clinical practice, 80% of patients with PMN have nephrotic syndrome and 20% have non-nephrotic proteinuria. Untreated, about a third experience spontaneous remission, especially those with absent or low levels of anti-PLA2R. Proteinuria may persist for months after circulating anti-PLA2R antibody is no longer detectable (immune remission). All patients with PMN must be treated with supportive care from the time of diagnosis to minimize protein excretion. Patients with elevated anti-PLA2R levels and proteinuria greater than 3.5 g/d at diagnosis, and those who fail to reduce proteinuria to less than 3.5 g after 6 months of supportive care or have complications of nephrotic syndrome, must be considered for immunosuppressive therapy. Accepted regimens include steroids/cyclophosphamide, calcineurin inhibitors, and B-cell depletion. With proper management, only 10% or less will develop ESRD over the next 10 years. According to the author, the clinical consequences of PMN can be considered short- and long-term. In the short term, these include complications of nephrotic syndrome, such as the development of thrombotic and thromboembolic events, which are proportional to the degree of hypoalbuminemia and significantly increase below albumin levels of about 2.8 g / L. There is also an increased risk of infection, mainly due to urinary loss of antibodies and cardiovascular diseases.

The research Pourcine et al, 2017, evaluated the clinical significance of biomarkers and measured circulating anti-PLA2R autoantibodies, and also studied how immune deposits of the PLA2R antigen are major advances in understanding the disease15. In this 14-year retrospective study, we collected data from 108 patients with MN and assessed the relationship between the clinical course. Eighty-five patients suffered from PMN and 23 patients from a secondary form. The median follow-up was 30 months. Among the 77 patients with PMN and available serum and/or biopsy, 69 (89%) had PLA2R-related disease as demonstrated by anti-PLA2R, while 8 patients (10%) were negative for both. There was no significant difference between these two groups in age at diagnosis and outcome assessed by proteinuria, serum albumin level and Glomerular Filtration Rate (GFR). In patients with PLA2R-related PMN, younger age, lower proteinuria, higher eGFR, and lower PLA2R level at baseline and after 6 months were associated with remission of proteinuria. In rituximab-treated patients, a lower PLA2R titer at baseline and the absence of PLA2R and a higher serum albumin level at 3 months were significantly associated with remission. Remarkably, 82% of patients who achieved remission completely eliminated PLA2R. PLA2R depletion and increased serum albumin level preceded the decrease in proteinuria. Accordingly, in the work De Vriese et al, 2017, an individualized approach

based on serology for MN was proposed, used to complement and refine the traditional approach based on proteinuria. Anti-PLA2R antibody levels are strongly correlated with disease activity. Low baseline levels and decreasing levels of anti-PLA2R antibodies strongly predict spontaneous remission, thus favoring conservative therapy. On the other hand, high baseline or rising levels of anti-PLA2R antibodies are associated with nephrotic syndrome and progressive loss of renal function, thus encouraging the immediate initiation of immunosuppressive therapy.

Another study, Xin L. et al, 2016, used 2 standardized methods to assess anti-PLA2R antibody in sera from Chinese patients with primary membranous nephropathy (PMN) and determine whether the immune reactivity reflected by the antibody titer correlates with the parameters of renal function8. Thus, 82 subjects with biopsy-proven PMN, 22 cases of secondary MN, 40 non-MN patients with established glomerulonephritis, and 20 healthy volunteers were recruited from the Division of Nephrology in Hospital in China. Fifty-three patients with PMN (64.6%) were found to be positive for the anti-PLA2R antibody. The 2 anti-PLA2R test systems correlated very well with each other and reached a 95.7% agreement for patients with PMN. The level of antibody detected by ELISA in patients with PMN was also significantly correlated with proteinuria and nephritic range proteinuria (>3.5 g/day).

The article Li L. et al, 2016, aimed to evaluate clinical biomarkers of MN in blood, tissue and urine samples from Chinese patients. In total, 195 patients with MN and 70 with other glomerular diseases were prospectively included in the study. Participants were followed for an average of 17 months (range 3-39 months). Anti-PLA2R was only detected in sera from patients with MN. Of the 54 patients with MN whose serum was collected cross-sectionally, 23 had circulating anti-PLA2R antibodies. Anti-PLA2R was detected in 8.33% of patients with complete remission (CR), 31.58% of patients with partial remission (PR) and 69.57% of patients without remission. Of the patients who were followed longitudinally (n = 136), the majority of patients with PLA2R-related MN were male (58.87%), aged between 15 and 83 years (median = 39.8). Anti-PLA2R and glomerular PLA2R positive serum rates were 69.50% and 83.21%, respectively, in this population. Finally, there was no statistical difference in gender, age, time to renal biopsy from baseline, or time to follow-up between PLA2R and PLA2 in patients with non-R-related MN. Furthermore, there was no significant difference in any relevant clinical parameters such as serum creatinine or GFR among the four groups. More anti-PLA2R positive patients developed nephrotic interval proteinuria (80.90%) than anti-PLA2R negative patients (50.00%, P=0.003). All 136 MN biopsies were analyzed for the extent of tubulointerstitial fibrosis and glomerular lesions. Interstitial fibrosis was found in 117 of 136 samples. There were no significant differences in the percentage of patients with interstitial fibrosis, glomerular lesions or segmental glomerulosclerosis between the four groups.

In the clinical trial Akiyama S. et al, 2015, the prevalence of anti-PLA2R antibodies in Japanese patients with MN was determined. The survey revealed that anti-PLA2R antibodies were detected in 53 (53%) of 100 patients with MN. The prevalence of anti-PLA2R antibodies was higher in patients with nephrotic syndrome (61%) than in patients without nephrotic syndrome (43%). The number of patients with serum albumin ≤3.0 g/dL was significantly higher in those with anti-PLA2R antibodies (92%) than in

those without them (68%). The prevalence of anti-PLA2R antibodies was lower than in any other Asian country. In this context, this may indicate that the presence of other pathogenic antigens plays a significant role in Japanese patients with MN.

A multicenter, randomized, controlled study in 31 French hospitals, Dahan K. et al, 2017, aimed to evaluate patients with biopsy-proven PMN and nephrotic syndrome after 6 months of Non-Immunosuppressive Antiproteinuric Treatment (NIAT). They were randomly assigned to 6 months of therapy with NIAT and 375 mg/m² of intravenous rituximab on days 1 and 8 (n = 37) or NIAT alone (n = 38). The primary endpoint was a combined endpoint of complete or partial remission of proteinuria at 6 months. Antiphospholipase A2 receptor antibody (anti-PLA2R-Ab) depletion rates in the NIAT-rituximab and NIAT groups were 14 of 25 (56%). The positive effect of rituximab on remission of proteinuria occurred after 6 months. These data suggest that PLA2R-Ab levels are early markers of rituximab effect and that the addition of rituximab to NIAT does not affect safety. For Obrisca B. et al, 2015, the accumulation of clinical data supports a pathogenic role for anti-PLA2R antibodies, but confirmation in an animal model is still lacking14. However, circulating PLA2Rs were related to disease activity and outcome, as well as response therapy.

In another perspective, in the study Ruggenenti P. et al, 2015, in order to evaluate the relationships between the effect of the treatment, nephritogenic anti-phospholipase A2 autoantibodies (anti-PLA2R) and genetic polymorphisms that predispose to the production of antibodies, it was monitored serially measure proteinuria and antibody titers in 24 hours in patients with primary and long-term MN15. Thereafter, all complete remissions were preceded by complete depletion of anti-PLA2R antibodies. The resurgence of circulating antibodies predicted disease relapse. The outcome was independent of PLA2R1 polymorphisms and prior immunosuppressive treatment. Therefore, assessment of circulating anti-PLA2R autoantibodies and proteinuria may help in monitoring disease activity and guiding personalized rituximab therapy in nephrotic patients with primary MN.

Scientific evidence from Sinico R. et al, 2016, reveals that the M-type phospholipase A2 receptor (PLA2R) has been identified as the main target antigen, as it can be found in approximately 70% of patients with idiopathic MN, but only rarely in other glomerulonephritis17. Podocyte damage in the experimental model of Heymann's nephritis is mediated by complement. In humans, the presence of complement within subepithelial deposits is well established, but IgG4, which does not activate complement by classical or alternative pathways, represents the predominant subclass of anti-PLA2R IgG.

The review Kattha A. et al, 2015, aimed to determine whether patients with pre-transplant anti-PLA2R (tx) are at increased risk of recurrence compared to seronegative patients and to determine whether post-Tx changes in anti-PLA2R correspond to to the clinical course6. It was observed that the persistence or reappearance of anti-PLA2R post-Tx was associated with increased proteinuria and resistant disease in many cases; little or no proteinuria occurred in cases with pre-Tx anti-PLA2R and biopsy evidence of recurrence, in which antibodies resolved with standard immunosuppression. Therefore, patients with pre-Tx positive anti-PLA2 R must be closely monitored for recurrent MN, as the persistence or reappearance of post-Tx antibody may indicate more resistant disease.

DISCUSSION

Current knowledge of the roles of IgG autoantibody and complement in PMN pathogenesis yields better B-cell depleting agents and complement inhibitors of particular interest (Couser et al, 2017). New therapeutic approaches to suppress antibody production or interfere with antibody-induced podocyte injury include improved B-cell depleting agents, B-cell depleting agents specifically targeted to anti-PLA2R-reactive cells, and suppressors of B-cell activation. A recent pilot study of belimumab, an inhibitor of B-cell activation, in 11 anti-PLA2R positive patients reported a 90% reduction in anti-PLA2R levels and a 70% (delayed) reduction in proteinuria in patients receiving monthly intraoperative doses. venous drug. medication for a period of 28 weeks.

In addition, other approaches under development include antibody traps or decoys and efforts to directly protect the podocyte itself from the consequences of immune injury, such as endoplasmic reticulum stress, autophagy, and oxidation injury. Pending the identification of PLA2R peptides that neutralize antibodies, peptide blocking agents will likely also be developed. Although a study of the C5 inhibitor eculizumab was negative in PMN, adequate doses of complement inhibition were not used and other studies with newer complement inhibitors, including oral agents, recombinant complement regulatory proteins, small molecules, new monoclonal antibodies, small interfering RNA agents and approaches that up-regulate natural complement inhibitors are underway or under development.

In the study, Lu P. et al, 2017, the prognostic role of chronic tubulointerstitial injury in the renal outcome of PMN was found. This study highlighted the value of renal biopsy under the widespread use of anti-PLA2R antibodies for diagnosis and prognosis11.

For Pourcine et al, 2017, the assessment of PLA2R autoimmunity is essential for patient management. The combination of surrounding PLA2R and immune deposits of the PLA2R antigen increases diagnostic sensitivity. Surrounding PLA2R titer is a biomarker of disease severity at baseline, and antibody kinetics is significantly correlated with disease progression.

For Xin L. et al, 2016, the anti-PLA2R antibody is sensitive and extremely specific for the diagnosis of Chinese patients with primary membranous nephropathy. The concentration of autoantibody against PLA2R may be an ideal marker to monitor immune disease activity. In fact, according to Vriese D. et al, 2017, the resurgence or increase in antibody titers precedes a clinical relapse. The persistence or reappearance of anti-PLA2R antibodies after kidney transplantation predicts the development of recurrent disease. From the study, we proposed an individualized serology-based approach to MN, used to complement and refine the traditional proteinuria-based approach, to improve the outcome of this disease. Incidentally, high baseline or rising levels of anti-PLA2R antibodies are associated with nephrotic syndrome and progressive loss of renal function, thus encouraging the immediate initiation of immunosuppressive therapy. Anti-PLA2R antibody serum profiles reliably predict response to therapy, and levels after completion of therapy can predict long-term outcomes.

For Li L. et al, 2016, it is confirmed that the anti-PLA2R was specifically detected in the sera of patients with MN. Indeed, several recent studies have correlated anti-PLA2R levels with clinical manifestations of disease status, specifically decreasing anti-PLA2R levels during remission and increasing levels during relapse. Detection of PLA2R in kidney biopsies or of circulating anti-PLA2R can discriminate between MN but not between

idiopathic and secondary MN.

The multicenter study, Dahan K. et al, 2017, in this randomized trial, analyzed the effect of rituximab combined with NIAT in patients with PMN and severe nephrotic syndrome who resisted maximally tolerated antiproteinuric therapy. Indeed, NIAT-rituximab was compared with NIAT alone because there was no evidence-based evidence of rituximab's efficacy in PMN, although several non-randomized studies suggested that rituximab was effective. From this, this study shows that serum levels of albumin and PLA2R-Ab are early markers of NIAT-rituximab efficacy, while the effect on proteinuria remission appears after 6 months. The addition of rituximab to NIAT does not affect safety. This first randomized clinical trial is another step towards the use of rituximab as first-line therapy in severe forms of PMN. It also suggests that criteria for defining remission must include serum levels of albumin and PLA2R-Ab, particularly in trials where rapid responses on drug efficacy and surrogate criteria are needed.

For Francis J et al, 2016, the discovery of autoantibodies for PLA2R and, more recently, for THSD7A, added a new dimension to the monitoring and treatment of MN, as it opened a window on the immunological course of the disease. It can be anticipated that future research will investigate whether a high positive predictive value of anti-PLA2R seropositivity will prevent the need for renal biopsy in these patients, assist in the selection of appropriate, immunologically active patients for therapeutic research studies, and ultimately help to type and duration of therapy on an individual basis. Understanding the repertoire of targeted epitopes in an individual can help predict disease severity and someday lead to the development of small inhibitory peptides or even the induction of self-antigen tolerance. Although patients with primary MN for whom no association with PLA2R or THSD7A has been detected appear to behave similarly to their peers in terms of baseline characteristics, prognosis and response to treatment.

Finally, for Obrisca B. et al, 2015, the circulating PLA2R assay seems to be a promising tool not only for diagnosing MN, but also for predicting the course of the disease and may pave the way for customizing therapy. However, validation of a universal trial with high precision and definition of cut-off levels, followed by larger studies with a prolonged follow-up period, is necessary to confirm these perspectives.

FINAL CONSIDERATIONS

MN is one of the main causes of nephrotic syndrome in adults. The pathogenesis of MN involves the formation of the subepithelial immune complex and current evidence indicates that the anti-PLA 2 R antibody is strongly associated with primary MN and proteinuria is caused by a complement-mediated process. Currently, the diagnosis of MN still depends on the pathology, but the discovery of anti-PLA 2R may provide a useful tool for diagnosing and predicting the outcome of MN.

All patients with PMN must be treated with supportive care from the time of diagnosis to minimize protein excretion. Patients with elevated anti-PLA2R levels and proteinuria >3.5 g/d at diagnosis, and those who fail to reduce proteinuria to <3.5 g after 6 months of supportive care or have complications of nephrotic syndrome, must be considered for immunosuppressive therapy. Accepted regimens include steroids/cyclophosphamide, calcineurin inhibitors, and B-cell depletion.

Patients with PMN must be evaluated for persistent proteinuria, impaired renal function, or severe complications. Several studies suggest that the combination of

steroids and spontaneous remission have excellent results. Immunosuppressive agents and alkylating agents are the most effective evidence-based therapy. However, clinical features and response to treatment vary among different ethnicities, and further trials are needed to validate the efficacy of newer agents. Incidentally, the anti-PLA2R antibody is the first serological marker that has promising evidence to be used as a tool to predict the course of the disease. More importantly, therapeutic agents such as rituximab and adrenocorticotropic hormone analogues are new therapeutic options that must be considered in the therapy of primary MN.

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