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The utility of phospholipase A2 receptor autoantibody in membranous nephropathy after kidney transplantation

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Abstract

Membranous nephropathy (MN) is estimated to cause end-stage renal disease in ∼5% of patients, in whom renal transplantation is the therapy of choice. Among patients receiving a transplant for MN, the disease will recur in the graft in 30–50%; among these, graft loss will occur in 50% within 10 years. Several studies have suggested that phospholipase A2 receptor autoantibody (aPLA2R) levels before transplantation might be useful in predicting recurrence, and their titration after transplantation is clinically relevant to assess the risk of recurrence and progression, to guide treatment indications and to monitor treatment response. In this review we describe the evolving role of aPLA2R as a biomarker in primary MN and its current usefulness in predicting recurrence of this autoimmune podocytopathy after renal transplantation.

Key words: kidney transplantation, phospholipase A2 receptor autoantibody, primary membranous nephropathy, recurrence

Introduction

Membranous nephropathy (MN) is a podocytopathy caused by subepithelial immune deposits that produce glomerular basement membrane thickening and podocyte foot process effacement. It is the most common cause of adult-onset nephrotic syndrome and can be secondary to various autoimmune diseases, infections, drugs or cancer; however, in most cases (∼80%) it is a primary autoimmune disease limited to the kidney, also known as primary membranous nephropathy (pMN). The clinical course is variable, with spontaneous remission reported in one-third of patients. A similar number of patients will develop end-stage renal disease (ESRD), for whom kidney transplantation is the treatment of choice. Like other autoimmune diseases, MN can also recur and cause graft loss. Knowledge of the pathophysiology of MN and identification of factors associated with its recurrence are crucial for its prevention. In this review we describe the evolving role of phospholipase A2 receptor antibodies (aPLA2R) as a biomarker in pMN and their current usefulness in predicting recurrence of this autoimmune podocytopathy after renal transplantation.

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pMN: an overview of the autoimmune podocytopathy

In 1959, an experimental model by Heymann *et al.* [1] reproduced clinical and morphological features of MN in rats similar to those of human MN by intravenous injection of anti-rat kidney serum obtained from rabbits. In the late 1970s, other observational studies in animal models demonstrated that rat MN was caused when circulating autoantibodies bind to an intrinsic antigen in the glomerular podocyte and form *in situ* immune deposits. Subsequently, that antigen was identified as megalin [2]. Those models consistently supported the autoimmune nature of MN in rats, but the initial excitement faded quickly as subsequent studies failed to identify megalin in human podocytes [3]. Many aspects of the pathogenesis of pMN remained elusive until 2009, when Beck *et al.* [4] reported the identification of the M-type phospholipase A2 receptor (PLA2R) as a major target antigen in human pMN by using a Western blotting approach associated with mass spectrometry. Nowadays, it is known that ∼70% of patients with active pMN have circulating aPLA2R.

The presence of PLA2R has been known for many years. In fact, Lambeau *et al.* [5] determined its nucleotide sequence in rabbits in 1994, after the identification of phospholipase A2 (PLA2), a membrane lytic enzyme, in the organs of different mammals and their circulation [6]. Although PLA2R is now known to reside in the plasma membrane of podocytes, the physiologic function of the PLA2/PLA2R system in the kidney and elsewhere remains unknown.

In the last few years we have learned many aspects of the natural history of the MN. The use of enzyme-linked immunosorbent assay (ELISA) kits has allowed detailed knowledge of the role of aPLA2R in the pathogenesis of this autoimmune podocytopathy. aPLA2R bind to the protein antigens and form *in situ* immune complexes responsible for glomerular damage. Thus, knowledge of the role of these antibodies in MN has allowed new diagnostic techniques. However, aPLA2R are not only detected in the circulation, but also on immunostaining for subepithelial PLA2R deposits in kidney biopsy specimens [7]. In fact, some patients show positive histological immunostaining but negative circulating levels. This situation could correspond to a very early stage of the disease, where very low initial levels of antibodies deposit on the antigen, or could correspond to an immunologically inactive aPLA2R MN. The detection of these antibodies has ushered in a new era in the care of patients with pMN.

Three techniques have been described to identify circulating aPLA2R in serum samples. Indirect immunofluorescence is the more sensitive technique but, despite its good performance, it is limited by its semi-quantitative method and by being observer dependent. ELISA is currently the diagnostic test of choice in the clinical setting because it is uncomplicated and allows quantification of antibody levels over time with a sensitivity and specificity of 0.68 and 0.97 [8], respectively. Other tests, such as the original Western blotting, are costly and highly laborious.

As previously stated, the specificity for pMN for the presence of aPLA2R is ∼97%. Thus the presence of these antibodies in the context of MN is almost always indicative of primary disease. However, some studies have found positivity for aPLA2R in a few patients with MN and concurrent disease, such as lupus, hepatitis B, sarcoidosis, graft-versus-host disease in the setting of allogeneic bone marrow transplantation or cancer [9, 10]. Some of these cases may represent pMN superimposed on a concurrent disease, but determining whether the MN is a secondary process is a challenge. In addition to anamnesis and physical examination, some histological data may help to determine whether the pMN is of secondary origin, such as deposition in the mesangium and intramembranous C1q deposition and positivity for an immunoglobulin G (IgG) subclass other than IgG4 [11]. This differentiation is highly important to prescribe a more specific treatment.

Subsequently, another minor target protein was described: thrombospondin type 1 domain-containing 7A (THSD7A). Anti-THSD7A antibodies can be detected in a small proportion (<5%) of patients with pMN without aPLA2R [12]. A higher incidence of neoplasias in these patients has been reported, but the precise role of this antigen in this clinical context is currently a matter of investigation [13].

No autoantibodies have yet been identified in the remaining pMN patients (15–20%).

In terms of therapy, circulating aPLA2R levels have been repeatedly shown to correlate with treatment response, disease activity and outcome and have become a helpful tool for deciding the timing of treatment. Since this finding in 2009, many groups have studied the correlation of these antibodies and the clinical activity of MN and have found a strong association between the evolution of antibody levels and the immunological activity of the disease in native kidneys [14–17]. Moreover, a high level of circulating aPLA2R at disease onset indicates a lower likelihood of spontaneous remission and might therefore be used as a rationale for early therapy in patients with less severe disease. Conversely, in patients with low levels of aPLA2R at diagnosis, a delay in treatment initiation might be appropriate because these findings may herald a subsequent partial or complete spontaneous remission. Furthermore, patients who are PLA2R antigen positive in glomeruli and aPLA2R negative in serum but have persistent proteinuria may have immunologically inactive disease and chronic glomerular damage. For these reasons, serial aPLA2R measurement during and at the end of a scheduled treatment regimen should be routine as a biomarker of treatment response and in the near future it may determine the duration of treatment in aPLA2R-associated MN patients.

In addition to clinical practice optimization, the use of aPLA2R has generated some fundamental questions on the autoimmunity process associated with pMN. Genome-wide association studies of single-nucleotide polymorphisms have suggested that autoimmunity against PLA2R may be correlated with some specific alleles involving the *HLA-DQA1* genes, and several studies from Asia and Europe have linked antibody levels and disease severity with certain HLA Class II antigens, including DQA1 and DQB1. The role of these antigen associations has yet to be determined [18, 19].

Two studies have recently shown that the critical epitope in PLA2R is composed of a 31-residue stretch within the folded cysteine-rich domain (CysR) at the outmost portion of the PLA2R molecule. Other epitopes have been also related, such as CTLD1 [20, 21]. A study by Seitz-Polski *et al.* [22] has also investigated this, and in addition to identifying CTDL7 as another epitope, they have linked the identified epitopes and disease activity: aPLA2R against CysR was associated with favourable outcome while reactivity against CTLD1 and CTLD7 was associated with active disease and poor renal prognosis. Furthermore, in that study they suggest that epitope profiles could change during follow-up. This finding has opened the door to personalized medicine in pMN, with a potential molecular inhibitor of this identified epitope.

Taken together, the results in pMN-affected native kidneys suggest that aPLA2R concentration is an important predictor of long-term renal outcomes.

aPLA2R may also predict pMN recurrence after renal transplantation

Overall, this glomerular disease is estimated to be the cause of ESRD in ~5% of the patients. In fact, one-third of patients with MN will have ESRD; in these patients, renal transplantation is the replacement therapy of choice. MN will recur in the graft in 30–50% of transplant recipients [23], with graft loss occurring in 50% of patients by 10 years. These figures reflect differences between centres performing protocol biopsies and those that only perform biopsies for clinical indication [24, 25]. The time of presentation of the MN recurrence varies widely, the main period being the first post-transplant year (sometimes manifested only as histological findings in protocol biopsies performed in the initial period after transplantation). Relapse has even been described in the very first week after transplantation [26]. A second group of patients are at increased risk of relapse at 5 years, and a third group develops the disease after this period. Some groups have suggested that biopsies performed by protocol, instead of performing them when there is a clinical indication, detected earlier and in a mild stage of the disease the recurrence in the allograft [23]. Nevertheless, due to this variability of presentation over time, it was of vital importance to find non-invasive tools to identify the first signs of the disease.

In this regard, a finding of great interest was that recurrence was more likely in patients showing the presence of aPLA2R than in those with non-aPLA2R related-MN. For example, Kattah *et al.* [27] evaluated 26 patients with MN and compared a group with recurrent MN and another without recurrence. They established that having aPLA2R before transplantation had a positive predictive value of 83% of recurrent MN, compared with patients with negative aPLA2R prior transplantation, who relapse in 58% of cases.

However, recurrence risk has not only been associated with the presence of aPLA2R before transplantation but also with their levels, and several studies have suggested cut-off values to identify at-risk patients. In 21 Spanish patients, aPLA2R concentrations were evaluated, measured with ELISA, to determine if they could predict pMN recurrence. The results showed that there was a significant correlation between pMN recurrence and a high level of aPLA2R before transplantation (P = 0.03) and also with the existence of a positive ELISA assay at graft biopsy (P = 0.017) independent of titres. They established a cut-off level of 45 U/mL during the pre-transplant period as a strong predictor of recurrence, with a sensitivity of 85.3% and a specificity of 85.1%. An association was also found between *HLA-DQA1*05:01* and *HLA-DQB1*02:01* in almost all the patients with recurrence in that study (six of seven),

Table 1. Main studies evaluating recurrent MN in transplanted patients, relevant highlights

Kattah *et al.* [27]

- In all, 26 patients with pMN with kidney transplantation: 18 with recurrent MN, 8 without recurrence. Protocol Bx.
- PPV of positive pre-Tx aPLA2R for recurrence: 83%. NPV of 42%.
- Median time for recurrence: 4.1 months (2.6–38 months), median proteinuria at time of recurrence: 0.5 g/day (253–1679 g/day), median creatinine at time of recurrence 1.8 mg/dL (±1.05).
- Four patients with aPLA2R pre-Tx became seronegative without additional immunosuppression.
- Four patients were seronegative at time of recurrence and had positive tissue staining for aPLA2R.

Quintana *et al.* [28]

- A total of 21 patients with pMN biopsied for clinical indications: proved recurrence in 7 patients (median at 22 months, 0.23–73 months).
- rMN was correlated with existence of positive ELISA at graft biopsy (P = 0.017) or with high aPLA2R activity before transplantation (P = 0.03). A cut-off level of 45 U/mL during pre-transplantation period predicted rMN with a sensitivity of 85%, specificity of 85% and NPV of 92%.
- An association was also found between *HLA-DQA1*05:01* and *HLA-DQB1*02:01* in almost all the patients with recurrence in that study (6/7), and this association of DQ alleles was linked with the highest aPLA2R levels before transplantation.

Gupta *et al.* [29]

- In all, 16 patients with history of pMN for pre-transplant aPLA2R. A total of six of them had proven biopsy of recurrence, of which five had positivity aPLA2R in serum pre-Tx (median 82 RU/mL, range 31–1500). The rest (10 patients) had no recurrence in biopsy, and none of them had previous aPLA2R in serum PreTx.
- Combining these data with those of Quintana *et al.*, Pre-Tx aPLA2R >29 RU/mL predicted rMN with a sensitivity of 85% and a specificity of 92%.

Debiec *et al.* [30]

- In all, 19 patients: 10 with rMN and 9 with *de novo* MN. aPLA2R was involved in five and zero patients of each group, respectively. Association of aPLA2R with rMN is not as marked as in the other cases, but it should be noted that they used a qualitative method of detection and some patients had incomplete sampling before and after Tx.
- Median time for recurrence: 15 months (8 days–49 months). Median time for the novo MN 54.4 months (19–99 months).

Seitz-Polski *et al.* [31]

- A total of 15 transplanted patients with MN. In all, 10 patients had aPLA2R positive at the time of Tx, of which only 4 patients had proven rMN. Five patients had negative aPLA2R, and only one presented rMN. Presence of IgG4 aPLA2R at the time of kidney transplantation does not imply MN recurrence (P = 0.6). However, positive IgG4 aPLA2R activity during follow-up (>6 months) was a significant risk factor for rMN (P = 0.004, 10 patients).
- It should be noted that four patients of this cohort never had a kidney graft biopsy for rule out the presence of rMN, because they did not present with a urinary protein:creatinine ratio >0.5 g/g.

Bx, Biopsy; pMN, primary membranous nephropathy; PPV, positive predictive value; Tx, treatment; NPV, negative predictive value; MN, membranous nephropathy; rMN, recurrent membranous nephropathy.

and this association of DQ alleles was linked with the highest aPLA2R levels before transplantation [28]. After combining these data from the Spanish cohort with data from an American cohort of 16 patients, Gupta *et al.* [29] found a cut-off level of antibodies pre-transplantation >29 RU/mL (sensitivity 85%, specificity 92). A limitation of these data was that they came from retrospective studies performed in stored samples. Prospective studies are needed to set a reliable titre for monitoring these antibodies.

Although several case series have reported that high aPLA2R titres at the time of transplantation strongly predicted subsequent recurrence, others such as Debiec *et al.* [30] or Seitz-Polski *et al.* [31] found only a low positive predictive value (50% and 40%, respectively) (more data about these studies evaluating recurrence in MN is available in Table 1). The more feasible explanations for this inconsistency could be related to the role of anti-rejection therapy to induce immunologic remission and the not infrequent possibility of a subclinical recurrence with low-grade proteinuria that could be masked by treatment with renin–angiotensin system blockers associated with calcineurin inhibitors.

Follow-up studies after transplantation have also suggested that serial titration of aPLA2R is clinically relevant to assess the risk of recurrence. Kattah *et al.* [27] found that persistence or reappearance of antibodies after transplantation were associated with increasing proteinuria and resistant disease in many patients. This would be consistent with the hypothesis that the amount of antibody titre after transplantation is a strong risk factor for recurrence.

There is very little information on the clinical course of aPLA2R in the post-transplant period, and more data including protocol biopsy findings are needed to determine the role of these antibodies in the follow-up of recurrence of pMN in the allograft.

Given that an association has been established between aPLA2R titres and the development of active disease, probably because of an inherent pathogenicity of these antibodies to the glomeruli, a sensible approach might be to prevent pMN or its recurrence before transplantation on detection of a certain level of antibodies. Moreover, due to the high risk of recurrence of MN in the allograft despite established anti-rejection immunosuppression, and the potentially severe recurrent disease form that previously led to renal failure, it seems reasonable to have a more active attitude than in the case of disease over native kidney.

Currently there are no established guidelines for the treatment of these transplant recipients to prevent or treat recurrence. Many drugs are effective for pMN [32]; anti-rejection therapy itself in kidney transplantation, including calcineurin inhibitors, has a beneficial effect in decreasing the production of these antibodies and sometimes the induction therapy for transplantation might be sufficient to achieve a negative PLA2R antibody titre. However, the long-term nephrotoxic effect of calcineurin inhibitors is concerning. Levels may also decrease because of binding to the free phospholipase receptors of the graft early in the post-transplant period, causing harm instead of the expected benefit of a negative serum level. Other alternatives, including alkylating agents such as cyclophosphamide,

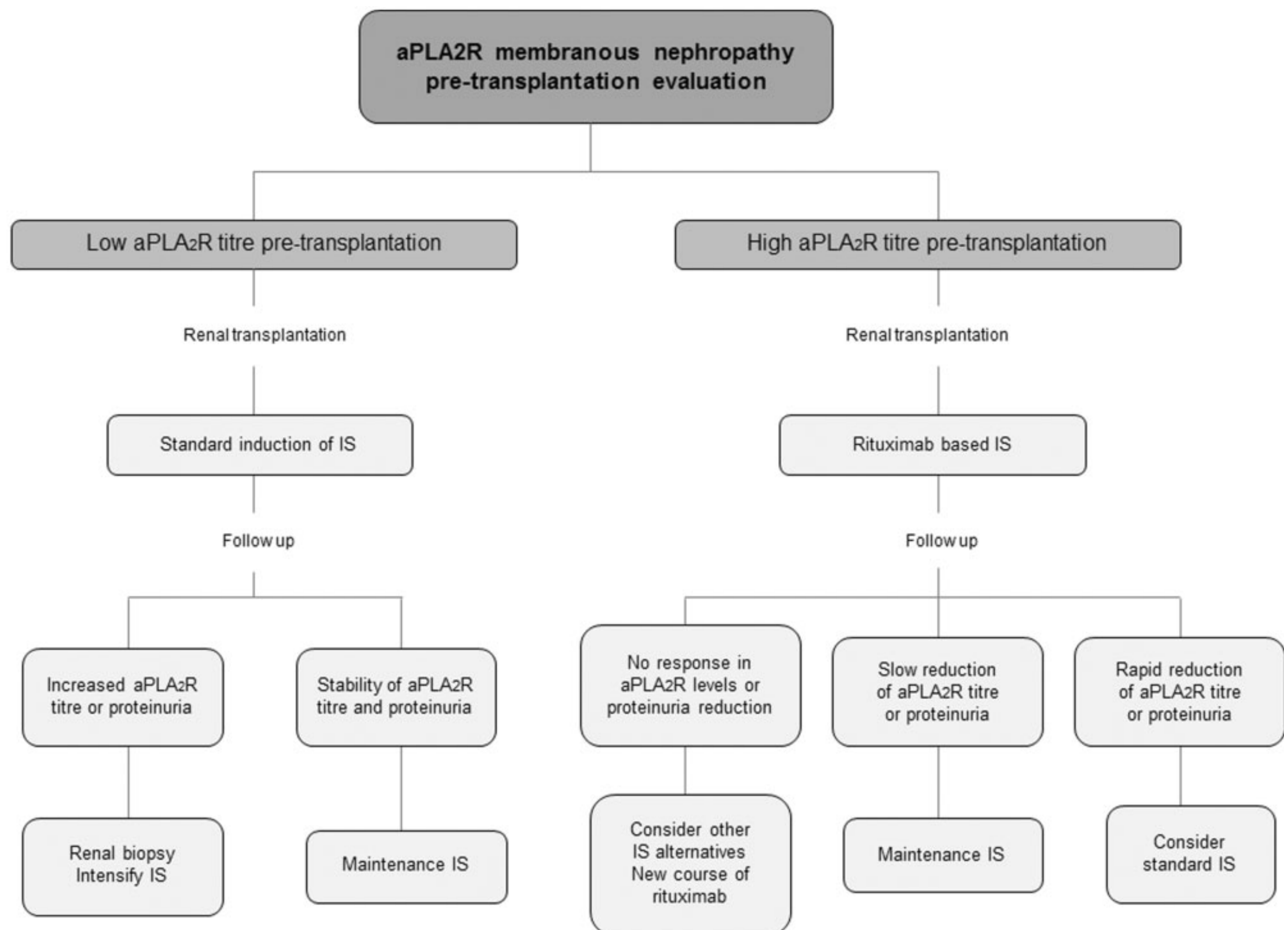

Fig. 1. Treatment algorithm in MN after kidney transplantation. IS, immunosuppression.

are available, but the adverse effects, such as leucopoenia, associated with this therapy in the transplantation setting makes the use of other alternatives advisable.

Rituximab, an anti-CD20 antibody, is increasingly being used in the treatment of post-transplant MN recurrence, based on favourable data from rituximab treatment in patients with MN in native kidney [33], but currently there are no randomized controlled trials on the topic and rituximab use is based on observational data, both for prevention (if elevated antibody titres are present before transplantation) and for treatment, in case of early recurrence [36, 37]. El-Zoghby *et al.* [23] evaluated eight patients with recurrent MN who received rituximab. At 12 and 24 months, 75% and almost 90% of patients, respectively, had partial or complete remission. Furthermore, post-treatment biopsies showed resorption of electron dense immune deposits in six patients. Similar favourable results were found in four patients treated with rituximab in a study of Sprangers *et al.* [38], where it was an effective treatment in all patients in stabilizing or reducing proteinuria and stabilizing renal function. A possible advantage of this therapy, beside the large number of patients with complete or partial remission, is that it is not necessary to modify anti-rejection therapy. Moreover, rituximab rapidly decreases aPLA2R, and the B-cell depletion appears to last longer in transplanted patients, as observed in the El-Zoghby *et al.* study [23], likely the result of the additional immunosupressants, but it is usually necessary to wait >1 year to achieve proteinuria remission [35]. Prospective trials using rituximab in recurrent MN are needed to confirm these data.

In this sense, our proposal (Figure 1) to prevent recurrence in transplantation would be to measure aPLA2R levels before transplantation and individualize the immunosuppression depending on the titre. Patients with documented aPLA2R-associated MN with low or negative levels before transplantation could receive a standard immunosuppression scheme, but if during the follow-up aPLA2R or proteinuria levels rise, a renal biopsy should be performed and the immunosuppressive treatment should be intensified in case of recurrence, including considering the use of rituximab. In patients with high aPLA2R levels before transplantation, we strongly recommend a rituximab-based immunosuppresion scheme.

The usual dose of rituximab consists of 375 mg/m^2 once weekly for 4 weeks or the alternative protocol of 1 g rituximab on days 1 and 15, with the regimen repeated at 6 months if B cells are >15/μL or elevated aPLA2R levels persist. Proteinuria may persist after the administration of rituximab, but this persistence over months should provoke a new course of treatment.

Recurrent versus *de novo* MN

In patients with ESRD due to MN who have received a kidney transplant, the appearance of MN in the graft requires a differential diagnosis between primary disease recurrence and MN secondary to another underlying process, representing *de novo* MN. In such cases, this distinction is a diagnostic challenge.

These patients should be evaluated for hepatitis B and C virus infection and other causes of secondary MN such as cancer (especially in patients with late presentation years after transplantation). aPLA2R levels are also useful in this regard. Negative circulating aPLA2R or on biopsy staining is more common in *de novo* disease [30, 39]. However, when present, identification of the subclass may serve as a guide. IgG subclass 4 is highly predictive of recurrent disease, whereas IgG subclass 1 predominates in *de novo* MN [40]. However, it is worth mentioning that positivity for aPLA2R in *de novo* MN is rare and it is more common in recurrent disease. Larsen and Walker [39] reported a sensitivity and specificity of 83% and 90%, respectively, in recurrent MN if these antibodies were present [39].

Histologic features may also help in this differential diagnosis. Mild or moderate mesangial proliferation might be more frequent in *de novo* MN [41], or at different stages of the disease in the image of the electron microscopy. Other characteristics of immunostaining, such as localization of antibody deposition, with focal segmental distribution of subepithelial deposits instead of diffuse distribution, can also aid diagnosis [42].

The appearance of MN in the graft in patients with well-documented primary renal disease different from MN, associated with clear signs of humoral rejection and the presence of donor-specific anti-HLA antibodies (DSA), raises the possibility that *de novo* MN may also appear in the transplanted kidney as an allogenic manifestation of antibody-mediated rejection (AMR) [43]. In fact, Honda *et al.* identified one patient with *de novo* MN who presented donor-derived HLA in the subepithelial deposits on the capillary walls combined with IgG. Moreover, El Kossi *et al.* [44] reported a case of MN in a kidney graft in which levels of proteinuria where clearly associated with DSA levels. In these cases, concomitant histologic findings are those of allograft rejection, such as peritubular capillaritis or transplant glomerulopathy. In addition, other tests, such as determination

Summary

- M-type PLA2R is the major target antigen in human pMN (∼70% of patients). The remaining patients have antibodies against THSD7A (5%) or no currently identified antibodies.
- ELISA is currently the diagnostic test of choice because its use is straightforward and allows quantification of antibody levels over time with a sensitivity and specificity of 0.68 and 0.97, respectively.
- Typically aPLA2R in pMN is only deposited in subepithelial space of podocytes. Deposition elsewhere, such as the mesangium or within membranes, might suggest a secondary cause. aPLA2R is usually in IgG4 subclass 4 in pMN, and there is no C1q deposition in kidney biopsy.
- MN is the cause of ESRD in 5% of patients. From 30 to 50% of patients transplanted for MN transplanted will recur in the graft, leading to graft loss in 50% of them within 10 years.
- Levels of aPLA2R correlate well with treatment response, disease activity and outcomes in native kidneys. In transplant recipients, aPLA2R levels before transplantation might be useful in predicting recurrence and their titration after transplantation predicts the risk of recurrence and progression and are a good indication for treatment initiation and for monitoring treatment response.
- MN may appear in the transplanted kidney as an allogenic manifestation of AMR. In these situations, aPLA2R may help to distinguish recurrent from *de novo* MN.
- Treatment with rituximab may be considered in patients with high aPLA2R levels pre-transplantation, or when serial aPLA2R levels increase during the first year after transplantation, especially when proteinuria increases. Other therapeutic alternatives may be intensification of maintenance immunosuppression.

of DSA or immunostaining of C4d in histologic samples, are helpful for diagnosis. Treatment in these cases should be managed according to the standard treatment for rejection [45].

Nevertheless, the aetiology of *de novo* MN after kidney transplantation is still uncertain. DSA and AMR might play a role in the pathogenesis in some patients. However, signs of rejection were absent in a number of cases, and in some instances the disease developed in recipients of 'full house' HLA-matched kidneys. Thus it seems possible that *de novo* MN is not only because of allograft rejection per se, but is triggered by different kinds of injuries that can create an inflammatory environment and expose hidden antigens, probably different from those observed to be involved in pMN [42].

Finally, using these guides, aPLA2R may help guide the diagnosis of transplant recipients in whom the original cause of ESRD was unknown [7].

Future directions

MN in the native kidney should be classified as PLA2R- or non-PLA2R-associated based on the previous clinical history or, if necessary, by performing PLA2R antigen staining on archived biopsies. In those patients with high aPLA2R levels before transplantation, treatment with rituximab to prevent recurrence may be a reasonable option, but further studies are needed to confirm this statement.

In deceased donor transplantation with high antibody levels at the time of transplantation, rituximab-based induction therapy and more intense maintenance immunosuppression may be required. Serial determination of aPLA2R levels in the first year after transplantation and yearly thereafter, or whenever proteinuria increases, may guide the decision for rituximab treatment in this clinical setting.

Conclusions

PLA2R antibody levels not only have a direct impact on the renal outcomes of patients with pMN in the native kidney but also in the prediction of recurrence of this entity and graft outcomes after transplantation.

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