Phospholipase A2 Receptor Autoantibodies and Clinical Outcome in Patients with Primary Membranous Nephropathy

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ABSTRACT

Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults, with an uncertain clinical outcome. The characterization of the phospholipase A2 receptor (PLA2R) as the major target antigen in primary MN and the detection of circulating autoantibodies in these patients is a major advance in understanding this disease. To test whether PLA2R antibody levels reflect disease activity or clinical outcome, we performed a prospective multicenter study of 133 adult patients with primary MN and detectable serum PLA2R antibodies who had not received immunosuppressive therapy. Patients were followed ≤24 months. PLA2R antibody levels associated with clinical disease activity (proteinuria) in patients with immunosuppressive therapy (n=101) or supportive care (n=32). Within 3 months, immunosuppressive therapy led to a sustained 81% reduction in PLA2R antibody levels paralleled by a 39% reduction in proteinuria. Patients who experienced remission of proteinuria after 12 months had significantly lower PLA2R antibody levels at the time of study inclusion compared with patients with no remission. Patients with high PLA2R antibody levels achieved remission of proteinuria significantly later than patients with low PLA2R antibody levels. PLA2R antibody levels fell over time in patients with spontaneous remission but remained elevated in patients who did not show a reduction in proteinuria. Multivariable Cox regression analysis confirmed PLA2R antibody level as an independent risk factor for not achieving remission of proteinuria. We conclude that a decrease in PLA2R antibody level is associated with a decrease of proteinuria in patients with primary MN.


Since the landmark discovery that circulating autoantibodies against the phospholipase A2 receptor (PLA2R) are specific for patients with primary membranous nephropathy (MN) completely new paradigms for the diagnosis and clinical care of these patients are possible.1 These are urgently needed because the clinical outcome of patients with primary MN varies and ranges from spontaneous clinical remissions to end stage renal failure.2,3 Because of the absence of reliable predictors of clinical outcome, the best documented methods to predict outcome and hence make a decision to treat patients with an immunosuppressive agent or maintain them on supportive medications currently require prolonged follow-up measurements of proteinuria.4,5 Furthermore, in patients who receive immunosuppressive therapy, the intensity and duration of the treatment currently depend on changes in proteinuria, which do not necessarily reflect the severity or activity of the immunologic disease. On the other hand, patients who clinically do not respond to immunosuppressive agents may have insufficient therapy and still have active immunologic disease. A marker that reflects immunologic disease activity in real time and indicates clinical outcome could substantially improve the care of these patients. The availability of recently
developed and easily applicable assays to measure PLA$_2$R antibody levels in the serum makes it possible to study patients prospectively and to analyze whether PLA$_2$R antibody levels are related to disease activity. To address this question, we conducted a multicenter open prospective study in patients with biopsy-proven MN.

RESULTS

Clinical Baseline Characteristics

We screened 163 patients with biopsy-proven MN for the presence of PLA$_2$R antibodies. Of these patients, 133 individuals were positive for PLA$_2$R antibodies and were included in this study. Patients were followed for up to 24 months after recruitment. As summarized in Table 1, the majority of patients were men (75.9%). At the time of study inclusion (and first serum measurement), the mean age of the patients was 54.4±15.2 years. The time from renal biopsy until the first measurement of the PLA$_2$R antibody levels was 1.2±1.5 months. Almost all patients (127 of 133) were treated with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Most patients received diuretics (114 of 133) and lipid-lowering drugs (87 of 133) and 61 of 133 of patients were treated with anticoagulants. A detailed analysis of the baseline characteristics and the analyzed parameters is summarized in Table 1. While in the study, 101 patients received immunosuppressive agents (Figure 1). The initial immunosuppressive agent was cyclosporine A in most patients (n=53) (40 of which received cyclosporine A in combination with steroids). One patient received tacrolimus. Thirty-four patients were treated with cyclophosphamide (32 of which received cyclophosphamide in combination with steroids) and one patient received chlorambucil and steroids. Nine patients were treated with rituximab. Three patients received steroids alone. Thirty-two patients remained on supportive care only.

Proteinuria, PLA$_2$R Antibody Levels, and Serum Albumin

Findings from All 133 Patients

Considering the goal of our study to correlate clinical changes (proteinuria) with serum PLA$_2$R antibody levels, Figure 2 shows a clear association between both parameters. Over the follow-up period, there was a steady decrease in proteinuria that was statistically significant (P<0.001 for all time points), starting already at 3 months after patient recruitment. This decrease in proteinuria was accompanied by a steady and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole Patient Cohort</th>
<th>Initial Immunosuppressive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (No IS)</td>
<td>CNI</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>133</td>
<td>32</td>
</tr>
<tr>
<td>Sex, ratio of men to women (% men)</td>
<td>101/32 (76)</td>
<td>25/7 (78)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>54.4±15.2</td>
<td>51.7±12.1</td>
</tr>
<tr>
<td>Time from renal biopsy to first serum measurement (mo)</td>
<td>1.2±1.5</td>
<td>1.0±1.4</td>
</tr>
<tr>
<td>Time from first serum measurement to start of IS treatment (mo)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>9.6±5.0</td>
<td>7.4±3.2</td>
</tr>
<tr>
<td>At the time of first serum measurement</td>
<td>—</td>
<td>7.3±3.0</td>
</tr>
<tr>
<td>At 3 mo (no IS) or start of IS</td>
<td>23.7±4.1</td>
<td>25.0±3.5</td>
</tr>
<tr>
<td>At 3 mo (no IS) or start of IS</td>
<td>26.9±4.6</td>
<td>23.3±4.8*</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>1.2±0.6</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>At the time of first serum measurement</td>
<td>—</td>
<td>1.3±0.9</td>
</tr>
<tr>
<td>At 3 mo (no IS) or start of IS</td>
<td>282±355</td>
<td>218±276</td>
</tr>
<tr>
<td>At 3 mo (no IS) or start of IS</td>
<td>137±165</td>
<td>240±250</td>
</tr>
<tr>
<td>PLA2R antibody level (total IgG ELISA)</td>
<td>40±53</td>
<td>32±45</td>
</tr>
<tr>
<td>At the time of first serum measurement</td>
<td>—</td>
<td>16±23</td>
</tr>
</tbody>
</table>

There were no significant differences in any of the clinical characteristics between patients treated with calcineurin inhibitors, alkylating agents, or rituximab at the first serum measurement (study inclusion) or at the start of immunosuppression. There were no significant changes in the PLA$_2$R antibody levels, proteinuria, or any other clinical characteristic from the time of first serum measurement to the start of immunosuppression. There were statistically significant differences in proteinuria, PLA$_2$R antibody levels, and serum albumin between patients on supportive care only and patients who received immunosuppression (P<0.05). —, not applicable; IS, immunosuppression; CNI, calcineurin inhibitor; Alk, alkylating agent; RTX, rituximab.

*P<0.05.
statistically significant increase of serum albumin ($P<0.001$ for all time points). The decrease in PLA2R antibody serum levels was associated with a decline in proteinuria and an increase in serum albumin. Within 3 months of observation, proteinuria fell by 25% in the 133 patients. After 0–3 months, immunosuppressive treatment is switched from one agent to another in 17 patients. After 3–6 months, immunosuppressive agents are changed in an additional nine patients. After >6 months, eight patients received a different immunosuppressant. *Five patients for whom no ELISA PLA2R antibody levels are available at the time of study inclusion.

Patients Receiving Immunosuppressive Treatment
In the 101 patients who were treated with an immunosuppressant, the average time from the first measurement of the PLA2R antibody levels to the start of immunosuppression was 2.6–3.2 months. There were no significant changes in proteinuria or antibody levels between the time of first serum measurement (study inclusion) and the start of therapy (Table 1). There was also no statistical significant difference in antibody levels and proteinuria between the different immunosuppressive treatment groups (Table 1), even though patients who received rituximab had numerically lower levels. Patients who received immunosuppression during the follow-up had higher proteinuria and PLA2R antibody levels at study inclusion compared with patients who received supportive treatment only. Within 3 months after the start of an immunosuppressive therapy, PLA2R antibody levels fell by 69%–81% (depending on the method of PLA2R antibody analysis) and proteinuria fell by 38.8% (Figure 3). During the further follow-up, proteinuria consistently fell by approximately 17%–21% every 3 months for the first 12 months, whereas antibody levels remained low. Thus, there was a remarkable time lag between the rather rapid fall in antibody levels at 3 months and the protracted reduction in proteinuria. Serum albumin steadily increased in those patients over time.

Effects of Individual Immunosuppressants
We could analyze 101 patients who were treated with an immunosuppressant (Figure 1, Supplemental Figure 2). Clinical characteristics of patients treated with calcineurin inhibitors, alkylating agents, or rituximab were not
significantly different at the start of immunosuppressive treatment (Table 1, Supplemental Figure 3). In all three treatment groups (calcineurin inhibitors, alkylating agents, and rituximab), PLA2R antibody levels fell significantly (by 83%–96%) within 3 months (Figure 4, Supplemental Figure 4).

**PLA2R Antibody Levels, Renal Function, and Response of Proteinuria**

The levels of PLA2R antibodies were correlated with proteinuria and serum creatinine at the time of study inclusion. No correlation was detected between total IgG or IgG4 PLA2R antibody levels measured with either method and renal functional parameters (Supplemental Figure 5). Patients were divided in two groups according to the changes in proteinuria during 12-month follow-up (remission, no remission) to assess the potential role of PLA2R antibody levels on clinical response (proteinuria). As summarized in Table 2, 67 patients could be followed for 12 months. Of these individuals, 39 patients reached remission and 28 patients did not reach remission of proteinuria. There were no significant differences in sex, age, proteinuria, serum albumin, serum creatinine, or the percentage of patients receiving immunosuppressive therapy between the two groups at the time of study inclusion. When the groups were compared according to the PLA2R antibody levels at the time of study inclusion, the antibody levels were significantly higher in the group who did not experience remission compared with the patients who experienced remission of proteinuria. This difference was observed for total IgG and IgG4 subclass PLA2R antibody levels. After 12 months, patients who reached a remission of proteinuria had significantly lower PLA2R antibody levels compared with patients who did not reach remission of proteinuria (Figure 5).

Patients were divided in two groups depending on PLA2R antibody levels at study inclusion (Figure 6). Patients with PLA2R antibody levels lower than the median PLA2R antibody level at study inclusion reached remission of proteinuria significantly faster than patients in whom PLA2R antibody levels at study inclusion were higher than the median PLA2R antibody levels. A multivariable Cox regression
We analyzed proteinuria and PLA2R antibody levels in patients who reached a complete or partial remission of proteinuria. PLA2R antibody levels in all 11 patients who reached complete remission of proteinuria after 18 months, and in all 6 patients with complete remission after 24 months, were no longer detectable. At both time points, patients with complete remission of proteinuria had lower PLA2R antibody levels compared with patients with partial remission of proteinuria, whereas patients without remission of proteinuria had the highest PLA2R antibody levels (Supplemental Figure 7).

Patients not Receiving Immunosuppressive Treatment

During the follow-up period, 32 patients did not receive immunosuppressive therapy. In the first 3 months after the study start, PLA2R antibody levels fell by 37% in these patients. Twelve of these patients were followed up to 15 months (Figure 8). Five patients reached a remission of proteinuria that averaged 1.2 ± 1.0 g/24 h at 15 months. In these patients with clinical remission of disease, PLA2R antibody levels fell significantly by 15 months compared with the time of study inclusion. In contrast, seven patients did not experience

Table 2. Clinical baseline characteristics and PLA2R antibody levels at the time of study inclusion of patients reaching remission or no remission of proteinuria after 12 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remission</th>
<th>No Remission</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>39</td>
<td>28</td>
<td>—</td>
</tr>
<tr>
<td>Sex ratio of men to women (% men)</td>
<td>29/10 (74.4)</td>
<td>22/6 (78.6)</td>
<td>—</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.2 ± 16.3</td>
<td>55.8 ± 12.7</td>
<td>0.88</td>
</tr>
<tr>
<td>Time from renal biopsy to first serum measurement (mo)</td>
<td>1.0 ± 1.4</td>
<td>1.4 ± 1.6</td>
<td>0.36</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>9732 ± 5429</td>
<td>10022 ± 5164</td>
<td>0.83</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>24.2 ± 4.3</td>
<td>24.0 ± 3.3</td>
<td>0.78</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.4 ± 0.6</td>
<td>1.1 ± 0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Patients on immunosuppressive therapy (%)</td>
<td>33 (85)</td>
<td>23 (82)</td>
<td>—</td>
</tr>
<tr>
<td>PLA2R antibody level (total IgG ELISA)</td>
<td>179 ± 207</td>
<td>311 ± 297</td>
<td>0.04</td>
</tr>
<tr>
<td>PLA2R antibody level (IgG4 ELISA)</td>
<td>23 ± 30</td>
<td>54 ± 56</td>
<td>0.01</td>
</tr>
</tbody>
</table>

For 67 patients of the whole study cohort (treated and not-treated with immunosuppression), proteinuria after 12 months was available. After 12 months of follow-up, 39 patients reached remission and 28 patients did not reach remission of proteinuria. Patients with no remission of proteinuria had significantly higher anti-PLA2R antibody levels at the time of study inclusion compared with patients who experienced remission of proteinuria. This difference was seen for total IgG and IgG4 subclass antibody levels. Patients with or without remission of proteinuria after 12 months did not show differences in sex, age, proteinuria, serum albumin, or serum creatinine at the time of study inclusion. There was no difference in the percentage of patients who received immunosuppressive therapy between the groups. —, not applicable.
clinical remission. Their PLA2R antibody levels did not fall significantly over time and were significantly higher at 15 months than levels in patients who experienced remission of proteinuria. At the time of inclusion in this study, PLA2R antibody levels and proteinuria of patients who had a remission of the disease were not different from patients with no remission. All changes in PLA2R antibody levels were seen with both methods applied for total IgG as well as for the IgG4 subclass. The remaining 20 patients in this subgroup did not reach the 15-month follow-up (Figure 1).

DISCUSSION

The recent availability of sensitive and specific assays for serial measurements of PLA2R antibody levels in the follow-up of patients with primary MN allows the serial monitoring of immunologic and clinical activity in these patients.

We performed a prospective study in a large cohort of patients with MN to test whether PLA2R antibody levels may serve as markers of clinical activity at the time of diagnosis and during follow-up. We assessed total IgG and IgG4 subclass PLA2R antibody levels to determine whether there is a potential difference in the response because it has been originally described that IgG4 antibodies may be the pathogenetic subclass in primary MN.1

There were 133 patients who were included in the study and observed for up to 24 months. When followed over time, these patients showed a steady decrease in proteinuria that was inversely related to an increase in serum albumin. In the total patient cohort, there was a significant decrease in proteinuria and PLA2R antibody levels within the first 3 months of observation due to the decrease in the 59 patients in whom immunosuppressive treatment was started at study inclusion. There were 101 patients who received immunosuppressive therapy, which was started on average 2.6 months after the first serum measurement. In 42 patients who received immunosuppression later in the course of the study, no significant changes in antibody levels and proteinuria were detected between the time of first serum measurement and the start of immunosuppression. PLA2R antibody levels fell by 81% within 3 months after immunosuppressive therapy. This was paralleled by an approximately 39% decrease in proteinuria after 3 months. Whereas antibody levels remained low, proteinuria continuously fell over time, which shows that reduction in proteinuria has a time lag compared with reduction in antibody levels. This pattern of a relatively steeper fall of PLA2R antibody levels confirms data from a retrospective analysis in patients treated with rituximab,9 has been found in individual patients,6,10 and has earlier been shown in an animal model of MN.11 The data also show that proteinuria fell even though some circulating antibody remained detectable in the blood. This finding fits observations made in the passive Heymann nephritis model of MN, in which the onset and the degree of proteinuria require the amount of deposited antipodocyte antibodies to exceed a threshold level, and proteinuria persists for extended periods of time even after antibody deposition has ceased.12 Our findings that there were no differences between the changes

Figure 5. Proteinuria, serum albumin, and PLA2R antibody levels in patients with remission or no remission of proteinuria after 12 months. Patients who reach a remission of proteinuria after 12 months have statistically significant lower proteinuria than patients who do not have a remission in proteinuria. In the patients with a reduction in proteinuria, serum albumin levels normalize after 12 months, but remain lower in the patients who did not have remission. In patients with remission of proteinuria, antibody levels fall during the follow-up and are significantly lower than in patients who do not have a remission in proteinuria. Time 0 refers to the time of study inclusion and first serum measurement. The bars show the SD values. *P<0.05.
in total IgG or IgG4 subclass PLA2R antibody levels does not support the notion that IgG4 antibody levels might be a better parameter for immunologic disease response.7,13 In the group of patients who received immunosuppressive therapy, the relative reduction in the antibody levels after 3 months was greater than in patients with spontaneous remission and in the total cohort of 133 patients. This suggests that the immunosuppressants actively reduced the antibody levels and led to the clinical response. Because this was an open study and the treating physicians decided on the therapy, different immunosuppressive protocols were applied. Most patients received calcineurin inhibitors, followed by alkylating agents and rituximab. The doses of the immunosuppressants that our patients received were very similar to doses reported in earlier protocols.14–16 When the three immunosuppressive regimens were compared, the initial pretreatment antibody levels and proteinuria as well as the fall in antibody levels and in proteinuria after start of immunosuppressive therapy were not different between the treatment groups (Figure 4). The reduction in proteinuria in the calcineurin inhibitor treatment group might be partially due to effects on podocyte biology or renal hemodynamics; however, we could not detect statistically significant differences between the patients receiving calcineurin inhibitors and other treatment groups. Because our study was not controlled, we cannot draw definitive conclusions regarding the efficacy of the individual protocols or resolve ongoing discussions about the best immunosuppressive approach to treat patients with primary MN.18,19

To eventually define a potential pathogenetic role of PLA2R antibody levels, they were correlated with proteinuria and serum creatinine at the time of study inclusion. We did not find any correlation and cannot confirm earlier observations by others, who showed a positive correlation between proteinuria and PLA2R antibody levels at a defined time point.7 Our findings, however, suggest that levels of PLA2R antibodies may influence clinical response. Patients who experienced remission of proteinuria after 12 months had significantly lower PLA2R antibody levels at study inclusion (Table 2). There were no significant differences between the groups in proteinuria or serum albumin and in the relative number of patients who received immunosuppressive therapy. This excludes an eventual bias of immunosuppressive therapy on proteinuria. Patients who had a remission of proteinuria after 12 months had significantly lower PLA2R antibody levels (Figure 5). Patients with low PLA2R antibody levels at study inclusion reached remission of proteinuria significantly faster than patients with high PLA2R antibody levels at study inclusion (high group). N gives the number of patients at the different time points.

Figure 6. Time to achievement of remission of proteinuria in patients with high versus low PLA2R antibody levels at study inclusion. (A) Mean and median time to remission of proteinuria. The 128 patients for whom ELISA PLA2R antibody levels are available are divided in two groups. In patients in the low group, PLA2R antibody levels at study inclusion are lower than the median PLA2R antibody level. In patients in the high group, PLA2R antibody levels at study inclusion are higher than the median PLA2R antibody levels. For five patients, there are no ELISA PLA2R antibody levels available at the time of study inclusion and they are not included in this analysis. (B) Kaplan–Meier analysis. Patients with low PLA2R antibody levels at study inclusion (low group) reach remission of proteinuria significantly faster than patients with high PLA2R antibody levels at study inclusion (high group). N gives the number of patients at the different time points.
these patients would be unnecessarily treated with an immunosuppressive regimen, it would be very helpful to have a marker to identify these patients. Because our study had an open design, we cannot finally predict how many patients would in fact have experienced spontaneous clinical remission, but we did observe patients who went into spontaneous remission within a 15-month follow-up period. In parallel with the decrease in proteinuria in patients with spontaneous remission, PLA2R antibody levels also decreased and were significantly lower compared with the time of study inclusion and compared with patients who remained nephrotic. Thus, spontaneous clinical remission is associated with a decrease in PLA2R antibody levels. In summary, our data show that a decrease in PLA2R antibody levels is associated with a fall in proteinuria. PLA2R antibody levels may serve as useful biomarkers for immunologic and clinical activity of patients with primary MN.

CONCISE METHODS

Patients and Study Design

This prospective multicenter open clinical study included 133 consecutive patients with the histologic diagnosis of MN and a positive PLA2R antibody test result in the serum. The serum test for the presence of PLA2R antibodies had to be performed within 6 months after renal biopsy. Only patients with a proteinuria of ≥3.5 g/24 h and a serum albumin of ≤30 g/L were included. No immunosuppressive therapy was allowed before inclusion in this study. All other medications were allowed. After study inclusion, the treating physicians decided on the therapeutic strategy without any recommendations. In the case of a decision for an immunosuppressive therapy, the dose and the duration of the applied agents had to be documented. PLA2R antibody levels, 24-hour protein excretion, serum creatinine, and serum albumin levels were measured at 3-month intervals. This study was approved by the local ethics committee of the Chamber of Physicians in Hamburg and was conducted in accordance with the ethical principles stated by the Declaration of Helsinki. Informed consent was obtained from all participating patients.

PLA2R Antibody Measurement

Serum levels of total IgG and IgG4-subclass PLA2R antibody were measured by two methods: an indirect immunofluorescence test, which was previously published and validated, and an ELISA test, which was recently developed by EUROIMMUN AG (Lübeck, Germany). According to the manufacturer, the ELISA results were considered positive at a level >20 U/ml for IgG PLA2R antibodies and >0.259 U/ml for IgG4 PLA2R antibodies.

Proteinuria and Serum Albumin Levels

Proteinuria is given as the total 24-hour excretion and serum albumin is given in grams per liter. Remission of proteinuria was defined as proteinuria <3.5 g/24 h and at least 50% reduction from the time of inclusion. Complete remission of proteinuria was defined as proteinuria <0.5 g/24 h.

Statistical Analyses

Data are given as the mean±SD and as the median for nonparametric data. Statistical significance was defined as P<0.05. Multivariable Cox regression analysis was performed. In the multivariate analysis, we included and adjusted for all clinical parameters that might influence the remission of proteinuria in patients with MN (age, sex, proteinuria, serum creatinine, serum albumin, and immunosuppressive treatment). Hazard ratios are expressed per natural logarithm unit of serum creatinine, proteinuria, and PLA2R antibody levels measured by ELISA per unit of age and dichotomized for sex and treatment. Statistical analyses were performed using SSPS software.
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