REVIEW ARTICLE

THE BENEFICIAL ROLE OF ANTI-PHOSPHOLIPASE A2 RECEPTOR AUTO-ANTIBODIES AND RITUXIMAB IN THE MANAGEMENT OF RECURRENT PRIMARY MEMBRANOUS NEPHROPATHY AFTER KIDNEY TRANSPLANTATION

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Background: Recurrence of the primary kidney disease causing graft loss in an otherwise good functioning graft in post renal transplantation period is a well-known entity. Approximately 15% of the graft failure occurs secondary to recurrence of the primary glomerulonephritis in post renal transplant period. Regarding primary glomerulonephritis, almost 33–35% of patients suffering from primary membranous nephropathy (PMN), an organ specific auto-immune podocytopathy reach end stage renal disease (ESRD) and renal transplant is then the only treatment modality of choice for them. But, unfortunately 30–50% will experience the disease recurrence and 40–50% will end up with graft loss. The discovery of M-type anti phospholipase auto antibodies (APLA2R-ab) has changed the paradigm. Different remarkable studies are available in the literature that have concluded that APLA2R-ab titers if performed before the renal transplantation are helpful in predicting the disease recurrence and their titration in post-renal transplant period is clinically relevant to see the risk of disease recurrence and its progression, help in treatment monitoring and also to observe the treatment response in terms of complete or partial remission of the disease. Till now, there are no evidence-based guidelines available for the prevention of rPMN in post renal transplant period. The traditional treatment regimens beneficial for the management of PMN in native kidneys are associated with certain serious side effects in post renal transplant period. Rituximab, an anti-CD20 monoclonal antibody (anti CD20 mAb) has emerged as a promising treatment option for such patients. **Conclusion:** In conclusion an approach intending an early diagnosis of the rPMN by using the APLA2r levels in serum and its management by utilizing rituximab has proved worthy in minimizing the risk of allograft loss secondary to recurrence of PMN in post renal transplant period. However further studies are still awaited regarding the efficacy, dose and duration of the treatment.

Keywords: Primary kidney disease; Anti-Phospholipase A2 receptor; Kidney transplant

Citation: Anjum N, Nabi Z. The Beneficial role of Anti-Phospholipase A2 receptor auto-antibodies and Rituximab in the management of recurrent primary membranous nephropathy after kidney transplantation. J Ayub Med Coll Abbottabad 2021;33(2):315–8.

INTRODUCTION

PMN is an auto-immune podocytopathy caused due to the deposition of immune complexes in sub-epithelial space resulting in glomerular basement membrane (GBM) thickening with a typical spike pattern and effacement of podocyte foot processes leading to damage of filtration barrier and producing proteinuria.[1–4] Membranous nephropathy (MN) is the most common cause of adult onset nephrotic syndrome (NS) and it can be secondary to different auto-immune diseases, drugs, malignancies and infections.[4,5] But in about 80% of cases it is a renal limited auto-immune disease . Rest of 15–20% are idiopathic cases in which no cause has been found so far.[6–9]

The natural history of PMN includes three different clinical courses, spontaneous remission, persistent proteinuria and progressive disease leading to ESRD.[10,11] For those patients of PMN who fall in third category have kidney transplantation as the treatment modality of choice. Unfortunately, PMN has a high recurrence rate post renal transplant of about 30–50% resulting in decreased graft survival and progressive graft loss in about 40–50% in ten years.[12–18]

In this review we will be describing the evolving beneficial role of APLA2R as a biomarker in PMN, their utility in prediction of PMN recurrence in post renal transplant period and their role in monitoring of disease progression. Secondly, we will be discussing the beneficial emerging role of CD20 monoclonal antibody-Rituximab in management of recurrent PMN in post renal transplant period.

Beneficial role of apla2r in recurrence of PMN –a changing paradigm

The exact underlying pathogenetic mechanism of PMN remained debatable until it was in 2009, when Beck *et al*,[1] first reported the identification of the M-type PLA2R as significantly important and major target antigen regarding human PMN[1]. The journey of further discoveries continued and now it is well known that about 70% of patients suffering from active PMN have circulating APLA2R-ab.[2–4] A number of different

techniques are available for their diagnosis including immunofluorescence (IF), western blot(WB) and enzyme linked immunosorbent assay(ELISA).Among them ELISA is currently the diagnostic test of choice .It quantifies the antibodies titers with the sensitivity and specificity of 0.68 and 0.97 respectively.[20] The risk of histological recurrence of PMN is 60–76% in patient with APLA2R as compared to much lower risk of disease recurrence 28–30% in antibody negative patients.

High titers of APLA2R at the time of renal transplant and at the time of disease recurrence was first reported by Stalh *et al* in.[23] Since then, a number of studies were done to assess the relevance of monitoring of APLA2R activity and the risk of disease recurrence in post kidney transplant era. A study by Katteh *et al* was done in which total 26 patients were evaluated, 18/26 had recurrent PMN and 8/26 had no recurrence. Serial graft biopsies and serum APLA2R levels were performed and it was determined that in recurrent group 10/17 patients had APLA2R at the time of renal transplant compared to 2/7 patients in the non-recurrent group. The positive predictive value of pre-transplant APLA2R for recurrence was 83% and the negative predictive value (NPV) was 42%. It was observed that persistence or reappearance of APLA2R in post renal transplant period was associated with progressive proteinuria in 6/18 patients and no proteinuria occurred in patients in whom APLA2R antibodies resolved after standard immunosuppression treatment.[24]

Table-1: PLA2R positivity and recurrent MN

References	N (%) recurrence MN	PLA2R+ at Tx	PLA2R+ at recurrence	Median (range) pre-Tx titer in rMN	PPV/NPV (%)	COMMENT
Kattah *et al.*[36]	18/26 (69)	10/17 with recurrence 2/7 without recurrence	7/18 in post-Tx period	19 (0–1,200) Western blot	83/42 for pre-Tx PLA2R	---
Quintana *et al.*[40]	7/21 (33)	6/7 with recurrence 5/14 without recurrence	6/7	741 (11-1500) ELISA	85/92	-Recurrence significantly associated with high level PLA2R+ before Tx (P = 0.03) -A cut–off level of 45 U/mL during pre-Tx period predicted rMN with a sensitivity of 85%, specificity of 85% and a NPV of 92%
Debiec *et al.*[11]	10/10 (100)	4/4 with available serum	5/10	NA	NA	
Seitz-Polski *et al*.[17]	5/13 (38)	4/5 with recurrence 6/8 without recurrence	4/5	748 (137–3000)	40/80	Presence of PLA2R at the time of Tx does not imply recurrence (p = 0.6). Positive PLA2R activity during follow up (>6 months) significantly correlates to recurrence (p = 0.048)

PLA2R, anti-phospholipase A2 receptor; Tx, transplant; PPV, positive predictive value; NPV, negative predictive value; NA, not available.[24]

Further studies were done to establish the cut-off levels of APLA2R regarding the identification of patients with PMN at risk of post-transplant disease recurrence. Quintana *et al* demonstrated the significant correlation between a positive ELISA association at graft biopsy (0.017) or with increasing levels of APLA2R before transplant (0.03) and the risk of recurrence of PMN in post renal transplant period .By performing receiver open characteristics (ROC) analysis, it was established that cut-off level of APLA2R of 45 U/ml during pre-transplant period accurately predicts recurrence of PMN with a sensitivity and specificity of 85.3% and 85.1% ,respectively, NPV of 92% and area under curve (AUC) of 90.8%. This study also reported a significant correlation that existed between DQ alleles (HLA-DQA 1 *05:01/05 and DQB 1 *02:01) and high APLA2R titers.[25]

Gupta G *et al*, evaluated 16 consecutive transplant patients of PMN for pre transplant APLA2R levels and after performing ROC analysis by combining data from Quintana e*t al* study,[25] determined that pre transplantation levels of APLA2R performed by ELISA of more than 29U/ml predicted Rpmn, with a sensitivity and specificity of 85% and 92% respectively.[24]

Although some small studies including studies conducted by Seitz P *et al* and Debiec *et al*[29] demonstrated a low PPV (40–50%) respectively. However, a much reasonable explanation regarding this controversy would be the role of strong immunosuppressive therapy given in post-transplant period that may cause decrease antibody production and anti-body absorption in allograft.

The beneficial role of rituximab in management of recurrent primary membranous nephropathy

Though better understanding of underlying pathogenetic mechanism of PMN paralleled the new advances in the management of recurrent PMN, however currently there are no evidence based recommended guidelines

available for management of recurrent PMN in post renal transplant period.[32] It was reported in by Debade *et al* that conservative management including strict blood pressure control and standard immunosuppressive regimen remain unsuccessful in preventing the increasing proteinuria in majority of the patients.[33,34] Different immunosuppressive therapies providing promising results in management of PMN in native kidneys have not been found much beneficial in management of recurrent PMN and their use in post-transplant period may complicate leukopenia.[35]

Since 2002, a well remarkable study that was undertaken by Remuzzi *et al*[36], Rituximab, an anti CD20 monoclonal antibody (anti-CD20Mab) has emerged as a promising treatment modality in patients with PMN in native kidneys.[36–38] Now it has been successfully used in managing recurrent PMN in post renal transplant period. Gallon *et al*, first reported the first successfully treated case of recurrent PMN. It was treated with rituximab, by using a regimen of intra venous rituximab, 375 mg/m2, four doses one week apart.[38] This opened new dimensions for further studies. Overall complete or partial remission was achieved in 15–205 and 35–40%, respectively and resolution of sub epithelial deposits has been documented in about 40% of the patients.[39–42] However randomized control trials are still awaited regarding its use in post renal transplant PMN recurrence. It has been recommended to treat recurrent PMN at a much earlier stage when there is progressive proteinuria and it has reached 1 gm/24 hours.[26] This would help in reducing the permanent loss of graft secondary to recurrent PMN. It has also reported that immunological suppression precedes the clinical remission, even by months, therefore APLA2R monitoring has been found helpful in observing treatment effectiveness as compared to the clinical response of proteinuria decrement.[33,37]

Although no data has been found regarding the pre-emptive use of rituximab, theoretically rituximab administration 4-6 months before renal transplant may be used to decrease APLA2R titers and prevent the disease recurrence in post-transplant period.[26] However small center based experience published in literature are available.Further RCT are needed for further evaluation.

The recommended optimal dose of rituximab that could be used in treatment of recurrent PMN is still a matter of debate. Two different regimens including one consisting of 375 mg/m2 intra venous, once weekly for 4 consecutive weeks or the second regimen consisting of two doses of 1 gm of rituximab each fourteen days apart have been used. Either regimen can be used and it can be repeated in case of persistence of B cells >15/microliter or persistently high APLA2R titers.[37–43] The major concern is increased infection rate in post renal transplant period when other immunosuppressive drugs are also being used.

CONCLUSION

Discovery of M-type PLA2R and its significant role in human PMN has opened the new doors in the management of PMN. It has well established that high levels of APLA2R before transplant might be beneficial in predicting disease recurrence and their level after transplant are helpful in predicting the serious risk of disease recurrence and progression. They are also helpful in monitoring disease activity and treatment response. Rituximab an anti CD20 monoclonal antibody is currently considered the most useful treatment for recurrent PMN but further prospective RCT regarding efficacy of rituximab, dose and timing are required to confirm the validity of available reported data.

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Submitted: November 30, 2020	*Revised: April 17, 2021*	*Accepted: April 18, 2021*

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