www.nephropathol.com DOI: 10.15171/jnp.2019.25 J Nephropathol. 2019;8(3):e25

Journal of Nephropathology

Efficacy and safety of a modified- 'modified Ponticelli' regimen for treatment of primary membranous nephropathy

Indu Ramachandra Rao[1], Ravindra Prabhu Attur[1], Dharshan Rangaswamy[1], Srinivas Shenoy[1], Sindhura Lakshmi Koulmane Laxminarayana[2], Shankar Prasad Nagaraju[1*]

[1]Department of Nephrology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India
[2]Department of Pathology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 7 May 2018
Accepted: 18 July 2019
Published online: 8 August 2019

Keywords:
Nephrotic syndrome
Steroids
Alkylating agents
Glomerular disease
Membranous nephropathy
Immunosuppression

ABSTRACT

Background: Modified Ponticelli regimen (mPR), consisting of cyclical steroids and cyclophosphamide, is the most established therapy for primary membranous nephropathy (MN). Yet, the potential toxicity of this treatment regimen poses a significant concern.

Objectives: The aim of this study was to assess the efficacy and safety of a modified version of the conventional mPR for primary MN using lower-than-standard dose pulse steroids.

Patients and Methods: This was a retrospective single-center analysis of patients admitted between January 2008 to December 2017. All treatment-naive patients with biopsy-proven primary MN treated with a lower-than-standard dose pulse steroid-based modification of the conventional mPR (intravenous pulse of 500 mg methyl-prednisolone, instead of 1000 mg) were included. We report the remission rates at the end of 6 months (both complete and partial), relapses and adverse effects of treatment at the end of follow-up.

Results: A total of 41 individuals were included. Of 31 individuals who completed six months of treatment (six were lost to follow-up, while four discontinued immunosuppression due to infections), 71% (n=22) responded to treatment [complete remission in 25.8% (n=8), partial remission in 45.2% (n=14)]. Most common complications detected throughout the treatment were steroid induced diabetes mellitus in 40% (n=14/35), infections in 25.7% (of which immunosuppression was discontinued for four participants), and leucopenia in 8.5% (n=3/35). Relapses were seen in 29% (n=9) during follow-up (mean follow-up period: 36 months).

Conclusions: The modified- 'modified Ponticelli' regimen with lower-than-standard dose intravenous steroids and cyclophosphamide was efficient in attaining remission in primary MN.

Implication for health policy/practice/research/medical education:
Although the efficacy of the mPR is well-proven, it is associated with a high risk of serious adverse events. Whether lowering dose of intravenous pulse steroids would result in reduction of treatment-associated toxicity is unclear. In this retrospective study, we report the response to a lower-than-standard dose intravenous pulse steroid-based modification of the modified Ponticelli regimen (500 mg methyl-prednisolone, instead of the standard 1000 mg dose).

Please cite this paper as: Ramachandra Rao I, Prabhu Attur R, Rangaswamy D, Shenoy S, Laxminarayana SLK, Nagaraju SP. Efficacy and safety of a modified- "modified Ponticelli" regimen for treatment of primary membranous nephropathy. J Nephropathol. 2019;8(3):e25. DOI: 10.15171/jnp.2019.25.

1. Background

Primary membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults worldwide, accounting for 20-40% cases in most series (1-3). Optimal treatment of primary MN has been a matter of debate in the nephrology community for decades. Although clinical trials on immunosuppressive therapy for primary MN have spanned more than two decades, universal consensus regarding choice of therapy to decrease proteinuria and halt the progression of renal disease does not exist.

The 'modified Ponticelli' regimen (mPR) is the most

*Corresponding author: Shankar Prasad Nagaraju,
Email; shankar.prasad@manipal.edu

Original Article

widely used treatment option for primary MN and consists of a 6-month course of alternating monthly cycles of steroids and oral cyclophosphamide (4). Despite evidence that use of mPR reduces proteinuria, all-cause mortality and progression to end-stage renal disease, there has always been a concern regarding adverse effects (5). Steroids are associated with numerous side-effects including weight gain, acne, glucose intolerance, infections, delayed wound healing, osteoporosis, myopathy, gastrointestinal ulceration and perforation. Prolonged use of high dose steroids also impairs the hypothalamic-pituitary-adrenal (HPA) axis and abrupt withdrawal of steroids can precipitate adrenal crisis. In fact, a study found an occurrence of HPA axis suppression in 23% patients treated with mPR (6). Additionally, adverse effects of cyclophosphamide include myelosuppression, especially leucopenia, infections, hemorrhagic cystitis, and gastrointestinal issues, and risk of infertility and cancer.

Rituximab monotherapy has been emerging as a promising therapeutic option for primary MN, given the favorable safety profile (7-11). However, the high cost of therapy is a barrier to widespread use, and mPR continues to be the treatment of choice, especially in resource-limited settings.

At our center, in an attempt to minimize therapy-related adverse effects, we have been using a lower-than-standard dose intravenous pulse steroid-based modification of the conventional mPR, along with a lower dose of cyclophosphamide as per Kidney Disease Improving Global Outcomes (KDIGO) guidelines (2 mg/kg/d instead of 2.5 mg/kg/d) (Figure 1).

2. Objectives

In this study we sought to report the remission rates and adverse events with the use of this regimen in primary MN.

3. Patients and Methods

3.1. Study design

The study was a case-record based single-center retrospective analysis conducted at a tertiary care center in India. The study was approved by the institutional ethics committee. All patients with primary MN presenting between January 2008 to December 2017 fulfilling the following criteria were included (1) Biopsy proven primary MN, and (2) treated with a lower-than-standard dose pulse steroid-based modification of the conventional mPR (Figure 1).

Exclusion criteria: 1) Evidence of secondary causes of MN (infections, systemic lupus erythematosus or malignancy), 2) Relapse cases, and 3) Other immunosuppression received in the past e.g. calcineurin inhibitors (cyclosporine, tacrolimus) or rituximab.

Demographic, clinical, histopathological and laboratory parameters of all patients were collected. Follow-up data (till June 2018) was also collected. The following outcome measures were studied;

Primary outcomes: Remission rates (both complete and partial).

Secondary outcomes: 1) Therapy-related adverse effects (including impaired glucose tolerance/diabetes mellitus, infection and cytopenia), 2) Relapse rate at follow-up, 3) Progressive renal dysfunction

The study definitions used are as follows:

Complete remission: Proteinuria < 0.3 g/day or protein-to-creatinine ratio (UPCR) <0.3 mg/mg, with normalization of serum albumin (≥3.5 g/dL) (as per KDIGO 2012 guidelines).

Partial remission: Reduction of 24-hour urine protein (or UPCR) to < 50% of baseline to < 3.5 g/d (or UPCR <3.5 mg/mg), but > 0.3 g/d (or UPCR > 0.3 mg/mg) (as per KDIGO 2012 guidelines).

Relapse: Proteinuria >3.5 g/day or >3500 mg/g urine creatinine after remission has been attained (as per

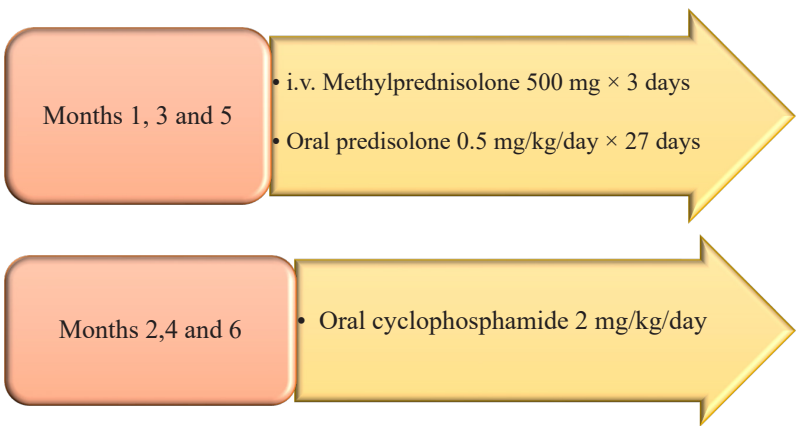

Figure 1. A lower-than-standard dose pulse steroid based modification of the conventional 'modified Ponticelli' regimen.

KDIGO 2012 guidelines).

Progressive renal dysfunction: Doubling of serum creatinine or need for renal replacement therapy.

3.2. Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from patients. The study protocol was approved by the institutional ethics committee of Kasturba Medical College and Kasturba Hospital, Manipal (#721/2018).

3.3. Statistical analysis

Statistical analysis was carried out using SPSS version 18. Descriptive analysis was performed and data were expressed as mean ± SD or median (interquartile range) for continuous variables and as frequencies for categorical variables. Comparison of responders and non-responders were done using unpaired t test for continuous variables, and χ^2 test and Fisher's exact test for nominal variables. For non-parametric data, Mann-Whitney U test was used. *P* value of < 0.05 was considered statistically significant.

4. Results

A total of 41 patients were included. Baseline characteristics are shown in Table 1. Mean age at presentation was 47.6 ± 11.2 years, with 63.4% (n=26) males. Mean proteinuria was 7.4 ±3.31 g/day, with estimated glomerular filtration rate (eGFR) of 89.9 ± 34.8 mL/min/1.73 m^2. Anti-PLA2R antibody ELISA was available in 22 patients, of which 63.6% (n=14) were PLA2R-positive with median titers of 230 RU/mL (IQR 0-406).

All individuals were administered either angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBS) and statins as supportive therapy concurrently.

Immunosuppression was stopped prior to completion of 6 months for four individuals due to infection, while six individuals were lost to follow-up. Of 31 individuals who completed six months of therapy, 71% (n=22) responded to therapy. Complete remission was noted in 25.8% (n=8) and partial remission in 45.2% (n=14) (Table 2).

Steroid induced diabetes mellitus seen in 40% (n=14/35), was the most common adverse effect (Table 3). None of these patients required insulin for glycemic control and were managed with oral hypoglycemic agents alone. Infections were seen in 25.7% (n=9/35) including upper respiratory tract infection in two, pneumonia in two, cellulitis in two, urinary tract infection in one,

Table 1. Baseline characteristics of study population

Clinical parameter	Total (N =41)
Age, years (mean ± SD)	47.6 ± 11.2
Male, n (%)	26 (63.4%)
Female, n (%)	15 (36.6%)
Diabetes mellitus, n (%)	4 (9.8%)
Hypertension, n (%)	23 (56.1%)
Serum creatinine, mg/dL (mean ± SD)	1.1 ± 0.71
Baseline eGFR, mL/min/1.73m^2 (mean ± SD)	89.9 ± 34.8
Microscopic hematuria, n (%)	10 (24.4%)
Proteinuria, g/day (mean ± SD)	7.4 ± 3.31
Albumin, g/dL (mean ± SD)	2.1 ± 0.5
Hemoglobin, g/dL (mean ± SD)	12.1 ± 2.1
Cholesterol, mg/dL (mean ± SD)	343.8 ± 78.1
Anti-PLA2R positive, n (%)	14/22 (63.6%)
Anti-PLA2R titre, RU/mL (median (IQR))	230 (0-406)

Table 2. Study outcomes

Outcome	Total (N =31)[a]
Complete remission, n (%)	8 (25.8%)
Partial remission, n (%)	14 (45.2%)
No remission, n (%)	9 (29%)
Time of remission, months (mean ± SD)	4.9 ± 1.8
Creatinine at 6 months, mg/dL (mean ± SD)	0.9 ± 0.4
Proteinuria at 6 months, g/day (median, IQR)	1.2 (4.6-6.8)
eGFR at 6 months, mL/min/1.73m^2 (mean ± SD)	93.3 ± 27.8
Duration of follow-up, months [median (IQR)]	36 (9-58)
Relapse on follow-up, n (%)	9 (29%)
Time to relapse, months [median (IQR)]	11 (8-42)

[a] Of the included 41 patients, 6 were lost to follow-up, while 4 discontinued immunosuppression due to infections. 31 patients who completed 6 months of therapy were included for analysis of outcome.

Table 3. Adverse effects of therapy

Adverse effect	No. of patients [a] (Total =35)
Steroid-induced diabetes mellitus, n (%)	14 (40%)
Infection, n (%)	9 (25.7%)[b]
Upper respiratory tract infection	2
Pneumonia	2
Cellulitis	2
Urinary tract infection	1
Pulmonary TB	1
Oral candidiasis	1
Leukopenia, n (%)	3 (8.5%)
Others, n (%)	0 (0%)

[a] Of the included 41 patients, six were lost to follow-up.
[b] Immunosuppression was stopped in four patients due to infections.

oral candidiasis in one and pulmonary tuberculosis in one patient. Of the five (14.2%) patients who required hospitalization, immunosuppression was discontinued in four. Leucopenia was seen in 8.5% (n=3/35).

Median follow-up period was 36 (IQR 9-58) months. Relapse rate was 29% (n=9), with median time to relapse of 11 (IQR 8-42) months. Progressive renal dysfunction was seen in 6.5% (n=2), with both patients progressing to end-stage renal disease.

On comparison of responders and non-responders (Table 4), anti-PLA2R titers ($P=0.019$) and percentage of glomerulosclerosis at presentation ($P=0.003$) were significantly related with response at six months. There was no significant difference in age, gender, duration of symptoms, baseline creatinine or eGFR, severity of proteinuria and presence of interstitial fibrosis/tubular atrophy (IFTA) between the two groups.

5. Discussion

The 2012 KDIGO guidelines recommend the use of the mPR for the treatment of patients with primary MN at risk of disease progression (12). First described by Ponticelli et al in 1998, the modification involved replacement of the chlorambucil component of the 'classical Ponticelli' regimen by oral cyclophosphamide (4). Following this randomized controlled trial, which showed similar rates of remission (82% versus 93%) and better safety profile of the modified regimen when compared to the classical regimen, cyclophosphamide replaced chlorambucil as alkylating agent of choice in the treatment of primary MN. In 2007, Jha et al reported remission rates of 72.3% (31.9% complete remission and 40.4% partial response) (13). A lower dose of cyclophosphamide compared to that used by Ponticelli et al (2 mg/kg/d versus 2.5 mg/kg/d) was used in this study. Despite favorable results, the short- and long-term side-effects of the mPR makes clinicians wary of its use and alternative therapeutic options have been studied. Remission rates of 70%-75% have been reported with the use of calcineurin inhibitors, which is comparable to mPR (14,15). However, high relapse rates of 40%-45% and risk of nephrotoxicity is a concern. Rituximab is now emerging as an important contender for first-line therapy of primary MN with reported remission rates of 65% and favorable safety profile (7-11). But considering the high cost of therapy and the absence of prospective head-to-head trials comparing the rituximab and mPR, we believe that the mPR remains the most well-established therapy for primary MN.

It is noteworthy that, the one-gram pulse methyl-prednisolone dose used in both the classical and mPR was largely empirical and based on the doses used for treatment of acute renal allograft rejection and lupus nephritis (4). With the focus shifting towards steroid minimization/avoidance in the current era, the administration of high-dose pulse steroids for treatment of primary MN is questionable. This is especially so in developing countries where infections are common.

With the use of the modified 'modified Ponticelli' regimen (Figure 1), we found remission rate of 71%, with complete remission of 25.8% at our center. This is comparable to that reported by Jha et al (72% remission) and Ramachandran et al (remission rates of 60% and 77% at 6- and 12- months, respectively) (13,16). The relapse rate in our study was 29%, which is also similar to previous studies, with Jha et al and Ram et al reporting relapse rates of 23.5% and 18.9%, respectively (13,17).

The most common therapy-related adverse effect in our study was steroid-induced diabetes mellitus seen in 40% of patients. Ramachandran et al reported an incidence of diabetes mellitus/glucose intolerance of 14.3% (16).

Table 4. Comparison of responders and non-responders

Parameter	Responders (n=22)	Non-responders (n=9)	P value
Age, years (mean ± SD)	46.77 ±11.78	47.75 ±9.95	0.809
Gender, n			0.323
Male	13	7	
Female	9	2	
Duration of symptoms, months (mean ± SD)	4.09 ±4.93	7.75 ±6.44	0.073
Baseline serum creatinine, mg/dL (mean ± SD)	1.0 ±0.64	1.34 ±0.88	0.203
Baseline eGFR, mL/min/1.73 m^2 (mean ± SD)	95.1 ±33.7	76.9 ±35.8	0.152
Baseline proteinuria, g/day (mean ± SD)	7.2 ±2.7	8.5 ±4.3	0.301
Anti-PLA2R titres, RU/mL (mean ± SD)	150 ±166.8	640± 597.2	0.019
Glomerulosclerosis, % (mean ± SD)	3.86 ±7.44	18.95±17.81	0.003
IFTA[a] > 25%, n	3	4	0.198

IFTA, Interstitial fibrosis/tubular atrophy.

Regional factors could account for the higher incidence of steroid-induced diabetes mellitus in our study population despite reduced dose of steroids.

Serious infections requiring hospitalization were seen in 14.2%. Previous studies by Jha et al and Ramachandran et al have reported serious infection rates of 21.2% and 25.7% (13,16). The overall infection rate in our study was 25.7% (n=9/35), which is again lower than that reported by Ramachandran et al (37.1%) (16). Although the infection rate in our study is lower compared to previous studies, in the absence of a control group treated with the standard dose of intravenous steroids, we cannot comment on whether the use of reduced steroid doses truly resulted in a reduction of short- or long-term adverse events.

The lower-than-standard pulse steroid therapy in our study resulted in a cumulative dose reduction of 4.5 g. Studies have shown that higher the cumulative steroid dose used, higher the risk of adverse events and health-care expenditure (18,19).

To the best of our knowledge, this is the first study to use a lower-than-standard dose intravenous methylprednisolone in the treatment of primary MN along with the standard dose of cyclical oral cyclophosphamide. Although variations of the steroid/cyclophosphamide combination have been attempted in the past, regimens avoiding/reducing intravenous methylprednisolone have used cyclophosphamide either concurrently or for a prolonged duration, thus increasing risk of cyclophosphamide toxicity (20).

6. Conclusions

The modified- 'modified Ponticelli' regimen with lower-than-standard dose intravenous steroids was effective in achieving remission in primary MN. The dose of steroids to be used in mPR regimen needs to be readdressed and warrants further studies.

Limitations of the study

The limitations of this study are the lack of a control group, small patient number and retrospective nature of the study. These limitations notwithstanding, we believe our study raises an important question about the necessity for high dose pulse steroids for primary MN as recommended in the modified Ponticelli treatment protocol. Whether reduction in intravenous steroid dose in mPR would reduce toxicity of this regimen while maintaining efficacy needs to be evaluated in further studies.

Acknowledgments

The authors wish to thank Dr. Ganesh Paramasivam, Kasturba Medical College, Manipal for his valuable insights. The authors wish to declare that, the abstract of this study has been presented at the World Congress of Nephrology conference 2019 at Melbourne, and subsequently the conference abstract has been published in the ISN WCN 2019 abstracts supplement of Kidney International (https://www.kireports.org/article/S2468-0249(19)30625-4/fulltext) (reference; 21).

Authors' contribution

IRR and SPN contributed to study design, preparation of manuscript and final revision. IRR, SS, SLK and SPN participated in data collection. IRR, RPA and DR conducted data analysis and interpretation. All authors read and approved the paper.

Conflicts of interest

The authors have no conflicts of interest to declare for this study.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

Funding/Support

None.

References

1. Debiec H, Ronco P. Immunopathogenesis of membranous nephropathy: an update. Semin Immunopathol. 2014;36(4):381-97. doi: 10.1007/s00281-014-0423-y.
2. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. 2017;91(3):566-74. doi: 10.1016/j.kint.2016.09.048.
3. Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient's care. Lancet. 2015;385(9981):1983-92. doi: 10.1016/S0140-6736(15)60731-0.
4. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol. 1998;9(3):444-50.
5. Chen Y, Schieppati A, Cai G, Chen X, Zamora J, Giuliano GA, et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. Clin J Am Soc Nephrol. 2013;8(5):787-96. doi: 10.2215/CJN.07570712.
6. Ramachandran R, Jairam A, Bhansali A, Jha V, Gupta KL, Sakhuja V, et al. Study of hypothalamic pituitary adrenal axis in patients of membranous nephropathy receiving modified Ponticelli regimen. Indian J Nephrol. 2015;25(1):12-5.
7. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up.

J Am Soc Nephrol. 2017;28(1):348-58. doi: 10.1681/ASN.2016040449.
8. Michel PA, Dahan K, Ancel PY, Plaisier E, Mojaat R, De Seigneux S, et al. Rituximab treatment for membranous nephropathy: a French clinical and serological retrospective study of 28 patients. Nephron Extra. 2011;1(1):251-61. doi: 10.1159/000333068.
9. Busch M, Ruster C, Schinkothe C, Gerth J, Wolf G. Rituximab for the second- and third-line therapy of idiopathic membranous nephropathy: a prospective single center study using a new treatment strategy. Clin Nephrol. 2013;80(2):105-13. doi: 10.5414/CN107912.
10. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P. Rituximab for idiopathic membranous nephropathy. Lancet. 2002;360(9337):923-4.
11. van den Brand J, Ruggenenti P, Chianca A, Hofstra JM, Perna A, Ruggiero B, et al. Safety of Rituximab Compared with Steroids and Cyclophosphamide for Idiopathic Membranous Nephropathy. J Am Soc Nephrol. 2017;28(9):2729-37. doi: 10.1681/ASN.2016091022.
12. KDIGO clinical practice guidelines for glomerulonephritis. Kidney Int Suppl. 2012;S2:139-274
13. Jha V, Ganguli A, Saha TK, Kohli HS, Sud K, Gupta KL, et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol. 2007;18(6):1899-904. doi: 10.1681/ASN.2007020166.
14. Cattran DC, Appel GB, Hebert LA, Hunsicker LG, Pohl MA, Hoy WE, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. Kidney Int. 2001;59(4):1484-90. doi: 10.1046/j.1523-1755.2001.0590041484.x.
15. Praga M, Barrio V, Juarez GF, Luno J, Grupo Espanol de Estudio de la Nefropatia M. Tacrolimus monotherapy in membranous nephropathy: a randomized controlled trial. Kidney Int. 2007;71(9):924-30.
16. Ramachandran R, Hn HK, Kumar V, Nada R, Yadav AK, Goyal A, et al. Tacrolimus combined with corticosteroids versus Modified Ponticelli regimen in treatment of idiopathic membranous nephropathy: Randomized control trial. Nephrology (Carlton). 2016;21(2):139-46. doi: 10.1111/nep.12569.
17. Ram R, Guditi S, Kaligotla Venkata D. A 10-year follow-up of idiopathic membranous nephropathy patients on steroids and cyclophosphamide: a case series. Ren Fail. 2015;37(3):452-5.
18. Best JH, Kong AM, Lenhart GM, Sarsour K, Stott-Miller M, Hwang Y. Association Between glucocorticoid exposure and healthcare expenditures for potential glucocorticoid-related adverse events in patients with rheumatoid arthritis. J Rheumatol. 2018;45(3):320-8. doi: 10.3899/jrheum.170418.
19. Braz NFT, Rocha NP, Vieira ELM, Gomez RS, Barbosa IG, Malheiro OB, et al. Negative impact of high cumulative glucocorticoid dose on bone metabolism of patients with myasthenia gravis. Neurol Sci. 2017;38(8):1405-13. doi: 10.1007/s10072-017-2964-z.
20. Xu J, Zhang W, Xu Y, Shen P, Ren H, Wang W, et al. Tacrolimus combined with corticosteroids in idiopathic membranous nephropathy: a randomized, prospective, controlled trial. Contrib Nephrol. 2013;181:152-62. doi: 10.1159/000348475.
21. Rao IR, Nagaraju SP, Attur RP, Shenoy S, Mohan V, Ram A, et al. SUN-035 A Modified 'Modified Ponticelli' regimen for idiopathic membranous nephropathy. Kidney Int Rep. 2019;4(7):S167.

Copyright © 2019 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.