META-ANALYSIS

Efficacy and Adverse Reactions of Mycophenolate Mofetil Combined with Hormone in the Treatment of Idiopathic Membranous Nephropathy: A Meta-Analysis

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ABSTRACT

Background • The detection and prevalence of idiopathic membranous nephropathy in China are increasing yearly. However, the current treatment of idiopathic membranous nephropathy relies on empirical treatment regimens such as hormones and immunosuppressants, with unclear prognosis and easy recurrence.

Methods • Eight databases were searched to obtain controlled trials on the effects of mycophenolate mofetil combined with hormones in the treatment of idiopathic membranous nephropathy. After literature quality evaluation, data analysis was performed using RevMan 5.3 software.

Results • 12 studies were ultimately included in this meta-analysis. 12 studies reported that, compared with the control group, the effective rate (OR: 1.15; 95% CI: 1.06, 1.26; $P < .001$), 24hUP (SMD:-0.35; 95% CI: -0.47, -0.23; $P < .001$), Alb (SMD: 1.92; 95% CI: -0.51, 4.36; $P = .122$), Scr (SMD: 4.44; 95% CI: -10.26, 1.38; $P = .135$), TG (SMD: 0.51; 95% CI: 0.88, 0.15; $P < .01$) and adverse events (OR: 0.86; 95% CI: 0.67,1.11; $P = .255$) of the test group was significantly higher.

Conclusion • The results of this study suggested that mycophenolate mofetil combined with hormone may be effective on patients with idiopathic membranous nephropathy, as evidenced by effective rate, 24hUP, Alb, Scr, TG, adverse events, and the above conclusions need to be verified by more high-quality studies. (*Altern Ther Health Med.* 2024;30(1):403-407).

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INTRODUCTION

Chronic kidney disease is a global public health problem, whose incidence and prevalence rates are increasing yearly, and the prognosis is poor with high treatment costs. The prevalence of chronic kidney disease in China is approximately 10.8%.[1] The most common cause is glomerular disease, which is also the most common cause of end-stage kidney disease. Membrane nephropathy is a common chronic kidney disease, accounting for approximately 1/3 of glomerular diseases,[2] among which patients with unknown etiology are called idiopathic membranous nephropathy, accounting for approximately 4/5 of membrane nephropathy. With the progress of technology and economic development, the detection and prevalence of idiopathic membranous nephropathy in China are increasing yearly. However, the current treatment of idiopathic membranous nephropathy relies on empirical treatment regimens such as hormones and immunosuppressants, with unclear prognosis and easy recurrence. About one-third of patients, regardless of the hormone or immunosuppressive regimen used, will enter the stage of end-stage renal disease, seriously affecting their quality of life and survival.[3] Membranous nephropathy is characterized by the deposition of immune complexes under the epithelial cells of the glomerular basement membrane and the thickening of the glomerular basement membrane. It is a group of diseases that typically do not involve the proliferation of glomerular intrinsic cells and local inflammatory reactions. For patients with unknown causes, it is called idiopathic membranous nephropathy, also known as primary membranous nephropathy. Idiopathic membranous nephropathy has a long course and a hidden onset, with approximately 80% of patients presenting with nephrotic syndrome prone to complications such as thromboembolism. Significant differences exist in the clinical prognosis of patients with idiopathic membranous nephropathy, with about one-third of patients experiencing spontaneous remission, one-third presenting with persistent proteinuria, and one-third developing into end-stage kidney disease.[4] Immunosuppressive therapy and non-immunosuppressive therapy are commonly used methods in modern medicine to treat this disease. The former mainly includes glucocorticoids

and immunosuppressants, while the current treatment regimen dominated by immunosuppression has its advantages, disadvantages, and side effects.

Mycophenolate mofetil (MMF) is a 2-ethylated derivative of mycophenolic acid, which was gradually applied for the treatment of immune-mediated kidney disease in the mid to late 1990s. Comparative studies have shown that the new generation of immune suppressant, mycophenolate mofetil, has no hepatorenal toxicity and has good anti-inflammatory and immunosuppressive effects. Mycophenolate mofetil can specifically inhibit the dehydrogenation activity of hypoxanthine nucleotides in the lymphocyte purine synthesis pathway, block the de novo synthesis of guanine nucleotides, deplete guanine nucleotides, and then block DNA synthesis. It can selectively act on T and B lymphocytes to inhibit their cell proliferation but has no inhibitory effect on most non lymphocytes. There are very few common adverse reactions such as liver, kidney, and bone marrow, which are usually caused by other immunosuppressants. In recent years, mycophenolate mofetil has been widely used in some non-transplant fields, such as the treatment of systemic lupus erythematosus, rheumatoid arthritis, autoimmune hemolytic anemia, and other diseases, and has shown its unique efficacy.[5-6] Mycophenolate mofetil improves the infiltration of inflammatory cells in blood vessels and renal tissues and reduces the permeability of the glomerular filtration membrane, thereby reducing proteinuria and delaying kidney damage. Mycophenolate mofetil can reduce the production of IgA in lymphocytes, reverse the abnormal O-glycosylation level of IgA1 in peripheral lymphocytes, and thus reduce the deposition of IgA immune complexes under the endothelium and mesangium. It can significantly reduce proteinuria, protect renal function, and lower adverse reaction incidence.[7-8]

Thus, we conducted a meta-analysis to examine the effect of mycophenolate mofetil combined with hormones in patients with idiopathic membranous nephropathy.

MATERIALS AND METHODS

Selection of Studies.

The study design type was published in controlled trials on the effects of mycophenolate mofetil combined with hormone in patients with idiopathic membranous nephropathy. However, the animal trials were excluded.

Selection of Participants.

Patients with idiopathic membranous nephropathy treated with combined mycophenolate mofetil and hormone.

Types of Interventions.

Patinets in the intervention group received mycophenolate mofetil combined with hormone in the treatment of patients with idiopathic membranous nephropathy, and the control group received hormone combined with other drugs in the treatment of patients with idiopathic membranous nephropathy.

Types of Outcome Measures.

According to research, the assessment tools for the effects of mycophenolate mofetil combined with hormone in the treatment of patients with idiopathic membranous nephropathy were: 1) Effective rate; 2) 24-hour urinary protein quantity: 24hUP (g/24 h); 3) Serum albumin: Alb (g/L); 4) Serum creatinine: Scr (μmol/L); 5) Triglyceride: TC (mmol/L); 6) Adverse events.

Search Strategy.

Retrieved the following databases: Cochrane Library, PubMed, EMbase, Web of Science, CNKI, China Biomedical Literature Database (CBM), VIP, and WanFang. The search term is "Mycophenolate Mofetil" and "Idiopathic Membranous Nephropathy." The time span of the literature search was the database establishment until February 2022. The specific steps of the literature search were: 1) Search for relevant documents in the databases, reading the title, abstract, and keywords to further identify the search terms for this study; 2) "MeSH Terms" was used to identify the subject terms, and using a combination of subject words and keywords.

Data Extraction and Quality Assessment.

After initial screening of the abstracts, literature screening results were obtained by reading the full text, which were completed independently by 2 researchers. The researchers exchanged screening results, discussed dissenting literature and consulted a third researcher when necessary until the results were agreed upon. The information extracted from the data includes basic information about the literature, type of study, study objects, sample size, intervention content, outcome measures, etc.

Statistical Analysis.

This meta-analysis was conducted by using Review Manager (RevMan). Effects were combined: 1) The outcome measures in this study were all measured data. Given the different tools used to evaluate. There are differences between scores, the standardized mean difference (standardized mean difference, SMD) and 95% confidence interva (CI) was used as an indicator of effect. 2) Heterogeneity test: Chi-square tests were used to determine whether there is heterogeneity between studies. If $P > .1$, $I^2 < 50\%$, the included studies were considered more homogeneous, and a fixed-effects model Meta-analysis was used; If $P < .1$, $I^2 \geq 50\%$, the included studies were considered heterogeneous and a random-effects model Meta-analysis was used. Furthermore, possible differences of qualitative factors were subgroup analyzed.

RESULTS

Search Results

Based on the search strategy, 652 references were identified. After excluding duplicate studies, 47 studies were screened based on abstract and title. Then, 21 articles were evaluated in full text. After full-text evaluation, 9 records were excluded for the following reasons: data mismatch (n =

Figure 1. Flow Chart.

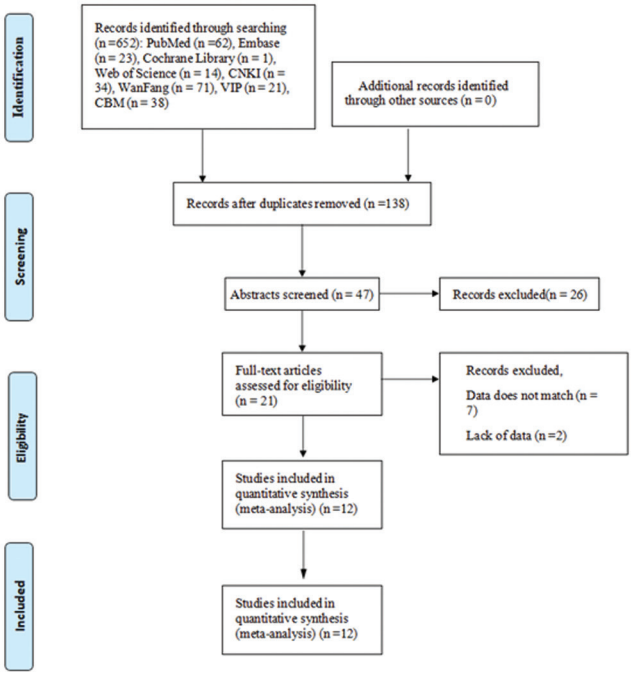


Table 1. The basic characteristics of the included studies.

Study (ref.)	Sample Size(T/C)	Man/ Woman	Age(years) (Mean±SD) (T/C)	T	C	Main Outcomes
Branten, 2007	32/32	48/16	55±14/ 56±12	MMF+Pre	CTx+Pre	①⑥
Choi, 2018	21/18	25/14	57.7±10.0/ 52.7±10.9	MMF+Pre	CTx+Pre	①②③④⑥
Peng, 2016	30/30	30/30	39.9±14.3/ 40.8±13.3	MMF+Pre	CTx+Pre	①②③⑥
Guo, 2020	51/51	54/48	48.79±4.85/ 48.62±4.78	MMF+Pre	Pre	①⑤⑥
Li, 2017	20/20	31/9	44.2±11.81/ 43.55±12.45	MMF+Pre+Tac	CTx+Pre	①②③⑥
Fu, 2012	13/13	17/9	43.1±11.9/ 42.7±14.5	MMF+Pre	CTx+Pre	①④⑥
Miao, 2020	50/50	65/35	53.57±9.12/ 53.36±8.92	MMF+Pre+Tac	Tac+Pre	①②④⑥
Long, 2011	32/32	36/28	47.0±6.1/ 42.74±7.3	MMF+Pre	CTx+Pre	①⑥
Ren, 2011	26/26	36/16	46.6±5.2/ 41.1±8.5	MMF+Pre	CTx+Pre	①②③④⑤⑥
Guan, 2013	20/20	19/21	25-53	MMF+Pre	CTx+Pre	①②③④⑥
Chen, 2018	20/20	18/22	58.73±6.91/ 59.44±5.68	MMF+Pre	CTx+Pre	①②③④⑤⑥
Ning, 2020	27/26	29/24	41.8±8.3/ 40.9±8.6	MMF+Pre	CTx+Pre	①②③④⑥

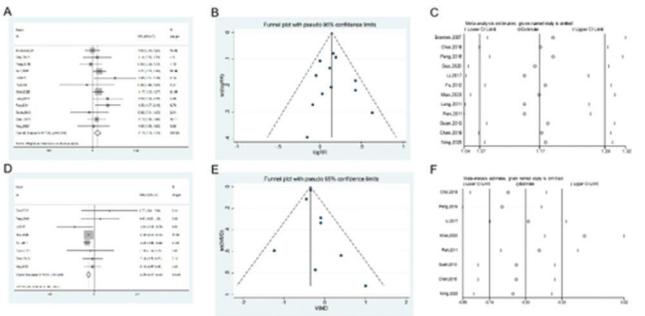
Abbreviations: T, test group; C, control group; MMF, Mycophenolate Mofetil; Pre, Prednisolone; CTx, Cyclophosphamide; Tac, Tarolimus; ①Effective rate; ②24-hour urinary protein quantity: 24hUP (g/24 h); ③Serum albumin: Alb(g/L); ④Serum creatinine: Scr(μmol/L); ⑤Triglyceride: TG(mmol/L); ⑥Adverse events.

7) and missing data (n = 2). Ultimately, 12 studies[9-20] were included in this meta-analysis (Table 1). The PRISMA statement flow chart shows this process (Figure 1).

Effective rate

12 studies reported the effective rate of the test and control groups. Meta-analysis showed that the effective rate of the test group was significantly higher (OR: 1.15; 95% CI: 1.06,1.26; $P < .001$, Figure 2A) than the control group. Funnel plot is relatively symmetrical (Figure 2B). These results showed low heterogeneity and a sensitivity analysis was conducted (Figure 2C). Compared with the control group, mycophenolate mofetil combined with hormones in treating patients with idiopathic membranous nephropathy increased the effective rate. The Begg's Test was 0.945, and the Egger's test was 0.810, so the results were relatively stable and there was no obvious bias.

Figure 2. Results of the Meta-analysis for effective rate and 24-hour urinary protein quantity. A: Forest illustration of the effective rate. B: Funnel plot of the effective rate. C: Sensitivity analysis of the effective rate. D: Sensitivity analysis of the effective rate. E: Funnel plot of the 24-hour urinary protein quantity. F: Sensitivity analysis of the 24-hour urinary protein quantity.



24hUP

8 studies reported the 24hUP of the test group and the control group. Meta-analysis showed that the 24hUP of the test group was significantly lower than the control group (SMD: -0.35; 95% CI: -0.47,-0.23; $P < .001$, Figure 2D). The funnel plot was relatively symmetrical (Figure 2E). Compared with the control group, mycophenolate mofetil combined with hormones in the treatment of patients with idiopathic membranous nephropathy decreased the 24hUP. The results of all these trials showed low heterogeneity and a sensitivity analysis was conducted (Figure 2F).

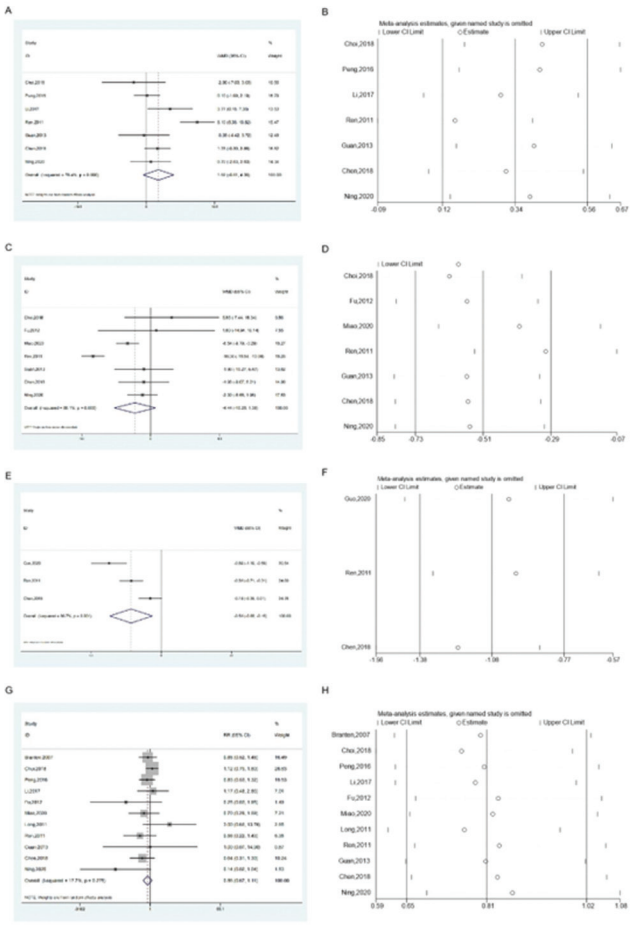
Alb

7 studies reported the Alb of the test group and the control group. Meta-analysis showed that the test group's Alb was not significant compared with the control group (SMD: 1.92; 95% CI: -0.51,4.36; $P = .122$, Figure 3A). Compared with the control group, mycophenolate mofetil combined with hormone in the treatment of patients with idiopathic membranous nephropathy did not increase the level of Alb. The results of all these trials showed high heterogeneity and a sensitivity analysis was conducted (Figure 3B).

Scr

7 studies reported the Scr of the test group and the control group. Meta-analysis showed that the Scr of the test group was not significant compared with the control group (SMD: 4.44; 95% CI: -10.26, 1.38; $P = .135$, Figure 3C). Compared with the control group, mycophenolate mofetil combined with hormone in treating patients with idiopathic

Figure 3. Results of the Meta-analysis for serum albumin, serum creatinine, triglyceride and adverse events. A: Forest illustration of the serum albumin. B: Sensitivity analysis of the serum albumin. C: Forest illustration of the serum creatinine. D: Sensitivity analysis of the serum creatinine. E: Forest illustration of the triglyceride. F: Sensitivity analysis of the triglyceride. G: Forest illustration of the adverse events. H: Sensitivity analysis of the adverse events.



membranous nephropathy did not decrease the level of Alb. All these trials showed high heterogeneity, and a sensitivity analysis was conducted (Figure 3D).

TG

3 studies reported the TG of the test group and the control group. Meta-analysis showed that the TG of the experimental group was significantly lower than the control group (SMD:0.51; 95% CI: 0.88,0.15; $P < .01$, Figure 3E). Compared with the control group, mycophenolate mofetil combined with hormones in treating patients with idiopathic membranous nephropathy decreases the TG. All these trials showed high heterogeneity and a sensitivity analysis was conducted (Figure 3F).

Adverse Events

11 studies reported adverse events in the test group and the control group. Meta-analysis showed that the test group's adverse dvents events were insignificant compared with the control group (OR: 0.86; 95% CI: 0.67,1.11; $P = .255$, Figure 3G). Compared with the control group, mycophenolate mofetil combined with hormones in treating patients with idiopathic membranous nephropathy did not increase the adverse events. All these trials showed low heterogeneity and a sensitivity analysis was conducted (Figure 3H).

DISCUSSION

The current treatment options for idiopathic membrane nephropathy include non-immunosuppressive therapy and immunosuppressive therapy. The 2020 KDIGO guidelines[21] recommend targeted treatment for patients with 24-hour urinary protein quantification levels consistently below 3.5g and no abnormalities in renal function. Immunosuppressants are recommended when the patient's urinary protein quantification level remains above 3.5g/24h, or after non-immunosuppressive treatment, the level remains above 50% of the baseline level without a downward trend, or the patient has serious complications related to nephrotic syndrome, or the patient's serum creatinine increases by ≥30% within 6 to 12 months. Non-immunosuppressive therapy includes a low-salt, low-fat, and high-quality-protein diet and uses ACEI/ARB therapy to reduce proteinuria, controlling blood lipids, edema, anticoagulation, and other basic Western medicine treatments. In addition, studies have shown that the combination of angiotensin-converting enzyme inhibitor (ACEI) and lipid-lowering drugs can significantly reduce proteinuria and effectively protect renal function. In patients whose ACEI drug alone cannot effectively reduce the severe renal damage caused by proteinuria, the clinical effect of the combination is more significant.

The classic immunosuppressive therapy regimen is glucocorticoid and cyclophosphamide, which is inexpensive, has a definite immunosuppressive effect, and is the only proven solution to prevent end-stage kidney disease. For patients who do not want to use glucocorticoid combined with cyclophosphamide or have contraindications to use it, calcineurin inhibitor, mainly represented by tacrolimus and cyclosporine, can be used to stabilize the podocyte actin cytoskeleton, thus reducing the content of plasma PLA2R antibody, to reduce proteinuria. Studies have shown that tacrolimus and cyclosporine A are equivalent in treating idiopathic membrane nephropathy. Monoclonal antibody drugs led by rituximab can efficiently kill and clear B cells, and reduce the production of autoantibodies, with stable therapeutic effect and high safety profile. There is no consensus in clinical practice on the optimal dosage, course of treatment, and whether combination therapy is necessary for rituximab. Other monoclonal antibody drug therapy types still require evidence-based medical evidence to clarify the conclusion. A preliminary attempt has been made to use multi target immunosuppressive therapy for idiopathic membrane nephropathy. Currently, in kidney diseases, the main multi-target immunosuppressive regimen is glucocorticoids + calcineurin inhibitors + mycophenolate

mofetil. -target immunotherapy is expected to further reduce the adverse reactions of immunosuppressantsreduce and further reduce the adverse reactions of immunosuppressants, but its effectiveness needs to be clinically validated.[22-25]

A total of 12 literatures were included in this study, including 342 patients in the test group and 338 patients in the control group. Meta-analysis showed that patients with idiopathic membranous nephropathy who received hormone combined with mycophenolate mofetil had a higher effective rate than those who recived hormone combined with other drugs. Meta-analysis showed a satisfactory effective rate for the test group (OR: 1.15; 95% CI: 1.06,1.26; $P < .001$). Based on the results of the Meta-analysis, the 24hUP of the test group was significantly lower than the control group(SMD: -0.35; 95% CI: -0.47, -0.23; $P < .001$). Based on the results of the Meta-analysis of Alb, the Alb of the test group was not significant compared with the control group (SMD: 1.92; 95% CI: -0.51, 4.36; $P = .122$). Based on the Meta-analysis of Scr results, compared to the control group, the Scr of the test group was insignificant (SMD: 4.44; 95% CI: -10.26, 1.38; $P = .135$). Meta-analysis showed that the TG of the test group was significantly lower than the control group (SMD:0.51; 95% CI: 0.88,0.15; $P < .01$). Compared with the control group, Meta-analysis showed that there was no significant difference in adverse events in the test group (OR: 0.86; 95% CI: 0.67,1.11; $P = .255$). These results provided a rationale for the clinical use of mycophenolate mofetil combined with hormones in idiopathic membranous nephropathy, and physicians should consider the actual situation of patients when using this regimen for treatment.

The limitations of this systematic review are: Only Chinese and English literature was searched, and there may be incomplete research inclusion and bias in selection. Therefore, you should be objective about some of the results of this Meta-analysis.

CONCLUSION

The results of this study suggested that mycophenolate mofetil combined with hormone may be effective on patients with idiopathic membranous nephropathy, as evidenced by effective rate, 24hUP, Alb, Scr, TG, adverse events, and the above conclusions need to be verified by more high-quality studies.

DATA AVAILABILITY

The data could be obtained by contacting corresponding author.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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All authors contributed to the study and agreed to be listed as authors.

REFERENCE

1. Zhang L, Wang F, Wang L, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. [published correction appears in Lancet. 2012 Aug 18;380(9842):650]. *Lancet*. 2012;379(9818):815-822. doi:10.1016/S0140-6736(12)60033-6
2. Xu X, Wang G, Chen N, et al. Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China. *J Am Soc Nephrol*. 2016;27(12):3739-3746. doi:10.1681/ASN.2016010093
3. Zhu P, Zhou FD, Wang SX, Zhao MH, Wang HY. Increasing frequency of idiopathic membranous nephropathy in primary glomerular disease: a 10-year renal biopsy study from a single Chinese nephrology centre. *Nephrology (Carlton)*. 2015;20(8):560-566. doi:10.1111/nep.12542
4. Wu L, Lai J, Ling Y, et al. A Review of the Current Practice of Diagnosis and Treatment of Idiopathic Membranous Nephropathy in China. *Med Sci Monit*. 2021;27:e930097. doi:10.12659/MSM.930097
5. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis*. 2021;80(1):14-25. doi:10.1136/annrheumdis-2020-218272
6. Cassone G, Sebastiani M, Vacchi C, Erre GL, Salvarani C, Manfredi A. Efficacy and safety of mycophenolate mofetil in the treatment of rheumatic disease-related interstitial lung disease: a narrative review. *Drugs Context*. 2020;2021(10).
7. Wu L, Lai J, Ling Y, et al. A Review of the Current Practice of Diagnosis and Treatment of Idiopathic Membranous Nephropathy in China. *Med Sci Monit*. 2021;27:e930097. doi:10.12659/MSM.930097
8. Cattran DC. Mycophenolate mofetil and cyclosporine therapy in membranous nephropathy. *Semin Nephrol*. 2003;23(3):272-277. doi:10.1016/S0270-9295(03)00051-2
9. Branten AJ, du Buf-Vereijken PW, Vervloet M, Wetzels JF. Mycophenolate mofetil in idiopathic membranous nephropathy: a clinical trial with comparison to a historic control group treated with cyclophosphamide. *Am J Kidney Dis*. 2007;50(2):248-256. doi:10.1053/j.ajkd.2007.05.015
10. Choi JY, Kim DK, Kim YW, et al. The Effect of Mycophenolate Mofetil versus Cyclosporine as Combination Therapy with Low Dose Corticosteroids in High-risk Patients with Idiopathic Membranous Nephropathy: a Multicenter Randomized Trial. *J Korean Med Sci*. 2018;33(9):e74. doi:10.3346/jkms.2018.33.e74
11. Peng L, Wei SY, Li LT, He YX, Li B. Comparison of different therapies in high-risk patients with idiopathic membranous nephropathy. *J Formos Med Assoc*. 2016;115(1):11-18. doi:10.1016/j.jfma.2015.07.021
12. Guo YL, Mu YF, Guan RP, et al. Study on the efficacy and safety of Mycophenolate Mofetil combined with prednisone in the treatment of adult idiopathic membranous nephropathy. *Modern Biomedical Progress*, 2020,20 (13): 2597-2600+2580.
13. Li L, Guo YY, Gou R, et al. Prospective study on multi target therapy for refractory idiopathic membranous nephropathy. *Henan Medical Research*. 2017;26(11):1933-1936.
14. Fu P, Yuan AH, Yu JP, et al. A prospective controlled study of mycophenolate mofetil combined with steroids in the treatment of idiopathic membranous nephropathy for 36 months. *Journal of Second Military Medical University*. 2012;33(03):270-273.
15. Miao QQ, Wei QL. Study on the effect of tacrolimus combined with mycophenolate mofetil on oxidative stress response and renal function protection in patients with idiopathic membranous nephropathy. *Pharm Biotechnol*. 2020;27(04):365-369.
16. Long Y. Clinical observation of low-dose prednisone combined with mycophenolate mofetil in the treatment of idiopathic membranous nephropathy. *Zhongguo Xiandai Yaowu Yingyong*. 2011;5(21):12-13.
17. Ren Y, Hu ZX, Luo YH, et al. Clinical observation of mycophenolate mofetil combined with low-dose prednisone in the treatment of idiopathic membranous nephropathy [J]. *Chinese Journal of Modern Physicians*, 2011,49 (26): 73-74+96.
18. Guan CJ, Qin SG, Fu JZ. Clinical efficacy and safety of mycophenolate mofetil combined with glucocorticoids in the treatment of idiopathic membranous nephropathy. *Guangzhou Medical Journal*. 2013;44(06):9-12.
19. Chen XX, Tang Y, Hu Q, et al. Observation of the efficacy of mycophenolate mofetil combined with glucocorticoids in the treatment of idiopathic membranous nephropathy. *Med Infant*. 2018;31(22):89-92.
20. Ning XL. Clinical observation of mycophenolate mofetil combined with glucocorticoids in the treatment of idiopathic membranous nephropathy. *Chinese Medical Guidelines*. 2020;18(08):162-163.
21. Zaghrini C, Seitz-Polski B, Justino J, et al. Novel ELISA for thrombospondin type 1 domain-containing 7A autoantibodies in membranous nephropathy. *Kidney Int*. 2019;95(3):666-679. doi:10.1016/j.kint.2018.10.024
22. Ronco P, Beck L, Debiec H, et al. Membranous nephropathy. *Nat Rev Dis Primers*. 2021;7(1):69. doi:10.1038/s41572-021-00303-z
23. Alsharhan L, Beck LH Jr. Membranous Nephropathy: core Curriculum 2021. *Am J Kidney Dis*. 2021;77(3):440-453. doi:10.1053/j.ajkd.2020.10.009
24. Fernández-Juárez G, Rojas-Rivera J, Logt AV, et al; STARMEN Investigators. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int*. 2021;99(4):986-998. doi:10.1016/j.kint.2020.10.014
25. Fervenza FC, Appel GB, Barbour SJ, et al; MENTOR Investigators. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. *N Engl J Med*. 2019;381(1):36-46. doi:10.1056/NEJMoa1814427