

Received: 2020.11.26

Accepted: 2021.01.15

Available online: 2021.01.27

Published: 2021.02.07

A Review of the Current Practice of Diagnosis and Treatment of Idiopathic Membranous Nephropathy in China

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The present study was supported by the Project of Administration of Traditional Chinese Medicine of Zhejiang Province of China (grant no. 2017ZA024) and the National Natural Science Foundation of China (grant no. 81703851)

Idiopathic membranous nephropathy (IMN), a common pathological type of nephrotic syndrome, is one of the main causes of kidney failure. With an increasing prevalence, IMN has received considerable attention in China. Based on recent studies, we discuss advances in the diagnosis of IMN and the understanding of its genetic background. Although the pathogenesis of IMN remains unclear, our understanding has been substantially enhanced by the discovery of new antigens such as phospholipase A₂ receptor, thrombospondin type-1 domain-containing 7A, exostosin1/exostosin2, neural epidermal growth factor-like 1 protein, neural cell adhesion molecule 1, semaphorin 3B, and factor H autoantibody. However, due to ethnic, environmental, economic, and lifestyle differences and other factors, a consensus has not yet been reached regarding IMN treatment. In view of the differences between Eastern and Western populations, in-depth clinical evaluations of biomarkers for IMN diagnosis are necessary. This review details the current treatment strategies for IMN in China, including renin-angiotensin system inhibitors, corticosteroid monotherapy, cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, adrenocorticotrophic hormone, and traditional Chinese medicine, as well as biological preparations such as rituximab. In terms of management, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines do not fully consider the characteristics of the Chinese population. Therefore, this review aims to present the current status of IMN diagnosis and treatment in Chinese patients, and includes a discussion of new approaches and remaining clinical challenges.

Keywords: Review • Diagnosis • China • Glomerulonephritis, Membranous • Time-to-Treatment

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/930097>

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Background

Idiopathic membranous nephropathy (IMN) is one of the main causes of pathological nephrotic syndrome and kidney failure. IMN is a common condition, but its pathogenesis is not entirely clear. The main clinical features of IMN are varying degrees of proteinuria. Approximately 60% of patients present with nephrotic syndrome, which may lead to secondary venous thrombosis. Although about 30-35% of IMN patients experience spontaneous remission, for the most part, the disease course is long and it is relatively difficult to cure. Approximately 30% to 40% of patients eventually end up in kidney failure within 5-15 years, requiring dialysis or kidney transplantation. Among Whites, IMN accounts for around 30-40% of primary nephrotic syndrome, with the peak age of onset being 40-50 years [1]. In China, the frequency of IMN has recently increased significantly among cases of renal biopsy. Hou et al reported that the frequency of membranous nephropathy (MN) has increased significantly, nearly doubling from 2003-2006 (10.4%) to 2011-2014 (24.1%) [2]. Xu et al reviewed changes in glomerular disease types in a Chinese population over the previous 11 years and found that IgA nephropathy remained the most common pathological type, with a frequency of 28.1%, followed by membranous nephropathy, with a frequency of 23.4% [3]. After data calibration, it was found that membranous nephropathy increased 13% annually, and its incidence had a tendency to exceed that of IgA nephropathy [3]. Xu et al analyzed the characteristics of Asian IMN patients and noted that treatment of these patients could not simply follow the guidelines proposed by Kidney Disease Improving Global Outcomes (KDIGO) because of differences in race, environment, economic factors, lifestyle habits, and other factors [4,5]. In view of the differences between Eastern and Western populations, in-depth clinical evaluations of biomarkers for the diagnosis of IMN is necessary. Recent research results have prompted KDIGO to review recent guidelines (post-2012) and to re-evaluate the

diagnosis and treatment processes for IMN [5]. Therefore, this review aims to present the current status of the diagnosis and treatment of Chinese patients with IMN, and includes a discussion of new approaches and remaining clinical challenges.

Research Progress in the Pathogenesis of IMN

The main pathological feature of IMN is accumulation of sub-epithelial immune deposits, which leads to thickening of the glomerular capillary wall matrix and the formation of spikes. Immune deposits include immunoglobulin G (IgG), complement membrane attack complex, and long-term dependent known or unknown antigens. As podocytes are the main target cells in IMN, podocyte antigens are most commonly involved in immune deposits, while IgG₄ is usually the most prominent subtype of IgG deposited in IMN [6]. Activation of these immune deposits and complement leads to damage of the glomerular filtration membrane and the formation of albuminuria (Table 1).

Experimental Animal Models

In the study of IMN, the Heymann nephritis model was the earliest autoimmune animal model, the target antigen of which is the podocyte membrane protein megalin, also known as low-density lipoprotein receptor-related protein 2 (LRP2) [7]. Anti-LRP2 antibodies can be detected in patients with anti-brush edge disease but not in immune deposits or the circulation in patients with IMN. Although LRP2-mediated MN is unrelated to human IMN, Heymann nephritis still contributes extensively to our understanding of MN. Researchers have also found that repeated immunization of experimental animals with cationic bovine serum albumin (C-BSA) can induce subepithelial deposition of IgG and C3 [8]. The renal perfusion test confirmed that C-BSA first binds with the anion heparin sulfate proteoglycan

Table 1. Recent advances and remaining challenges in the diagnosis and treatment of idiopathic membranous nephropathy in China.

Current advances	Remaining challenges
Anti-PLA ₂ R detection is used widely	Genetic differences and disease susceptibility
THSD7A was identified as a second antigen to facilitate diagnosis	Environmental factors and disease susceptibility
EXT1/EXT2 proteins may represent biomarkers for MN associated with autoimmune disease	The physiological roles of PLA ₂ R and THSD7A
Progress related to the complement system	The mechanisms of podocyte injury induced by IgG ₄ anti-PLA ₂ R and anti-THSD7A
Rituximab therapy	Defining the pathogenicity of complement and CRPs

CRPs – complement and complement regulatory proteins; EXT1/EXT2 – exostosin1/exostosin2; MN – membranous nephropathy; PLA₂R – phospholipase A₂ receptor; THSD7A – thrombospondin type-1 domain-containing 7A.

of the basement membrane and then forms an immune complex with an antibody, which activates complement and leads to MN [9]. Then, a new podocyte antigen, neutral endopeptidase (NEP), was detected in alloimmune neonatal nephropathy. Maternal anti-NEP antibody enters the fetus through the placenta and reacts with NEP on fetal podocytes, resulting in the formation of epithelial immune complexes, which causes MN in newborns as confirmed in an experimental rabbit model [10]. Animal models have various defects, but they all serve as useful tools for understanding IMN.

Complement Activation and IMN

The roles of complement and complement regulatory proteins (CRPs) in IMN are currently a hot topic. Complement activation is the main route by which IMN leads to renal injury. Patients with mannan binding lectin (MBL) deficiency can develop IMN, with complement activated mainly by the alternative pathway, whereas the lectin pathway is also activated in those with wild-type MBL2 promoter and coding region variations [11]. The functional evidence indicates that anti-Fx1A-induced Heymann nephritis is characterized by podocyte injury and proteinuria induced by C5b-9 [12]. C3, C4, and C5b-9 deposits were also found in human IMN. More interestingly, Leenaerts et al have shown that an active C6-deficient rat Heymann nephritis model can still develop proteinuria in the absence of C5b-9 [13]. Injection of human autoantibody against thrombospondin type-1 domain-containing 7A (THSD7A) in mice has also been reported to cause albuminuria, but no deposition of C3 was noted [14]. Therefore, further studies are needed to clarify complement-mediated damage and its mechanism before obtaining clinical data for complement inhibitors and regulators.

New Diagnostic Biomarkers

In recent years, the most important IMN research result has been the discovery of the M-type phospholipase A₂ receptor (PLA₂R), a specific target antigen of IMN that exists on the surface of normal podocytes [15]. This study demonstrated that anti-PLA₂R antibodies could be detected in the blood of IMN patients, with a sensitivity of 78% and a specificity of more than 99%. Subsequently, IMN was further recognized as an autoimmune disease because of the discovery of THSD7A. There is no doubt that the discovery of PLA₂R and THSD7A drove great progress in basic and clinical IMN research. It was proposed that the concept of IMN should be updated to autoimmune membranous nephropathy or PLA₂R antibody-related membranous nephropathy, and its treatment should also consider the targeting of PLA₂R antibodies [5]. The application of PLA₂R and THSD7A as biomarkers for diagnosis and

prognosis has been widely accepted worldwide, including in China, and their detection is also being performed in China's third-tier cities. The current problem is how to standardize the detection of PLA₂R antibodies and avoid test errors as much as possible. However, the value of renal biopsy in IMN cannot be denied because renal pathology provides necessary information for evaluating the severity of acute kidney injury (AKI) and chronic renal fibrosis. The 2019 KDIGO Guidelines suggest that for patients with positive anti-PLA₂R antibodies, low-risk patients do not need to have renal biopsies, while high-risk patients do need to have renal biopsies, to carry out risk stratification assessment [5].

Despite this progress, scientists are continuing to look for other, effective ways to identify IMN. Sanjeev et al reported that exostosin1/exostosin2 might be the target antigen for secondary membranous nephropathy (SMN), especially when it is comorbid with autoimmune diseases such as lupus nephritis [16]. Thus, the detection of exostosin1/exostosin2 may be a useful supplement for the differential diagnosis of IMN and SMN, but its clinical practicability remains to be identified. However, so far, circulating autoantibodies to exostosin1/exostosin2 have not been validated. Caza et al identified neural cell adhesion molecule 1 (NCAM1) as a membranous antigen by mass spectrometry analysis [17]. Patients with NCAM1-positive IMN were followed to identify whether they developed lupus, which is important in determining whether NCAM1-positive or anti-NCAM1 antibodies can be a precursor to SLE [17]. In recent years, increasing attention has been paid to the role of the complement system and its regulatory factors in the pathogenesis of IMN. Neural epidermal growth factor-like 1 protein (NELL-1) defines a distinct third type of auto-antigen on IMN podocytes [18]. Sethi et al demonstrated that the predominant subclass of IgG deposition of NELL-1-associated MN is IgG1, whereas the subclass of IgG of PLA₂R- and THSD7A-associated MN utilizes IgG4 as the principal antibody [18]. Recently, Sethi et al used mass spectrometry to identify moderate spectral counts of a unique protein, semaphorin 3B, in 3 cases of IMN, and revealed that semaphorin 3B-associated MN represents a unique type of primary MN [19]. Claudia et al pointed out that complement factor H might play a crucial role in PLA₂R-related IMN, since the deterioration of proteinuria in clinical cases of IMN was closely correlated with the titer of factor H autoantibodies [20]. Therefore, the researchers suggested that factor H autoantibodies are used to assess the risk of progressive IMN in patients. Paolo et al suggested that, based on the determination of anti-PLA₂R or anti-THSD7A autoantibodies, new techniques should be explored to evaluate specific B-cell immune responses and perform immune risk classification to formulate individualized treatment strategies [21]. Notably, the clinical value of these newly discovered potential biomarkers, namely, PLA₂R and THSD7A autoantibodies, has not been consistently confirmed, especially in

the Chinese population. Therefore, it is too early to establish an effective clinical evaluation index. For now, the PLA₂R antibody is still the most valuable biomarker, and it is advocated for the detection of both circulating and tissue-bound PLA₂R. In SMN, the positive rate of anti-PLA₂R antibody is relatively low, but in some other diseases, hepatitis B virus and active sarcoidosis [22] for instance, their correlation with MN should be considered carefully. Thus, it is necessary to analyze each case comprehensively in addition to performing clinical analysis.

Genetic Background

Current studies suggest that PLA₂R antibody-associated MN is likely caused by genetic susceptibility, loss of tolerance, changes in antigen expression, and other factors, which are closely related to environmental factors and the human leukocyte antigen (HLA) gene [23]. However, the HLA alleles involved may differ in diverse ethnic groups. There is evidence that HLA-DRB1*15: 01 and HLA-DRB3*02: 02 are independent and closely bound alleles of PLA₂R-related MN in the Chinese population [24]. Cui et al revealed that DRB1*15: 01 and DRB1*03: 01 are independent risk alleles in patients with IMN, which is associated with circulating anti-PLA₂R antibodies [25]. Recently, 2 other studies used candidate gene methods; their results showed that HLA-DRB1*15: 01 is an HLA risk allele in Chinese and Japanese populations [26,27]. A genome-wide association study (GWAS) of MN indicated that the HLA-DRB1*03: 01-DQA1*05: 01 haplotype associated with HLA-DRB3*02: 02 was higher in the European white population, and there was no evidence of HLA-DRB1*15: 01 in this population [23]. It can be concluded that there may be a difference in HLA alleles between MN patients in Asia and Europe. Approximately 10% of PLA₂R-negative MN patients in Europe and North America possess THSD7A target antigens. Jia et al screened 578 Chinese patients with IMN and found that 12 cases (2%) were positive for THSD7A, suggesting that the incidence of THSD7A-associated MN in Chinese patients is lower than that in European and American populations [28]. Accordingly, race and genes are responsible for different incidences, clinical manifestations, and drug responses between Eastern and Western IMN patients. Therefore, as Japan has done [29], the formulation of diagnosis and treatment guidelines should be adjusted such that they are suitable for each country's own national conditions.

Treatment of IMN

At present, treatment recommendations following the KDIGO guidelines for IMN mainly derive from evidence-based medicine for Whites. However, due to ethnic, environmental, lifestyle, and economic differences and other factors as mentioned above, the guidelines should not be strictly applied to Chinese people. For example, the KDIGO guidelines do not

recommend hormone monotherapy for IMN, but a number of observational studies from Asia suggest that Asian IMN patients respond better to hormone monotherapy than Western patients [29-31]. In addition, the timing of the use of immunosuppressants is controversial. The principles of treatment based on risk assessment proposed at a KDIGO meeting indicate that for patients with mild symptoms and good renal function, suspending the use of immunosuppressive therapy within 3 years after precise control of albuminuria, hypertension, hyperlipidemia, and other common symptoms, is acceptable [5]. As a result, risks still exist for patients lacking proper immunosuppressive therapy. In China, traditional Chinese medicine has always been applied in clinical practice for IMN, a practice that requires additional, objective evaluation. In summary, there has been no consensus on the treatment of IMN in Asia, and China specifically, so far (Table 2), and additional evidence-based data are required to build a treatment system suitable for the Chinese population.

Renin-Angiotensin System Inhibitors

Renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), can reduce proteinuria and protect the kidney by inhibiting the RAS system, reducing glomerular filtration pressure and restoring glomerular barrier dysfunction. These compounds are also clearly defined as the first-line drug treatment approach for general IMN according to the KDIGO guidelines. Although most IMN patients from Asia have massive albuminuria [32], there are few randomized controlled trials (RCTs) on the efficacy of ACEIs/ARBs in Asia. Previous studies have shown that RAS inhibitors can reduce proteinuria by 40% to 50% and delay the development of renal failure [33]. Thus, the maximum tolerable dose of ACEIs/ARBs is recommended as treatment. In fact, the use of RAS inhibitors stemmed from experience in the treatment of other glomerular diseases. According to current evidence-based medicine and treatment experience, RAS inhibitors are still essential drugs for the treatment of IMN; however, we need to pay attention to individual dose adjustments to avoid complications such as hyperkalemia, AKI, and hypotension. The strategy of dual RAS inhibition has some supporting evidence in Chinese patients with IgA nephropathy, and the curative effect in IMN is also worth exploring. Serum anti-PLA₂R antibody levels are positively correlated with the severity of IMN and decreased renal function, and negatively correlated with spontaneous remission rate and induced remission rate [34]. The change in the severity of IMN usually lags behind the change in the level of anti-PLA₂R antibody. If anti-PLA₂R antibody levels decrease progressively and renal function is stable, non-immunotherapy can be extended for 3 to 6 months, after which the necessity of immunosuppressive therapy can be re-evaluated [35].

Table 2. A summary of the advantages and disadvantages of various treatment approaches for idiopathic membranous nephropathy in China.

Treatment	Advantages	Disadvantages
Renin-angiotensin system inhibitors	Reduced proteinuria; renal protection	High potassium, AKI; lack of evidence regarding long-term prognosis
Glucocorticoids	Inexpensive and easy to obtain; considered to have some effect on Chinese patients	Lack of RCT evidence and recommendations; adverse effects with long-term use
Cyclophosphamide	Reduced proteinuria; renal function protection; can be used in severe cases	Adverse reactions, especially gonadal suppression; lack of evidence for oral and intravenous use
Calcineurin inhibitors	Reduced proteinuria; renal protection	Price; nephrotoxicity; high recurrence rate (CSA); hyperglycemia (TAC)
Adrenocorticotrophic hormone	Reduced proteinuria; renal protection	Price; difficult to obtain; limited clinical evidence; adverse reactions
Rituximab	Alternative therapy for patients with poor response to conventional therapy; potential as first-line therapy	Price; a certain probability of nonresponse; adverse reactions
Mycophenolate mofetil	Alternative therapy for patients with poor response to conventional therapy	Lack of RCT evidence; price; adverse reactions
Traditional Chinese medicine	Improved symptoms; increased efficacy of conventional drugs; reduced adverse reactions to conventional drugs	Lack of RCT evidence and pharmacological mechanism research

AKI – acute kidney injury; CSA – cyclosporine A; RCT – randomized controlled trial; TAC – tacrolimus.

Glucocorticoids

Glucocorticoids are widely used in the treatment of glomerular diseases because of their immunosuppressive, anti-inflammatory, and podocyte-protective effects. Since corticosteroid monotherapy has shown no significant benefit in RCTs in Western populations, KDIGO does not recommend it for the treatment of IMN. However, the situation in Asia is drastically different. A retrospective study of the Chinese population showed that initial hormone therapy was effective in young IMN patients with nephrotic syndrome [30]. A small-sample study from Hong Kong demonstrated that glucocorticoid therapy (0.5 mg/kg/day, orally) used for 9 months (median 7 months) induced remission in 71% of IMN patients [31]. Japanese guidelines on the treatment of nephrotic syndrome also suggested using glucocorticoid monotherapy to prevent a decline in renal function, although it was not clear whether glucocorticoid monotherapy can effectively reduce proteinuria [29]. In some areas of China, sufficient glucocorticoids are still sometimes used as the initial treatment in IMN patients. Due to the lack of effective evaluation methods and the characteristic of spontaneous remission of IMN, it is difficult to form reliable conclusions. Although some clinical studies have indicated that glucocorticoid monotherapy works well in Asian patients with IMN, and Japanese guidelines also affirm the value of glucocorticoids,

there is no prospective RCT involving Asian patients with a high risk of progression, so it is difficult to evaluate the actual efficacy. Since the current KDIGO guidelines do not recommend hormone monotherapy for IMN, additional convincing research data are indispensable before hormone monotherapy becomes a recognized strategy.

Cyclophosphamide

Cyclophosphamide (CTX) is the most commonly used cytotoxic drug in Asia, Europe, and the United States, and is the only drug that has been shown to prevent kidney failure and death [5]. The modified Ponticelli regimen – CTX combined with methylprednisolone (MP) for 6 months every other month – is a treatment scheme recommended by KDIGO for the treatment of IMN. This therapy has been shown to alleviate nephrotic syndrome and delay the deterioration of renal function [5]. Compared with oral administration, the intravenous CTX regimen is safe and effective. To be clear, intravenous CTX also has serious adverse effects; however, the intravenous regimen shows fewer adverse effects than the oral regimen, because the accumulated dose is lower. There is no significant difference in the remission of membranous nephrotic syndrome between oral administration and intravenous CTX. So far, there

has been no direct comparison research between intravenous CTX and oral CTX. At present, many doctors in China administer monthly intravenous CTX. Meta-analyses involving Asian populations compared intravenous CTX and cyclosporine A (CSA) and showed that monthly intravenous CTX and oral corticosteroids, for 6 months, improved the remission rate and delayed the progression of renal insufficiency [36,37]. Therefore, the evidence indirectly shows that intravenous CTX is useful and monthly intravenous CTX plus an oral hormone may be an alternative treatment for Chinese patients with IMN. In China, there are some limitations to the use of CTX owing to fertility issues. Some studies have adopted an improved CTX dosage regimen to treat Chinese patients with IMN, and this improved regimen has reduced adverse reactions [38]. In Japan, the guidelines recommend that clinical use should be considered with caution because patients often have adverse reactions after using alkylating agents, and their effectiveness is relatively low [29]. Thus, it is clear that due to ethnic differences, social factors, and other reasons, the drug treatment dose for the Asian population may be different from that for European and American populations to some extent. To explore the appropriate dose for the Chinese population and to improve the scientific scheme, large-scale clinical studies are needed.

Calcineurin Inhibitors

Calcineurin inhibitors (CNIs) can not only directly stabilize the podocyte actin cytoskeleton but can also reduce the level of PLA₂R, thereby reducing proteinuria [39]. In one CNI study, only the reduction in albuminuria was used as evidence of the curative effect, and the high recurrence rate was the main defect. For now, CNIs mainly include tacrolimus (TAC) and CSA. In North America, the prescription of CSA is quite common and deemed a first-line treatment [40]. In recent years, the use of CNIs in China has increased greatly [4]. Based on a favorable response to hormones in the Chinese population, medium-dose hormones (0.3-0.5 mg/kg/day) combined with CNI therapy is often adopted by Chinese clinicians, even though this dose choice is not supported by evidence-based medicine. In China, CNIs are often used for cases in which hormone monotherapy is not effective, or in patients with severe osteoporosis or fertility requirements or intolerance to cytotoxic drugs. Thus, it is a promising substitute for CTX.

CSA is a cyclic polypeptide, composed of 11 amino acids, that selectively inhibits helper T cells and cytotoxic T cells. In some small-sample RCTs, it was confirmed that long-term low-dose CSA combined with medium-dose prednisone is safe and effective in most Chinese patients with IMN nephropathy (including those who are unable to tolerate other immunosuppressive regimens) and has better efficacy with fewer adverse effects than traditional CTX regimens [41-44]. Lin et al performed a

meta-analysis to evaluate the efficacy and safety of CSA for the treatment of IMN of Asian patients [37]. This study found that the efficacy of CSA plus glucocorticoid in the Asian population was better than that of CTX plus glucocorticoid and similar to that of TAC, with mild adverse reactions but a high recurrence rate after short-term treatment [37]. CSA is a more widely used CNI than TAC in China because of its price advantage and its characteristic of not raising blood sugar.

As a CNI, TAC also inhibits T cells, but has the disadvantage of neurotoxicity. A meta-analysis of European and American populations showed that TAC had more advantages in terms of short-term efficacy and safety than CTX, and no significant difference was found in the long-term remission rate [45]. However, it has also been reported that the recurrence rate after TAC withdrawal is much higher than that after withdrawal from oral CTX [46]. Furthermore, the function of TAC in reducing the development of kidney failure in the long term has not been directly confirmed by RCTs. Most comparative studies of TAC and CSA demonstrate that they have equivalent efficacy [47,48]. In existing clinical studies involving Chinese populations, TAC combined with corticosteroids induced IMN remission effectively and quickly [49,50]. Further, it also worked effectively for IMN with refractory nephropathy syndrome [51]. Compared with European and American populations, for Chinese populations, even low-dose TAC combined with prednisone was sufficient to induce remission in most IMN patients [52-54]. An RCT study also showed that TAC monotherapy was an effective and safe treatment for Chinese IMN patients [55]. However, the long-term efficacy of this treatment strategy requires additional long-term followup studies.

Adrenocorticotrophic Hormone

Adrenocorticotrophic hormone (ACTH), a trace polypeptide hormone secreted by the adenohypophysis, is the main regulator of adrenocortical activity. Berg et al first reported the efficacy of synthetic ACTH in 14 patients with IMN-related nephrotic syndrome and found that it not only reduced blood lipids but also reduced urinary albumin excretion by 90% [56]. In a subsequent RCT, 32 patients with IMN received synthetic ACTH for 12 months or standard periodic treatment for 6 months. The results indicated that the remission rates of the 2 groups were similar (the rates in the ACTH and alkylating agent groups were 87% and 75%, respectively). However, ACTH treatment caused only mild adverse effects [57]. The positive results of the above trials have led to new interest in ACTH as a potential drug for the treatment of IMN, and additional small-scale studies have recently been reported [58-60]. However, a prospective open-cohort study evaluated the safety and efficacy of synthetic ACTH for the treatment of IMN patients at risk of renal failure [61], and these results showed that synthetic

ACTH was not as effective as CTX in inducing remission in high-risk patients with IMN. Moreover, it had many adverse events. Therefore, the study concluded that synthetic ACTH is not recommended as a standard treatment for IMN. The clinical use of ACTH remains relatively low.

Rituximab Therapy

In recent years, with the successive discoveries of the anti-PLA₂R and THSD7A antibodies, it has been suggested that IMN is associated with the deposition of immune complexes on the epithelial side of the glomerular basement membrane caused by humoral immunity mediated by B lymphocytes [62]. Rituximab (RTX) is a chimeric mouse/human monoclonal antibody that induces B-cell apoptosis and can be used to treat MN by eliminating B cells. According to the KDIGO guidelines, RTX should be considered for patients with severe nephrotic syndrome or for whom traditional immunosuppressive therapy is ineffective. Research from Peking University indicated that for IMN patients with high risk of progression of renal insufficiency, who were unresponsive to other immunosuppressive therapy, RTX could relieve albuminuria and stabilize renal function [63]. The cumulative incidence of partial remission with RTX was lower than that with CTX, but there were no significant differences in the probability of complete remission or the incidence of endpoint events [62]. Recent reports by Fervenza et al showed that RTX was not inferior to cyclosporine in inducing remission of MN [64]. After cyclosporine treatment, albuminuria was significantly relieved, but the recurrence rate was high, while the anti-albuminuria effect of RTX lasted longer than that of cyclosporine [65]. Therefore, at present, the call for RTX to become a first-line treatment for IMN is strong [65,66]. Recently, published membranous nephropathy trial of rituximab (MENTOR) studies have shown that rituximab may replace cyclosporine as a first-line immunosuppressive drug [64]. Some studies also evaluated the combination of RTX and other immunosuppressants that had achieved solid results [67]. Although some encouraging results have been obtained in the study of RTX, the nonresponse rate of RTX treatment is approximately 35%. Evidence suggests that its long-term safety and efficacy is superior to that of other immunosuppressants for the treatment of IMN [35,68]. However, this evidence is not yet convincing enough and needs to be further evaluated in clinical studies with large samples and long-term followup.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is often used for the treatment of glomerular diseases, as it inhibits T and B lymphocytes by inhibiting the activity of hypoxanthine nucleotide dehydrogenase in the ab initio synthesis pathway. However, for the

initial treatment of IMN, the KDIGO guidelines do not recommend MMF because of the low power of the evidence indicating that the effect of MMF plus corticosteroids is similar to that of CTX plus corticosteroids [65]. There are also studies on the treatment of IMN patients with severe albuminuria with MMF combined with low-dose corticosteroids; the results of these studies show efficacy similar to that of CSA [69]. MMF monotherapy has almost no effect on the treatment of IMN [70]. The data from an RCT in Hong Kong showed that MMF combined with hormones was effective in the treatment of IMN patients with nephrotic syndrome [71]. Compared with other commonly used cytotoxic drugs, MMF has the potential benefit of a reduced hormone dosage and reduced corresponding adverse reactions. Yet, due to the high price of MMF, some adverse reactions, the difficulty of concentration detection, and other factors, Chinese clinicians do not regard it as a first-choice treatment. Nevertheless, for patients with poor responses to conventional CTX and CNIs and patients who cannot tolerate RTX, MMF can be considered as an alternative choice.

Traditional Chinese Medicine

In China, traditional Chinese medicine is widely used for the treatment of IMN. Tripterygium wilfordii multiglycosides (TWGs) and Shenqi are the most widely used traditional Chinese medicines. A prospective cohort study of the Chinese population showed that the remission rate of the TWG plus hormone group was comparable to that of the TAC plus hormone group [72]. A Chinese multicenter RCT showed that the improvement in albuminuria in the 2 groups was similar to that of the traditional Ponticelli strategy, while Shenqi had the advantage of restoring the estimated glomerular filtration rates (eGFR) in patients with IMN. More importantly, Shenqi treatment did not cause serious adverse reactions [73]. Han et al studied the efficacy of Shenjiu prescription (SR) and Qingre Moshen granules (QMG) in the treatment of IMN, and found that SR plus QMG was effective in patients with IMN who failed to respond to a variety of Western medicines [74]. This strategy improves the level of cellular immunity and modifies the abnormal expression of IL-2. However, the main obstacle in the use of traditional Chinese medicine is obtaining medical evidence through high-level basic and clinical research to obtain international acceptance.

New Approaches and Remaining Clinical Challenges

Overall, IMN is not only a common pathological type of primary nephrotic syndrome, but also one of the main causes of kidney failure in China, and its treatment is still a major challenge in clinical practice. In view of the differences between Eastern

and Western populations, in-depth clinical evaluations of biomarkers for the diagnosis of IMN is necessary. Further study is warranted in PLA₂R and THSD7A antibodies, exostosin1/exostosin2, neural epidermal growth factor-like 1 protein, neural cell adhesion molecule 1, semaphorin 3B, factor H autoantibody, and the response of the Chinese population to these treatments. In terms of treatment, the current KDIGO guidelines, especially those regarding hormone and immunosuppression treatment timing, program selection, and other controversial aspects, do not fully take into account the characteristics of the Asian population. Therefore, a prominent problem that needs to be solved urgently is how to optimize the diagnosis and treatment of Chinese patients with IMN and improve their prognosis. The alternative use of CTX combined with glucocorticoids (CTX plus MP), which was once advocated, is not widely used in China, and the usage of CTX is not uniform in China. Moreover, due to outstanding adverse reactions caused by CTX, its use is subject to many restrictions. The use of CNIs has gradually increased in China over recent years. Although CNIs help improve the overall remission rate in IMN patients, the recurrence rate is high, and long-term use leads to nephrotoxicity, so its use should be considered on a case-by-case basis. In recent years, some new drugs, such as RTX and ACTH, have been tested worldwide. However, the sample sizes in the preclinical trials of these drugs were small, with short average followup times. In addition, the long-term kidney survival rate has not been evaluated. Therefore, continuous observation is still required. Small-sample observation of RTX in clinical practice has yielded results indicating that RTX could be a

promising alternative for refractory IMN. RTX-based or other B-cell targeted regimens represent the future direction of IMN treatment. The traditional Chinese medicine TWG has shown a degree of efficacy in the clinic, but clarifying its mechanism and carrying out effective RCTs is still a problem to be considered.

Conclusions

IMN is a disease with different diagnostic and therapeutic challenges in China compared with other countries. The recommendations from the 2012 KDIGO clinical practice guidelines may not apply to the Chinese population, due to ethnic, environmental, economic, and lifestyle differences. Although Chinese clinical guidelines are awaited, treatment strategies for patients with IMN in China include renin-angiotensin inhibitors, corticosteroid monotherapy, cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, adrenocorticotropic hormone, biologics such as rituximab, and also some traditional Chinese medicines.

Acknowledgements

Thanks to Lily Wu from The Chinese University of Hong Kong for the modification of the manuscript.

Conflicts of Interest

None.

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