Glomerular Diseases

Review Article

Glomerular Dis 2022;2:30–41
DOI: 10.1159/000520039

Received: July 4, 2021
Accepted: October 1, 2021
Published online: October 12, 2021

IgA Nephropathy: A Chinese Perspective

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Keywords
Genetics · Glomerulonephritis · IgA nephropathy · Pathogenesis · Treatment

Abstract
Background: IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide and remains a leading cause of chronic kidney disease and end-stage renal disease. The disease prevalence, clinical and pathological phenotypes, the underlying pathogenic molecular mechanisms, and the response to treatments are highly heterogeneous in different ethnic populations, which raise the concern that IgAN may differ across different parts of the world. ***Summary:*** From a Chinese perspective, we stated the disease burden of IgAN, summarized genome-wide association studies and research into pathological molecules, and compared them with findings based on other populations. The emerging biomarkers, indigenous clinical trials, and major challenges for Chinese researchers and nephrologists in studying IgAN are also discussed. ***Key Messages:*** In this review, we described a higher risk of major susceptible loci in mucosal immunity, IgA production, and complement activation pathways in Chinese patients with IgAN. With our understanding of the pathogenesis of IgAN, novel biomarkers are emerging. Although there are challenges for conducting high-quality clinical trials in China, it is still feasible to conduct innovative and well-designed studies of IgAN. In the future, international collaborations on research infrastructure would be helpful to advance clinical and basic research in China.

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Introduction

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide and remains a leading cause of chronic kidney disease and end-stage renal disease (ESRD) [1–3]. Diagnosis of IgAN is established by the presence of immunoglobulin A1 (IgA1) as the dominant or codominant immunoglobulin in the glomerular mesangium on examination of renal biopsy [4–7]. Although the exact pathogenesis of IgAN remains to be determined, a multi-hit theory has been proposed [8]. The fundamental steps are the generation of galactose-deficient IgA1 (Gd-IgA1); antibody formation against Gd-

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IgA1; immune complex formation and mesangial deposition; and complement activation. This culminates in macrophage infiltration and tubulointerstitial inflammation, leading to renal damage. However, there are substantial variations in the prevalence and phenotype of IgAN globally, which might reflect a complex, yet poorly understood, interaction between genetic and environmental factors that modulate the disease phenotype in individuals and across different populations. Notably, there is a clear West-to-East prevalence gradient, with the disease being most common in China (45–58% of primary glomerulonephritis) and other Asian countries (47% in Japan, 28% in Korea, and 45% in Singapore), compared with that in European countries (10–35% of primary GN) [9–16]. Generally, the disease affects males more frequently than females, with a male-to-female ratio as high as 3:1 in Europeans [17]; however, this ratio approximates to 1:1 in China, a pattern that might be shaped by differences in genetics or local environments [18, 19]. These differences might reflect differences in examination or biopsy policies among populations. For instance, systematic mass screening of urine is more common in some Asian regions (Hong Kong, Japan, Korea, and Singapore) than in Western countries. Persistent microscopic hematuria and/or mild proteinuria in apparently healthy individuals might not be recognized as possible IgAN, and therefore IgAN might be underestimated in Western countries. Furthermore, different indications for kidney biopsy are adopted by nephrologists in individuals with persistent urinary abnormalities [20]. Finally, the ethnic heterogeneity of IgAN might also result from a true geographical variation in the disease.

China's population exceeds 1.4 billion people and as a nation, it has among the highest prevalence of IgAN. This results in a heavy disease burden. Importantly, recent evidence from genetic, cell biology, and clinical studies has provided us with a chance to better understand IgAN from a Chinese perspective, which will advance our understanding and improve therapy in a more specific way.

Disease Burden of IgAN in China

Although in most cases IgAN is a chronically progressive disease and is not life-threatening, it is nevertheless important to develop effective treatment, especially because it often affects young people, in whom a long and progressive disease course might lead to ESRD. A high frequency of IgAN has been observed in children and junior high school students, both in clinical practice and in nationwide mandatory mass urine screening studies in Chinese, Japanese, and Korean schools [21, 22]. Moreover, 1 study analyzed 34,630 hospitalized patients undergoing native renal biopsy in China retrospectively and found that IgAN (24.09%) was the most common primary glomerulonephritis [23]. When the number of renal biopsies increased, the percentage of IgAN diagnoses also increased. Many retrospective studies have shown that 30–50% of biopsy-proven patients with IgAN develop ESRD in approximately 20 years after diagnosis [24, 25]. The increasing incidence of ESRD has a major impact on the need for dialysis, including maintenance hemodialysis and peritoneal dialysis [26]. However, not all patients have access to renal replacement treatment because of the high cost of treatment [26], which places a large economic burden on individuals and health care resources. Given the high prevalence and its associated morbidity and cost, IgAN has become a major public health problem for the Chinese government [27]. Thus, there is an urgent need to understand the underlying pathogenic mechanism of IgAN, especially from a Chinese perspective.

Pathogenesis of IgAN from a Chinese Perspective

Genetic Studies

Genome-wide association studies (GWASs) have revolutionized our capacity to identify genetic susceptibility loci in many diseases, including IgAN. To date, 6 large GWASs have been performed in European populations (France, Italy, UK, and the USA) and/or Chinese populations with IgAN [28–33]. Overall, 21 loci were detected (Table 1). Most of the detected susceptibility loci were shared between European and Chinese populations, and are involved in the regulation of mucosal immunity (*VAV3, DEFA*, and *CARD9*), IgA production (*ST6GAL1, TNFSF13*, and *HORMAD2*), antigen presentation and adaptive immunity (*MHC*), and complement activation (*CFH, CFHR3-1*, and *ITGAM-ITGAX*) pathways [34–36], which were largely consistent with the multi-hit pathogenesis model of IgAN. The risk allele frequencies and odds ratios of the genes involved in antigen presentation (*MHC*), mucosal immunity (*TNFSF13* and *HORMAD2*), leukocyte-specific complement receptor formation (*ITGAM-ITGAX*), and alternative complement pathway activation (*CFH* and *CFHR3-1*) tend to be higher and larger in Han Chinese populations than in European populations. Accordingly, more severe clinical presentation and higher risk of disease progression, as well as active lesions, such as mesangial hypercellularity and crescents [37, 38],

Table 1. Susceptibility loci of IgAN discovered in GWASs

Locus	SNP	RA	Gene	Asians			Europeans		
				RAF	OR	*p* value	RAF	OR	*p* value
1p13	rs17019602	G	VAV3	0.19	1.15	2.00E−03	0.19	1.19	8.00E−07
1p36.13	rs2240335	A	**PADI4**	**0.60**	**1.18**	7.07E−03	0.41	1.16	1.54E−02
1q23.1	rs6427389	C	**FCRL3**	**0.79**	**1.13**	1.01E−01	0.66	1.05	3.96E−01
1q32	rs6677604	G	**CFHR3,1-del**	**0.93**	**1.57**	6.70E−07	0.8	1.3	2.40E−09
6p21	rs7763262	C	**HLA-DR/DQ**	**0.72**	1.3	1.20E−10	0.69	1.49	1.20E−30
	rs9275224	G		**0.59**	**1.38**	7.70E−14	0.51	1.34	8.90E−18
	rs2856717	G		**0.77**	**1.38**	5.00E−10	0.62	1.21	4.70E−08
	rs2523946	C	**HLA-A**	0.54	1.21	1.74E−11			
	rs660895	G	**HLA-DRB1**	0.28	1.34	4.13E−20			
	rs1794275	A	**HLA-DQA/B**	0.19	1.30	3.43E−13			
	rs2071543	G	TAP2/PSMB9	–	1.41	2.10E−09	–	0.99	8.50E−01
	rs9275596	T	**HLA-DR/DQ**	**0.80**	**1.69**	1.10E−19	0.65	1.35	1.60E−15
	rs1883414	G	**HLA-DP**	**0.78**	**1.27**	4.60E−06	0.68	1.2	5.00E−07
	rs9357155	A	PSMB8, PSMB9	0.80	1.37	3.20E−08	0.87	0.97	5.40E−01
6p25.3	rs6942325	G	DUSP22.IRF4	0.79	1.33	1.04E−04	0.99	1.54	1.18E−01
8p23	rs2738048	T	**DEFA**	0.68	1.23	1.30E−07	0.69	1.02	5.80E−01
	rs10086568	A		0.27	1.2	1.10E−05	0.33	1.14	1.60E−05
	rs2738058	T		0.73	1.31	5.75E−10			
	rs9314614	C		0.40	1.19	3.54E−05			
	rs12716641	T		0.78	1.26	7.80E−07			
9q34	rs4077515	T	CARD9	0.28	1.11	8.00E−03	0.4	1.18	2.10E−08
16p11.2	rs11150612	A	**ITGAM-ITGAX**	**0.75**	1.17	2.50E−04	0.36	1.19	1.20E−08
	rs11574637	T		**1.00**	–	–	0.82	1.32	8.10E−13
	rs7190997	C		0.72	1.21	4.00E−05			
17p13.1	rs3803800	A	**TNFSF13**	**0.32**	**1.17**	4.60E−05	0.2	1.08	2.50E−02
	rs4227	G		0.24	1.23	4.31E−10			
22q12	rs2412971	G	**HORMAD2, MTMR3, LIF, OSM**	**0.67**	**1.35**	6.00E−11	0.54	1.13	1.50E−04
	rs2412973	A		–	1.33	2.20E−10	–	1.14	1.40E−04
	rs12537	T		0.16	0.78	1.17E−11			
Han Chinese									
3q27.3	rs7634389	C	**ST6GAL1**	0.45	1.15	6.80E−04			
8q22.3	rs2033562	C	**ODF1-KLF10-UBR5**	0.51	1.18	7.98E−05			
11p11.2	rs2074038	T	**ACCS, PHACS, EXT2**	0.32	1.21	3.36E−05			

Note: Genes with higher risk allele frequency or larger odds ratios in Asian/Chinese populations were highlighted in bold. SNP, single nucleotide polymorphism; RA, risk allele; RAF, risk allele frequency; OR, odds ratio; IgAN, IgA nephropathy; GWASs, genome-wide association studies; CFHR, complement factor H-related protein.

have been reported in Chinese patients with IgAN than in European patients. More interestingly, the relative importance of each "hit" might vary in different ethnic populations, providing genetic insights into more targeted treatment in China. In the following sections, we will focus more specifically on the well-studied mucosal immunity, Gd-IgA1 production, and complement activation.

Mucosal Immunity

IgA production and abnormalities in circulating IgA are the initial events in IgAN pathogenesis [8]. The deposited IgA and the ensuing response of the mesangium are crucial to IgAN development [2]. The source of this pathogenic IgA in IgAN is an emerging area of study. Both mesangial and serum IgA are polymeric, and because polymeric IgA is normally produced at mucosal surfaces, this suggests that IgAN is intimately linked with abnormal mucosal immune responses to microorganisms [2]. In addition, novel associations at *ST6GAL1* on chromosome 3q27.3, *ACCS* on chromosome 11p11.2, and *ODF1-KLF10* on chromosome 8q22.3 were identified in a Chinese population [39]. Most of these loci implicate

genes involved in mucosal immunity in the gut and IgA production [39]. These findings supported the concept that mucosal immunity might play a fundamental role in the pathogenesis of IgAN because hematuria is one of the typical clinical features of the disease and gross hematuria is frequently seen after mucosal infections [40]. The immune response activated against mucosal antigen exposure to bacterial, viral, or alimentary components can lead to the activation of dendritic cells, T cells, and B cells, and eventually, the production of IgA. Therefore, attempts to modulate the mucosal immune system would be beneficial for patients with IgAN.

As suggested, most of the identified mucosal-related loci fulfill the immunological function not only of gut-associated lymphoid tissue (GALT), but also nasopharyngeal-associated lymphoid tissues (NALT)/bronchial-associated lymphoid tissues. Using the gddY mouse model of spontaneous IgAN, NALT was suggested to be the major induction site of IgAN [41]. Accordingly, tonsillectomy has been shown to improve urinary findings and reduce IgA deposits in patients from China and Japan, but this was not observed in patients from European countries [42, 43]. By contrast, in a recent clinical survey on the presentation and clinical management of patients with IgAN in Europe and Japan, gastrointestinal complications, including inflammatory bowel diseases and celiac disease, were more frequent in European patients than in Japanese patients [44]. Such findings are compatible with the clinical trial NEFIGAN, in which targeted release of budesonide in the distal ileum was reported to reduce proteinuria and stabilize renal function in patients with IgAN [45]. Further exploration of the molecular mechanisms of GALT, NALT, and bronchial-associated lymphoid tissues, as well as the immune crosstalk between them, would provide more insights into the targeting mucosal therapy in different ethnic groups.

Gd-IgA1 Levels

Gd-IgA1 plays an essential role in the postulated pathogenesis of IgAN [8]. Elevated levels of Gd-IgA1 have been reported in patients with IgAN of Caucasian [46, 47], Asian [48, 49], and African ancestry [50]. A higher Gd-IgA1 quartile was associated with the progression of renal disease in a large cohort of Chinese patients with IgAN [49]. However, variations identified in *C1GALT1C1* and *C1GALT1* explain approximately 7% of the variability in circulating Gd-IgA1 in European patients, but only 2% in Chinese patients [51, 52]. A recent GWAS of Gd-IgA1 in China identified 2 new variants, *GALNT12* and *C1GALT1* [53]. Moreover, despite the higher incidence and poorer prognosis of IgAN in China, the *C1GALT1* risk haplotype is found 10 times less frequently in Chinese patients than in European patients [54], suggesting heterogeneity of the pathogenic role of Gd-IgA1 between Caucasian and Chinese patients with IgAN. Actually, there is a wide distribution in the proportion of IgA1 O-glycoforms in the serum, and there is significant overlap in the levels of these IgA1 O-glycoforms between patients with IgAN and healthy individuals. Moreover, levels of Gd-IgA1 in Chinese cases of IgAN were lower than in Caucasian cases and were even comparable with those seen in a healthy Caucasian population [55]. The overlap in the levels of Gd-IgA1 between patients with IgAN and healthy controls, as well as the comparable levels of Gd-IgA1 between Chinese patients with IgAN and healthy controls in Europe raise important and as yet unanswered questions concerning the pathogenic importance of changes in IgA1 O-galactosylation in different ethnic populations. Besides the quantity of Gd-IgA1, host genetic susceptibility and different sites of Gd-IgA1 [56] might also play an important role, representing features that deserve additional study.

Complement Activation

Complement proteins are activated in IgAN. Complement component C3 frequently colocalizes with IgA, while C1q is absent, suggesting that activation of complement mainly occurs via the alternative pathway or lectin pathway in IgAN. C3 is the most abundant complement component, found in up to 90% of cases in renal biopsy specimens [57, 58]. Apart from C3, other complement elements can also be codeposited with IgA. More recently, mass-spectrometry analysis of micro-dissected glomeruli from IgAN kidney biopsy specimens showed significant amounts of alternative-pathway regulation proteins, such as factor H, and complement factor H-related proteins (CFHRs) 1, 2, 3, and 5 [59]. Clinically, a Chinese study of 202 patients with IgAN showed that urinary factor H levels were significantly higher in patients with IgAN than in healthy controls, and were also associated with severe histological findings [60]. Concurrently, another study from China, including 1,126 patients with IgAN and regular follow-up and 153 unrelated healthy individuals, demonstrated that circulating CFHR5 levels were elevated significantly in patients with IgAN and were associated with a lower estimated glomerular filtration rate (eGFR), hypertension, and severe Oxford-T and Oxford-C scores [61]. Genetically, GWAS data showed that a common combined deletion of *CFHR1* and *CFHR3* has a protective function in IgAN in a Han Chinese pop-

Table 2. Prediction models of IgAN

Populations	Sample size	Clinical variables	Pathogenic index	C statistics	External validation	Reference
Japanese	790	Proteinuria, serum albumin, hematuria, diastolic blood pressure, total protein	Customized scoring	–	Yes [86]	[70, 71]
Chinese	1,025	Age, serum albumin, hypertension, serum uric acid, hematuria, urinary protein, serum creatinine	Oxford classification score (M, S, T)	0.89	No	[72]
Asian	349	Urinary protein, mean arterial pressure	Oxford classification score (M, T)	0.88	No	[73]
Caucasian	332	Blood pressure, proteinuria	Customized scoring	–	Yes [87]	[74]
Multiple ethnic	3,927	eGFR, blood pressure, and proteinuria at biopsy; kidney biopsy (MESTC), age, medication use, race	Customized scoring	0.82 (with race)	No	[75]
Chinese	934	Sex, age, eGFR, hemoglobin, proteinuria	Oxford classification score (M, T)	0.86	No	[88]

IgAN, IgA nephropathy.

ulation [62]. In addition, it was reported that rare variants of *CFHR5* contribute to genetic susceptibility to IgAN [61]. Moreover, the presence of mannan-binding lectin (MBL) with IgA, C3, and C4d is consistent with activation of the lectin pathway in some patients [1]. MBL deposits, found in about 25–35% of patients, have been associated with higher proteinuria, lower eGFR, and more severe histopathological lesions [63, 64]. In a Chinese study of 162 patients with IgAN, urinary MBL levels were associated significantly with impaired renal function and increased proteinuria [65]. A study that measured *MBL2* variants and MBL levels in 749 patients with IgAN and 489 healthy controls from a Chinese cohort also found that patients with IgAN and MBL deficiency had a higher incidence of prodromic infections and gross hematuria compared with those with sufficient MBL levels (100–3,540 ng/mL) and that patients with high MBL levels (>3,540 ng/mL) had more severe proteinuria and a higher proportion of crescents, which suggested that MBL contributes to IgAN pathogenesis through multiple mechanisms [66]. These observations have generated tremendous interest in the important role of complement activation in Chinese patients with IgAN, and targeting complement pathways could be a promising treatment approach.

Collectively, the identification of IgAN susceptibility loci from GWASs has greatly advanced our understanding of the disease pathogenesis of IgAN. The identification of susceptibility loci shared between different ethnic populations, as well as those detected in the Chinese population, suggests that the relative importance of each "hit," such as Gd-IgA1 production and complement activation, might vary in different ethnic populations. In the future, a better understanding of the pathogenic pathways operating in different ethnic populations and the discovery of better biomarkers might help to develop more precise targeted treatment for IgAN.

Risk Prediction and Monitoring of IgAN in China

IgAN is characterized by various clinical and histological manifestations, and some patients with high risk show a progressive disease course. Identifying the risk of progression early in the course of the disease remains problematic. Several well-established clinicopathogenic variables, including eGFR, proteinuria, blood pressure, body mass index, and Oxford classification scores, have been reported to be associated with disease progression [67–69]. Using these clinicopathogenic variables, several risk-prediction models have been developed (Table 2). Although their discrimination performance is well accepted (C statistics >0.85), only a few of them were confirmed using external validation and were able to identify high-risk patients accurately [70–74]. To account for ethnic differences, Barbour et al. [75] developed prediction models that were shown to be accurate and valid methods to predict disease progression and patient risk stratification in IgAN in multiethnic cohorts [75, 76]. An updated tool for use in children has been reported [77]. However, in an independent external validation study in China, the risk probability over 3 years was shown to be overestimated [78], suggesting the necessity to develop prediction models suitable for Chinese patients with

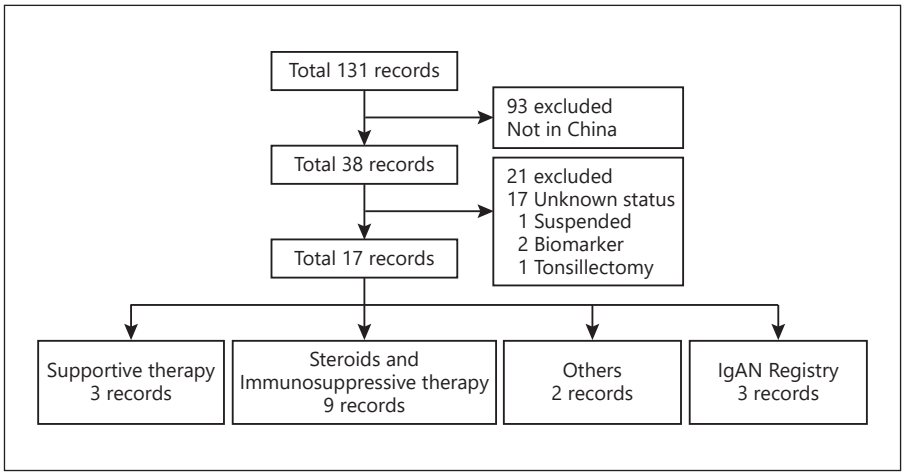

Fig. 1. Process for the identification of eligible clinical trials in IgAN in China. Results of a systematic search on IgAN in China using ClinicalTrials.gov (https://clinicaltrials.gov/). IgAN, IgA nephropathy.

IgAN. In recent years, the application of machine learning has greatly advanced, and efforts are being made to develop prediction and risk stratification models in the Chinese population [79]. Using routinely available characteristics (urine protein excretion, global sclerosis, and tubular atrophy/interstitial fibrosis) and the combination of a machine learning algorithm and survival analysis, Chen et al. [72] developed a prediction model in a multicenter retrospective cohort study of 2,047 patients with IgAN. This model was reported to stratify risk for kidney disease progression in the setting of Chinese IgAN. Although the risk of progression in IgAN can be predicted reliably based on clinical and histological parameters, as with all risk-prediction models, development and validation are only the first step, and further validation of the risk-prediction models in real-world cohorts are still needed.

More importantly, in recent years, novel biomarkers involved in the pathogenesis of IgAN, including serum IgA, the IgA/C3 ratio, polymeric and secretory IgA levels, Gd-IgA1 and circulating autoantibodies to Gd-IgA1, soluble CD89, complement components, microRNAs, and peripheral blood mononuclear cell phenotyping, are prime candidates to become diagnostic biomarkers [80]. Prediction models could be further improved by combining these biomarkers. In addition, with the development of novel molecular techniques, more biomarkers are emerging. For example, using single nuclei RNA sequencing and miRnomics, a cluster of miRNAs has been identified as being associated with kidney fibrosis and interstitial scarring. Some of these miRNAs are associated specifically with mesangial inflammation and modulation of endocapillary hypercellularity in Chinese patients with IgAN. Furthermore, a proof-of-concept study that integrates genomic data generated from next-generation sequencing, whole-exome sequencing, and whole-genome sequencing, into risk scores for prognostication and treatment decision-making has been attempted in European patients (IgAN-Genetic Risk Score, IgAN-GRS). Moreover, using updated proteomic or metabolomic methods, noninvasive biomarkers from blood or urine for the early diagnosis of IgAN are emerging rapidly.

Collectively, a wide range of studies have been conducted and various biomarkers have been introduced. Considering the heavy disease burden and the significant heterogeneity of IgAN in China, greater efforts should be made to develop risk-prediction models by combining these biomarkers, which would help to predict the risk of renal failure and identify patients who might benefit from more aggressive therapy.

Clinical Trials of IgAN in China

Our increased understanding of the pathogenesis of IgAN and racial differences, and the large number of patients with IgAN in China, provide a great potential to conduct clinical trials and seek precision therapies. We summarized the registered clinical trials of IgAN in China through searching ClinicalTrials.gov (Fig. 1). Overall, 17 trials (including 3 IgAN registries) of IgAN were conducted by investigators in China. However, as shown in Table 3, most of these trials tend to be limited by relatively small numbers of patients or their single-center nature, and few of them were cited in the KDIGO guidelines of glomerular diseases. Notably, despite challenges for high-quality clinical trials, it is feasible to perform innovative and well-designed studies in China.

Glomerular Dis 2022;2:30–41
DOI: 10.1159/000520039

Table 3. Chinese clinical trials in IgAN (including completed and ongoing trials)

No	Sponsor/institute	Participants	Completion time	Intervention	Conclusion	Reference
Supportive therapy						
NCT00922311	The University of Hong Kong	25	December 2010	Aliskiren	Aliskiren confers an antiproteinuric effect in IgAN patients with significant residual proteinuria	PMID: 21680850
NCT00426348	Guangdong Provincial People's Hospital	75	January 2013	Probucol in combination with Valsartan	Probucol combined with valsartan led to a more rapid decrease of 24-h urinary protein excretion than valsartan alone	PMID: 24191893
NCT02942381	Peking University First Hospital	60	January 2018	Hydroxychloroquine sulfate	HCQ in addition to optimized RAAS inhibition significantly reduced proteinuria in patients with IgAN over 6 months without evidence of adverse events	PMID: 30922594
Steroids and immunosuppressive therapy						
NCT01451710	Nanjing University School of Medicine	30	May 2012	Prednisone or prednisolone	Corticosteroid therapy is likely effective and safe for IgAN with minimal change-like lesions (MCD-IgAN) patients	PMID: 23787555
NCT01560052	Peking University First Hospital and The George Institute	262	June 2017	Methylprednisolone	Although there was potential renal benefit in the patients receiving corticosteroids, the study was terminated early as treatment with corticosteroids was associated with an increased risk of serious adverse events	PMID: 28763548 (TESTING full dose) (TESTING low dose is ongoing)
NCT00657059	Sun Yat-Sen University	151	May 2019	MMF	NA	
NCT01269021	Nanjing university School of Medicine	176	April 2014	MMF plus lower dose of prednisone	MMF was shown to be an effective steroid-sparing agent but did not increase the rate of proteinuria remission at 6 and 12 months	PMID: 28215945
NCT00301600	Nanjing University School of Medicine	40	January 2006	MMF	NA	
NCT00863252	The University of Hong Kong	40	March 2009	MMF	MMF was similarly shown to decrease proteinuria	PMID: 16014059 PMID: 20032964
NCT01854814	Nanfang Hospital of Southern Medical University	232	December 2021	MMF compared with losartan alone	On going	–
NCT04833374	Sixth Affiliated Hospital, Sun Yat-Sen University	200	December 2023	Steroid (methylprednisolone)	On going	–

Table 3 (continued)

No	Sponsor/institute	Participants	Completion time	Intervention	Conclusion	Reference
NCT04020328	Shenzhen Second People's Hospital	70	May 2022	Leflunomide plus low-dose corticosteroid	On going	–
Others						
NCT04525729	Ruijin Hospital	116	December 2023	Rituximab combining with RASi compared with RASi	On going	–
NCT03418779	Guang'anmen Hospital of China Academy of Chinese Medical Sciences	60	December 2023	Chinese medicine (Yi-Qi-Qing-Jie Herbal Compound) combined with immunosuppression therapies	On going	–

MMF, mycophenolate mofetil; IgAN, IgA nephropathy.

The TESTING study (NCT01560052) is an international clinical trial designed to evaluate the long-term efficacy and safety of oral methylprednisolone on a background of RAS inhibitor therapy in patients with IgAN at a high risk of progression. The TESTING full dose study, including 262 patients from 67 locations globally (majority Chinese) with proteinuria >1 g/day and eGFR 20–120 mL/min per 1.73 m^2, randomized to corticosteroids or placebo, demonstrated a potential renal benefit in the patients receiving corticosteroids [81], although the study was terminated early because treatment with corticosteroids was associated with an increased risk of adverse events [81]. Interestingly, the major outcome of the TESTING study was different from the STOP-IgAN study, which included 162 European patients with proteinuria >0.75 g/day randomized to optimal supportive care, with or without immunosuppression [82]. The STOP-IgAN study showed that the addition of immunosuppressive therapy to optimal supportive care did not change the rate of eGFR loss [82]. The difference in the ability to demonstrate benefit from immunosuppressive therapy in IgAN in TESTING versus STOP-IgAN is most likely explained by differences in patient characteristics. Patients in the TESTING study (majority Chinese) appeared to show more aggressive disease progression, as seen in the higher baseline proteinuria levels and more rapid rates of eGFR decline. Previously, in Chinese patients with IgAN with higher risk, mycophenolate mofetil (MMF) treatment was shown to be effective. In a Chinese clinical trial, 176 patients with IgAN with active proliferative lesions were randomized to MMF with low-dose steroids versus steroids alone. MMF was shown to be an effective corticosteroid-sparing agent in proteinuria remission at 6 and 12 months (NCT01269021) [83]; however, MMF efficacy was not observed in a non-Chinese IgAN population. Therefore, the successful experiences from the above-mentioned clinical trials highlight the importance of the "right population" and the "right time" for treatment. In the future, designing and conducting high-quality clinical trials, especially those with precision medicine designs, and clinical trials stratified by clinical or pathological phenotypes, might be more informative for Chinese patients, based on the high heterogeneity and more severe clinical and pathological phenotypes in Chinese patients with IgAN. Besides clinical trials conducted by independent investigators, Chinese nephrologists also actively participate in novel international clinical trials in IgAN, including those assessing therapies targeting specific targets in disease pathogenesis, such as the

complement Factor B Inhibitor-LNP023 [84], the MASP-2 Inhibitor-OMS721 (Narsoplimab) [85], and the targeted-release budesonide-Nefecon (45), among others. Pragmatic clinical studies based on real-world experience might offer an important option to Chinese patients with IgAN and investigators. Three upcoming IgAN databases are registered in China. One is the IgA Nephropathy Registration Initiative of High Quality (NCT03001947), which will recruit 10,000 participants with a 10-year follow-up duration and should be completed before 2026. Another is the Chinese Registry of Prognostic Study of IgA Nephropathy (NCT04858724), which will recruit 2,000 participants with a 12-month follow-up duration and will be completed before 2030. The last 1 is the Registry of IgA Nephropathy in Chinese Children (RACC) (NCT03015974), which aims to identify a safe and effective treatment option for IgAN in children and will perform prospective registration among 25 pediatric nephrology medical centers in China with 1,200 participants and a 24-month follow-up duration.

Challenges and Future Directions

Advances in genetic, basic, experimental, and clinical studies have greatly improved our understanding of the pathogenesis of IgAN and have provided us with potential novel biomarkers and therapeutic strategies. However, explaining the heterogeneity of IgAN remains a challenge.

First, a wide spectrum of clinical and pathological features of IgAN has been observed, implying that IgAN might not be the same disease across populations, or even within the same ethnic group. It is truly challenging that the diagnosis of IgAN mainly depends on renal biopsy with a demonstration of predominant IgA1 deposition in the glomerular mesangium. With a more in-depth understanding of IgAN pathogenesis, clearer diagnostic criteria could be expected in the future.

Second, the impact of confounding environmental factors and the difficulty of movement of human tissue across borders mean that we can never be sure if a difference across populations is simply the result of a difference in laboratory methodologies. In the future, trans-ethnic genetic studies or multicenter-based basic research collaborations are needed to truly compare the differences between populations.

Third, the current trials in developed countries might not benefit patients in China because of a distinct etiology. Although a culture of appreciation for high-quality clinical trials is developing in China, the lack of appropriate infrastructure, weak administrative capacity, and limited sources of funding make the performance of high-quality clinical trials challenging. In the future, collaborations like the IgA Nephropathy Registration Initiative of High Quality and the Chinese Registry of Prognostic Study of IgA Nephropathy could facilitate the conduct of large cohort and multicenter-based clinical trials to test the efficacy of novel therapies for patients with IgAN in China. In addition, international academic collaborations bringing the rigor of design and execution of multicenter trials will represent a most welcome evolution in the landscape of clinical trials for IgAN. In this regard, studies like the UK IgAN RaDaR cohort, which was expanded internationally using a web-based registry collecting standardized data and standardized samples, and which protocolized the monitoring and follow-up of patients with IgAN, have the potential to drive global studies of IgAN. This will allow systematic comparisons of the disease across ethnicities to understand variations in the susceptibility and severity of the disease in specific groups that traditionally have only been studied in isolation.

Conclusion

Understanding fundamental ethnic differences in IgAN has significant implications for both clinical care and future research. To date, many of the clinical trials of IgAN have been conducted in clinically homogenous, but histopathologically defined and ethnically restricted populations. The results of these studies might not necessarily be generalizable to other ethnic groups outside the study population. This is an important consideration when applying international treatment guidelines, such as the KDIGO guidelines, to the treatment of Chinese patients, and for the design of future studies. The identification of true differences in the pathogenic pathways of IgAN across different ethnic populations and from a Chinese perspective will influence treatment strategies across globally and eventually lead to targeted and personalized therapies.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This study was funded by the National Natural Science Foundation of China (grant number 82070733), the Clinical Medicine Plus X – Young Scholars Project of Peking University (grant number PKU2021LCXQ017), the Fundamental Research Funds for the Central Universities, and CAMS Innovation Fund for Medical Sciences (grant number 2019-I2M-5-046), and "PRO·Run" Fund of the Nephrology Group of CEBM.

Author Contributions

Z. Zhang and Y.M. Zhang wrote and edited the manuscript; H. Zhang conceived and edited the manuscript.

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