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Immunoglobulin A Nephropathy in China: Progress and Challenges

Guang-Yan Cai Xiang-Mei Chen

Department of Nephrology, PLA General Hospital, Beijing, PR China

Key Words
Immunoglobulin A · Nephropathy · End-stage renal disease · China

Abstract
Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in China. In about 20% of patients it will lead to renal insufficiency within 10 years, even in those with clinically early IgAN, which causes a great burden for patients and society. ***Methods:*** We reviewed basic and clinical research work in China. Comparisons between data from China and those from other countries were made. ***Results:*** The genetic variations conferring susceptibility to IgAN and disease progression as well as the pathogenic role of polymeric IgA1 were investigated in Chinese patients. Clinical features of Chinese IgAN with isolated microscopic hematuria, malignant hypertension, crescentic glomerulonephritis, intrarenal arterial and tubulointerstitial lesions have been characterized. Clinical trials showed that the combined therapy with urokinase + ACEI, or steroid + ACEI was more effective than with ACEI alone in reducing proteinuria and protecting renal function. The therapeutic role of MMF in IgAN remains debated, although two Chinese studies demonstrated its efficacy. Severe pneumonia can possibly occur in some cases after MMF administration for 3 months. ***Conclusion:*** IgAN remains a great challenge to Chinese nephrologists. In-depth basic studies and multicenter clinical trials are needed in the future.

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of primary glomerulonephritis in China. According to an epidemiologic study on 13,519 renal biopsies, IgAN accounted for 33.19% of total renal biopsy diagnoses and 45.26% of primary glomerular diseases [1]. This is in contrast to the United States and western Europe, where IgAN accounts for 10 and 30% of glomerulonephritis, respectively [2]. A retrospective survey of 3,331 patients with primary glomerular disease showed that the frequency of IgAN increased from 1993 to 2007 [3]. Based on the etiology of end-stage renal disease (ESRD) reported by the Chinese Dialysis and Transplantation Registration Group in 1999, IgAN was the most common cause of ESRD in China [4]. The prevalence had no significant changes in the years preceding the Shanghai Dialysis and Transplantation Registration Report in 2003 [5].

Study on Pathogenic IgA in IgAN in China

Patients with IgAN show abnormalities in circulating IgA, including an increased concentration and an abnormal glycosylation. Since only a fraction of the IgA seems to be affected, this suggests that alterations in glycosylation are present in only a subset of B cells. $CD19^+CD5^+$ B cells were recognized recently as producers of abnormal IgA [6]. Pathogenic IgA present in the circulation is de-

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Prof. Xiang-Mei Chen
Department of Nephrology, PLA General Hospital
Beijing (PR China)
Tel. +86 10 6693 5462, Fax +86 10 6813 0297
E-Mail xmchen301@126.com

rived not only from the bone marrow, but also from mucosal immunity. Serum secretory IgA (SIgA) level in IgAN was found significantly increased and the levels were closely associated with clinical and pathological parameters, suggesting its role in the pathogenesis of IgAN [7].

In vitro studies showed that polymeric IgA1 (pIgA1) had much higher maximal binding capacity to human mesangial cells (HMC) than monomeric IgA1 (mIgA1), and glycosylation of IgA1 molecules enhanced the binding characteristics [8]. Altered *O*-glycosylation of serum IgA1, which contain less galactose and sialic acid, might favor self-aggregation and the formation of an immune complex with IgG [9]. Less terminal α2,6-linked sialic acid and galactosylation increase exposure of terminal galactose and N-acetylgalactosamine in serum IgA1 [10]. The binding capacities of desialylated IgA1 and degalactosylated IgA1 (deS/deGalIgA1) to HMC were significantly higher than that of native normal IgA1, which was partly due to more macromolecular IgA1 in deGalIgA1 [11].

IgAN is generally not associated with marked infiltrating cells in the glomerulus, suggesting that glomerular injury is mediated by resident glomerular cells. IgA alone appears sufficient to provoke glomerular injury in the susceptible individual. Abnormal IgA1 binding to HMC elicits a phenotypic transformation in HMC, with cell proliferation, production of a variety of proinflammatory and profibrotic molecules and secretion of extracellular matrix component [12].

The composition of IgA1-containing macromolecules is related to different pathological phenotypes of IgAN, in which deS/deGalIgA1 was strongly pronounced in advanced sclerosing IgAN patients [13]. Follow-up investigation indicated that the α2,6-linked sialic acid level of serum IgA1 was associated with the progression of IgAN [14]. Further studies are required to unravel the mechanisms contributing to deS/deGalIgA1.

Gene Polymorphisms Related to the Susceptibility and Progression of Chinese IgAN

Genetic factors are considered to underlie the development of IgAN in Chinese, as the incidence of IgAN is much higher in China compared to western countries. Genes encoding enzymes involved in the *O*-glycosylation process of IgA1 are functional candidates. The genes encoding galactosyltransferase and its chaperone, Cosmc, are C1GALT1 and C1GALT1C1, respectively. A case-control study by Li et al. [15] found that the genetic polymorphisms in the regulatory region of the C1GALT1 gene were associated with susceptibility to IgAN in the Chinese population. This finding is confirmed by a recent study on an Italian population, which suggests the variation might influence the galactosyltransferase activity [16]. ST6GALNAC2 is a gene involved in the sialylation of the IgA1 molecule. The ADG haplotype of the ST6GALNAC2 gene was associated with deficient degrees of α2,6-linked sialic acid of IgA1 molecules, which may contribute to the genetic susceptibility in IgAN patients [17].

Megsin (SERPINB7) is predominantly expressed in the glomerular mesangium and upregulated in IgAN. The genetic variations of 2093C–2180T at the 3′ untranslated region of the megsin gene were revealed to be associated with susceptibility to IgAN and disease progression in a Chinese population [18]. However, results from Korea found a reversal, in which the 2093T–2180C haplotype was associated with disease progression in Korean IgAN patients [19]. Further studies are urgently required to elucidate the reasons of disparity.

MUC20, a novel mucin protein highly expressed in kidney, has been identified as upregulated in IgAN. A study on 1,147 Chinese subjects revealed that IgAN patients with SL/LL genotypes of the MUC20 gene had a higher risk of progression to ESRD, although there was no association between the polymorphism of the MUC20 gene and clinical manifestations at the time of renal biopsy [20]. The role of these genotypes has not been ascertained in other subjects of different genetic backgrounds.

Other candidate genes with polymorphisms were found to influence the progression of IgAN in the Chinese population, including the 38AA genotype of the uteroglobin G38A, the DD genotype of the ACE gene, the heterozygote NA1/NA2 of the Fcgr3b gene, and the CC genotype at the –2578 position of VEGF gene [4, 21, 22]. However, there are conflicting findings in Japanese and Korean studies as to whether or not some candidate genes, such as the uteroglobin G38A polymorphism, are associated with the development of IgAN [23]. Also, no functional data have validated the role of these genetic polymorphisms in IgAN.

Clinical Presentations and Pathologic Characteristics of Chinese Patients with IgAN

Several circulating biomarkers for the diagnosis of IgAN have been reported, such as anti-endothelial antibodies, IgA rheumatoid factors, IgA immune complexes

and pIgA1 [24]. However, none appear to be sufficiently disease-specific or reliably correlated with disease activity. Although increased serum levels of galactose-deficient IgA1 were recently claimed to be a key symptom in the diagnosis, the usefulness of this assay is still uncertain [25].

The diagnosis of IgAN is often suspected on the basis of the clinical history and laboratory data, but can be confirmed only by kidney biopsy with immunofluorescent detection of mesangial IgA deposits. Indicators for renal biopsy would be necessary for patients with isolated microscopic hematuria without proteinuria, hypertension or renal insufficiency. In a retrospective study, Shen et al. [26] found that urinary albumin/creatinine ratio, serum IgA level and serum IgA/C3 ratio were markers for distinguishing IgAN from thin basement membrane nephropathy and normal subjects, which helps to predict the necessity of renal biopsy.

Chinese patients with IgAN presenting with malignant hypertension or accelerated hypertension are not very rare. It is usually presumed that Chinese patients have a long-standing disease which was not detected earlier because the patient did not undergo routine urinalysis. According to a retrospective study, about 1.2% of all the IgAN patients presented malignant hypertension (IgAN-MHT) [27]. Compared to primary MHT, IgAN-MHT tended to have more proteinuria, a higher prevalence of hematuria and a higher serum IgA level. The occurrence of IgAN-MHT was not associated with the background glomerular lesions of IgAN [28]. Patients with IgAN-MHT share a similar renal survival rate with those with primary MHT. Anti-endothelial cell antibodies (AECA) were significantly more detectable in IgAN-MHT than primary MHT, which suggests AECA might be involved in the pathogenesis of IgAN-MHT [28].

Intrarenal arterial lesions (IRAL) are frequently observed in patients with IgAN, whether or not there is hypertension. We found the prevalence of IRAL was 54.6% in IgAN, which was much higher than 26.6% in non-IgAN and 47.1% in membranous nephropathy [29]. The IRAL in IgAN patients were severer, exhibited a higher degree of hyaline changes and were associated with a younger age, compared with those in controls. The severity of IRAL was linked to many clinical and pathological markers of disease progression. Zhang et al. [30] found that IRAL were associated with endothelial cell damage in IgAN, and von Willebrand factor was a useful serological biomarker of severe IRAL. AECA, especially IgG-AECA, may be involved in the pathogenesis of IRAL in IgAN. Nevertheless, their antigens and their actual significance still need further investigation.

Crescentic IgAN is the commonest type II crescentic glomerulonephritis in China, accounting for 16.4% of total crescentic glomerulonephritis [31]. Most diffuse crescentic IgAN were identified with rapidly progressive glomerulonephritis, gross hematuria, hypertension and nephrotic syndrome. Pathologically, severe glomerular and tubular interstitial damages were also prominent.

In our data, 38.3% of Chinese patients with IgAN had moderate or severe tubulointerstitial lesions (TIL) at the time of renal biopsy [4]. Recent in vitro studies provided a possible role of glomerulotubular cross-talk with mediators released from the pIgA-incubated HMC contributing to the pathogenesis of TIL in IgAN [32]. As TIL play an important role in the development of IgAN, it would be important to find a powerful marker of TIL at early stage. Neutrophil gelatinase-associated lipocalin (NGAL) is an acute phase protein that is rapidly released from a variety of cell types upon inflammation and injury. Urinary NGAL levels were recently regarded as an early biomarker for TIL of IgAN, as they were elevated more drastically than N-acetyl-β-D-glucosaminidase levels during the early stage of the disease [33].

Prognosis of Chinese Patients with IgAN

It is now generally agreed that up to 30% of patients with IgAN eventually progress to ESRD worldwide. Recent studies have revealed that the renal survival rate in Chinese patients with IgAN was similar to those reported from Australia, Europe and North America [34, 35].

A 6-year follow-up study on 204 Chinese patients with IgAN showed the renal survival rates at 5 and 10 years were 85.1 and 77.1%, respectively [34]. Another study from Hong Kong enrolled 168 Chinese patients with IgAN, and followed them for an average of 7.4 years. The renal survival was 87.5% at 5 years and 81.8% at 10 years. Family history of hypertension, hypertension and renal impairment at presentation, proteinuria >1 g/day and histological grading were independent predictors of renal survival [35]. Contrary to common beliefs and most Caucasian series, male gender was not associated with unfavorable renal outcome in Chinese IgAN patients. Interestingly, IgAN patients with histologically low-grade chronic lesions had a higher risk of disease progression, which suggests progressive IgAN may occur much earlier than perceived.

IgAN patients presenting with normal renal function, proteinuria of 0.4 g/day or less, and normal blood pressure are usually considered benign and to have a good prognosis. However, a recent follow-up study on IgAN patients of this kind demonstrated that 24% of patients developed renal insufficiency within an average of 111 months. In addition, IgAN with isolated microscopic hematuria might not imply a favorable outcome [36].

Treatment of IgAN in China

Patient selection for treatment is based in part upon acute or chronic onset and the perceived risk of disease progression. Generally, patients with persistent proteinuria (>500 mg/day), normal glomerular filtration rate (GFR), and mild histological findings are managed with renin-angiotensin-system (RAS)-inhibitor therapy and blood pressure control to slow progression. Patients with severer or rapidly progressive disease may benefit from immunosuppressive therapy in addition to general interventions. Current therapies in Chinese patients with IgAN are largely empirical and their long-term effects relatively uncertain, owing to small sample sizes and short follow-up durations.

Regarding the efficacy of therapy in IgAN, 2 aspects should be separately considered. Firstly, therapeutic regimens with a statistically significant improvement may not produce clinically significant results. Secondly, a more pronounced anti-proteinuric effect is thought to be a marker for better outcomes [37]. Instead, some reported treatments in IgAN have an anti-proteinuric effect, but may not preserve the GFR.

Although studies have demonstrated that tonsils may be a source of pathogenic IgA1 in IgAN, tonsillectomy as a treatment has been particularly controversial. A retrospective study did not demonstrate the efficacy of tonsillectomy on long-term clinical remission and renal survival of Chinese IgAN patients [38]. However, a recent prospective controlled study from Japan demonstrated better effects of tonsillectomy plus steroid pulse therapy than steroid pulse alone on inducing clinical remission in Japanese patients with IgAN [39].

Numerous studies have shown the efficacy of RAS inhibitors in the treatment of IgAN; however, many of these studies were limited to patients who presented with an overall favorable prognosis. There is emerging evidence for combination therapy with RAS inhibitors to provide additional benefits for progressive IgAN, but at present controlled trials are lacking.

Intraglomerular fibrin deposition is a documented feature of IgAN. The coagulation process has been suggested to contribute to the progression of glomerulosclerosis. Therefore, anticoagulant or fibrinolytic strategies were proposed to protect against accelerated sclerosis. We prospectively randomly evaluated the effects of therapy with urokinase + benazepril or benazepril alone on Chinese IgAN with Lee grades ≥ 3 and fibrinogen deposits. After 6 and 12 months of treatment, the urokinase + benazepril combination was superior to benazepril alone in decreasing proteinuria and stabilizing the GFR in severe IgAN [40].

Several prospective studies, including those from Japan, reported an anti-proteinuric and renoprotective effect of a 6-month steroid trial on IgAN patients with preserved renal function who did not respond to RAS inhibitors [41, 42]. Lv et al. [43] further demonstrated that in Chinese patients, the addition of steroids to ACE inhibitor (cilazapril) therapy produced a more potent anti-proteinuric effect and better protection of kidney function compared with an ACE inhibitor alone.

Mycophenolate mofetil (MMF) had been used in the treatment of lupus nephritis and primary glomerular diseases. The therapeutic efficacy of MMF in IgAN has remained under debate in different ethnic groups. Two clinical trials, including 1 study from our group, have confirmed that MMF is effective in Chinese patients with IgAN in lowering proteinuria and ameliorating some of the putative pathogenetic abnormalities, such as serum IgA [44, 45]. These trials were of a small size, and longer-term studies are required for more information. A recent meta-analysis stated that MMF provides no benefit in reducing proteinuria or protecting renal function in IgAN in comparison with placebos or steroids [46]. Larger international collaborations should be carried out to further address this issue.

Although MMF is considered to have relatively good tolerance in renal transplantation, a single center from China reported that 6 of 32 IgAN patients who received MMF (1–1.5 g/day) + corticosteroids developed severe pneumonia around the third month. Patients with advanced renal function impairment and lymphopenia were associated with susceptibility to pneumocystis pneumonia. This finding suggests the risk-benefit balance should be carefully evaluated during application of MMF in IgAN [47].

Uncontrolled reports suggest that crescentic IgAN patients without significant chronic damage may benefit from therapy that includes intravenous pulse methylprednisolone followed by oral prednisone, intravenous

cyclophosphamide and/or plasmapheresis [48]. Intensive immunosuppressive treatment improves renal damage in Chinese patients with crescentic IgAN. Only 20% were dialysis-dependent after being followed up for more than 6 months [31]. This is consistent with the benefit noted from a similar regimen in other forms of crescentic glomerulonephritis.

Conclusions

IgAN remains a great challenge for Chinese nephrologists. Up to now, IgAN is the most common form of chronic kidney disease and the most frequent cause of ESRD in China, which is different from western countries. Although in recent years Chinese nephrologists have made efforts towards understanding the pathogenesis and treatment of IgAN, much work still needs to be done in the field of IgAN to help China reduce the burden of chronic kidney disease and the number of patients who will require renal replacement therapy.

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