The phenotypic difference of IgA nephropathy and its race/gender-dependent molecular mechanisms

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Abstract

IgA nephropathy (IgAN), defined by the predominant deposition of IgA in the glomerular mesangium, is the most common form of glomerulonephritis throughout the world. However, its incidence, gender distribution, clinical presentation and progression and pathogenic initiating factors are largely variable on such simple definition. To assess the heterogeneity of this disease, we recently conducted clinical survey regarding presentation and clinical management of IgAN patients in Europe and Japan. This clinical survey highlights similarities and differences in patients from different continents. The survey revealed obvious differences between nations in the frequency of gastrointestinal complications including inflammatory bowel diseases (IBD) and celiac disease more frequent in European patients. Such findings are compatible with susceptibility loci related to intestinal immunity and IBD in recent genome wide association studies (GWAS) on IgAN. However, most of the molecules in these mucosal related loci fulfil the immunological function not only of gut-associated lymphoid tissue (GALT), but also nasopharyngeal/bronchial-associated lymphoid tissues (NALT/BALT). Indeed, similar frequency of macrohematuria coinciding with upper respiratory infection, known as hallmark manifestation of this disease, was found in the survey, emphasizing pathogenic roles of these molecules in NALT/BALT of IgAN patients. Recent experimental and clinical studies including GWAS on multiple common infections and IBD indicate immune cross talks between GALT and NALT/BALT and some related mediators such as TNF superfamily ligands (APRIL/BAFF). This review explains epidemiological heterogeneity of this disease with the clinical survey and discusses race and gender-dependent molecular mechanisms.
**Introduction**

If IgA nephropathy (IgAN) is a single disease remains of debate because of its variable clinical and pathogenic presentation, disease progression and complications, geographic and gender variation, and treatment response. It can be argued that IgAN is a glomerular pattern rather than disease because of its simple definition (1). Indeed, 5%–10% of kidney samples from the autopsies of trauma victims or people without a renal history showed mesangial IgA deposition (2-4), and 14%–17% of kidney donors without a renal history had evidence of mesangial IgA deposition with or without C3 (5).

IgAN is the most frequent biopsy-proven primary glomerulonephritis; however, its geographic prevalence varies. A systematic review suggests that IgAN has an incidence of at least 2.5 per 100,000 in adults (6). However, the prevalence of IgAN is much higher in East Asia compared with North America and Europe (6, 7). This is partly explained by the increased performance renal biopsies and national urine screening programs in East Asia. In Japan, Korea and Taiwan there is an annual urinalysis as a part of a health check program that encourages the early referral of individuals even with persistent microscopic hematuria with or without mild proteinuria, which increases the frequency of IgAN diagnosis (7, 8). A wide indication for a renal biopsy even in individuals with microscopic hematuria resulted in the identification of a large number of asymptomatic urinary abnormalities caused by IgAN not only in Asia but in Europe as well (9-11), suggesting that the true prevalence of IgAN globally is underreported. An observational study of renal biopsies in patients with hematuria without overt proteinuria reported a high proportion of IgAN (62%), and 31% of these IgAN patients have active glomerular lesions including crescent formation (9). This may be a part of the reason why persistent isolated microscopic hematuria is a risk for end stage kidney disease (12).

IgAN in East Asia has a male to female ratio of 1:1 or <2:1, which is different from that in Europe and the US and reports ratios as high as 6:1 (13-15). This strongly indicates that environmental and/or genetic factors may have certain roles in the pathogenesis of IgAN. The contribution of race to the etiology of ESRD in IgAN patients has been reported. Barbour et al. reported that individuals of Pacific Asian origin had a significantly increased risk of ESRD even after adjusting for the effects of currently known prognostic variables such as age, eGFR at biopsy, proteinuria and mean arterial pressure (16). Although this risk may be explained by racial differences, the effects of Asian origin on disease...
progression may not be explained by specific factors related to IgAN such as the number of nephrons at birth (17, 18).

Differences in the renal progression of male and female IgAN patients are still controversial. Recent Chinese studies reported that no significant differences were observed in the long-term renal survival of male and female patients despite matching with prognostic factors such as eGFR and serum uric acid (19-21). Catrnan et al. demonstrated that, in contrast with membranous glomerulonephritis and focal segmental glomerulosclerosis, baseline and follow-up urinary protein and patient sex did not influence IgAN progression (22). However, this is in contrast with a large meta-analysis (23). A recent study from Estonia has reported that renal progression occurs faster in males than in females with a correlation between a higher Oxford MEST score and disease progression in male patients (24). It is now widely accepted that galactose-deficient IgA1(Gd-IgA1) and Gd-IgA1 immune complex formed with autoantibodies against GdIgA1 are key effector molecules in IgAN, and are thus referred to as prognostic markers (25-28). A recent report indicates a significant difference in Gd-IgA1 level between UK and Chinese IgAN patients and healthy subjects (29). Enzyme core 1 synthase, glycoprotein-N-acetylgalactosamine 3-ß-galactosyltransferase (C1GALT1) is known to catalyze the transfer of galactose UDP-Gal to N-acetylgalactosamine (GalNAc) O-linked esters of threonine and serine residues of IgA1 (30). The C1GALT1 gene is strongly associated with Gd-IgA1 level in both populations without gender bias (29, 31); however, a different lead single nucleotide polymorphism (SNP) of C1GALT1 and a novel genetic interaction with GALNT12, which is a key enzyme for the O-glycosylation of GalNAc may exist only in Chinese patients (31), suggesting that serum elevation of Gd-IgA1 is the result of different regulation with the same enzyme in different races. Berthoux et al. reported that the serum levels of autoantibody against Gd-IgA1 is associated with IgAN progression (32). However, this French cohort comprised 75% male IgAN patients, and the absolute renal risk for dialysis or death was correlated with a high number male patients. Such male dominant elevation of antiglycan antibody with poor prognosis was not observed at least in Japanese patients (33). Therefore, the prognostic value of the serum level of anti-Gd-IgA1 antibody should be carefully evaluated in multiethnic cohorts, such as via an international collaborative study of an International IgAN prediction tool (34).
Clinical features and practice of IgAN in Japan and Europe: results from an international survey

To further understand the geographic heterogeneity of IgAN, recent clinical survey regarding the management of IgAN in Europe and Japan as a collaborative study between the Japanese Society of Nephrology and the European Renal Association-European Dialysis Transplantation Association (ERA-EDTA) may be helpful. A retrospective analysis comprising biopsy-proven IgAN patients from 2016 to 2017 was performed to compare the clinical and therapeutic features of European countries (Europe) (n = 437) and Japan (n = 470). The questionnaire was distributed to leader institutions in both regions (24 from Europe and 24 from Japan) following approval of ethics committee at each institution. Patients with IgAN were randomly selected from each institution for data collection.

1) Urinary abnormalities and renal function before renal biopsy
The frequency of a past history of macrohematuria was similar between Europe and Japan (Table 1). Hematuria was rarely (2.6-5%) associated with acute gastrointestinal disorders in both cohorts (Figure 1). However, the frequency of hematuria coincident with an upper respiratory tract infection was higher (22.7 % and 29.8% in Europe and Japan, respectively) (Figure 1), without significant differences between the two cohorts. Many of Japanese practitioners required a history of proteinuria (>300 mg/day) detected twice on urinalyses performed more than 3 months apart for the indication of renal biopsy. The rate of a renal biopsy being performed less than a year after the initial detection of proteinuria was higher in Europe (Table 1). The ratio of nephrotic syndrome before renal biopsy was much higher in Europe compared with Japan (21% and 4%, respectively). Moreover, multiple renal abnormalities were discovered during an annual health check-up in Japan (Table 1), and Japanese patients with IgAN were diagnosed at a relatively early stage.

In Europe, 21% of patients with IgAN had at renal biopsy an increase in serum creatinine (Table 1). The frequency of preserved eGFR at the time of renal biopsy (> 60 ml/min/1.73m2) was low in Europe (55%) compared with Japan (71%). Moreover, 20% of the European cohort had an acute renal injury (Table 1). IgAN possibly progressed in Europe at the time of the renal biopsy.
2) Gastro-intestinal disorders and upper respiratory tract infections coincident with urinary abnormalities
The frequent occurrence of episodic macroscopic hematuria with a concurrent upper respiratory or intestinal tract infection suggests that the mucosal immune system plays an important role in IgAN progression (35, 36). The ratio of gastrointestinal complications, such as Crohn’s disease (CD), ulcerative colitis (UC), and Celiac disease, were more frequent in Europe compared with Japan (17.2% vs. 1.1%) (Table 2). Although the serum level of IgA was found to be elevated in patients with CD and UC compared with healthy controls (37), patients with IgAN and an elevated serum IgA at the time of renal biopsy were much less common in Europe compared with Japan (11% vs. 34%) (Table 1). Of interest, there were no clear differences in the coincidence of episodic hematuria and gastro-intestinal disorders or upper respiratory tract infections between Europe and Japan (Figure 1).

3) Differences in current status of treatment between Europe and Japan
The major treatment options for adult IgAN are the use of renin-angiotensin system (RAS) inhibitors, corticosteroids, non-steroidal immunosuppressive agents, tonsillectomy (combined with high-dose intravenous corticosteroids), omega 3 fatty acid (fish oil) and antiplatelet agents. As several clinic studies have confirmed a favorable effect of tonsillectomy (38), it has now become a common treatment option in Japan. In fact, ~53% of patients with IgAN in Japan underwent a tonsillectomy (Figure 2). Treatment with RAS inhibitors is a common treatment option in both Europe and Japan, conversely, major therapeutic differences between Europe and Japan are reported on the use of high-dose intravenous corticosteroids and oral corticosteroids (Figure 3). Note that >60% of Japanese patients with IgAN were treated with corticosteroids. While several reports suggest a risk of adverse events following the use of corticosteroids in patients with IgAN (39), most patients with IgAN in Japan had completed corticosteroids during the two year study period, hence suggesting a rather safe treatment (Table 3).

Although clinical study in a large cohort in Japan and a recent meta-analysis of 14 studies in mainly Asian countries confirmed a favorable effect of tonsillectomy (38, 40), good outcomes of tonsillectomy for IgAN were not reported in European studies (41-43). Meanwhile the novel targeted-release formulation of budesonide targeting small intestine was shown to reduce proteinuria in IgAN
patients in European countries (44). There are epidemiological differences between Asia and European countries, such as gender ratios and frequency of intestinal complications, e.g., CD, UC and celiac disease. Thus, there are possibility that the effectiveness of tonsillectomy may depend on racial differences. However, the limited number of patients receiving tonsillectomy in Europe because of IgAN and not for ENT indications does not allow a comparison between the continents (41, 43). Despite negative results (41,42) in small European studies, a report from Germany indicated that many of the IgAN patients in the tonsillectomy group had progressive status of disease (serum creatinine level was over 2 mg/dL) (42). Meanwhile, a Hungarian report showed the positive effects of tonsillectomy in 98 Caucasian patients with IgAN (45). Thus, further basic and clinical studies are required to determine the efficacy of tonsillectomy in different races. The European ENT guideline do not support tonsillectomy in cases without repeated episodes of tonsillitis, hence this procedure remains not easily applicable in Europe.

- Potential underlying molecular mechanisms in race/gender-difference in IgAN

1) Mechanisms related to intestinal disorders
This clinical survey highlights the similarities and differences in European and Japanese IgAN patients and clinical care. The hallmark manifestation of IgAN is macrohematuria that often coincides with an upper respiratory tract infection, which is indicative of the pathogenic roles of the nasopharyngeal and bronchial mucosae. However, the survey also revealed obvious differences in the frequency of gastrointestinal complications between nations, including inflammatory bowel disease (IBD) and celiac disease in European IgAN patients (Europe: Japan; 17.2 : 1.1%, Table 2). IBD, including CD and UC, have been considered disorders that primarily affect patients of European ancestry (46, 47). Celiac disease is an autoimmune enteropathy triggered by dietary gluten in genetically susceptible individuals especially of European ancestry (48). However, the incidence of IBD and Celiac disease is increasing in non-European and non-White populations (49-51). Considering the altered etiology of IBD and celiac disease, the clear geographic difference in the prevalence of intestinal diseases in this survey may be more than coincidence and suggests a pathogenetic connection between gut inflammation in IgAN and the heterogeneity of European
IgAN patients.

Transgenic mouse models of IgAN overexpress a ligand for lymphotoxin β receptor (LIGHT) or B cell-activating factor (BAFF), which are both essential molecules for IgA class switching and intestinal IgA production by resident IgA+ plasma cells (PC), and thereby demonstrate that the overproduction of polymeric IgA in the intestinal mucosa results in high serum levels of IgA (~100 times higher) and IgAN disease phenotypes (37, 52). The polymeric immunoglobulin receptor (pIgR) is the key molecule for the luminal trafficking of mucosal dimeric IgA in the intestine and upper respiratory tract (53, 54). Excessive IgA remaining in the intestinal lamina propria is therefore considered to be the result of overwhelmed pIgR, which leads to the leakage of mucosal IgA into the circulation of transgenic mice. Serum IgA elevation has been observed in CD and UC patients (37, 55), suggesting that intestinal inflammation may interfere with IgA trafficking by pIgR. Intestinal inflammation in IgAN patients with celiac disease may share the same mechanism of the mesangial deposition of intestinal IgA (56). Interestingly, certain Swedish reports suggest that 33% of IgAN patients have a mucosal sensitivity to gluten without the clinical manifestations of celiac disease (57, 58). Furthermore, anti-gliadin antibodies were detected in association with high levels of IgA immune complexes in Italian patients with IgAN (59). More recently, the French IgAN cohort without the manifestations of celiac disease exhibited elevated serum anti-gluten antibody (60), suggesting that even subclinical intestinal inflammation may lead to glomerular IgA. A pathogenic mechanism was proposed using a humanized mouse model of IgAN, the α1KICD89Tg mouse, that expresses human IgA1 and the human myeloid CD89 IgA Fc receptor. Under normal diet, these mice displayed in their serum IgA1 antibodies to gliadin complexed with soluble CD89. A gluten-free diet resulted in a decrease of mesangial IgA1 deposits and hematuria. Disease severity depended on gluten and CD89, as shown by reappearance of IgAN features in mice on a gluten diet (61). However, a serological link with anti-gliadin antibody was absent in IgAN patients in Japan and the USA (62, 63). Moreover, most IgAN patients do not usually complain of any gastrointestinal disorder, indicating that certain specific environmental factors may facilitate such a link in European patients. In a direct comparison of IgAN patients from various continents, abnormal levels of IgA directed against various alimentary antigens were found to be less frequent in Japanese versus European patients (0-16% versus 19-28% respectively for IgA anti different alimentary components) (64)
It is known that IgA transcytosis and trafficking by pIgR in mucosal cells are strikingly augmented by estradiol (65). This is thought to be a part of the reason why female patients are more resistant against pneumonia after trauma (66-69). In this regard, the presence of a sex-hormone-based difference in mucosal IgA trafficking should be carefully examined for gender bias in European IgAN.

2) Immune cross-talk between nasopharyngeal/bronchial- and gut-associated mucosal tissues

A recent genome-wide association study (GWAS) on IgAN demonstrated a disease association with loci related to molecules responsible for intestinal immunity, maintenance of the intestinal barrier and IBD, reinforcing the importance of interstitial immune response in IgAN (70-72). However, most of the molecules in these mucosal immune-related loci fulfil the immunological function not only of gut-associated lymphoid tissue (GALT) but also nasopharyngeal/bronchial-associated lymphoid tissues (NALT/BALT), although much remains to be elucidated about NALT/BALT-mediated regulation of IgA immunity compared to that of GALT.

While a genetic association at the variants rs2412971, intronic in \textit{HORMAD2} at 22q.12.2 was reported in GWAS for IgAN involving Han Chinese and European cohorts (70-72), a GWAS for tonsillectomy revealed that the same SNP, rs2412971, is robustly associated with an increased risk of requiring a tonsillectomy (73), which is suggestive of \textit{HORMAD2}-related susceptibility of infection or hyper immune reaction in the palatine tonsil. Indeed, on the telomeric side of \textit{HORMAD2}, the two nearest neighboring genes, \textit{LIF} and \textit{OSM}, encode cytokines that are members of the IL-6 family and thus may play a role in the hyper immune response or inflammation (73, 74). Note that the GWAS for tonsillectomy demonstrated that rs2412971 is associated with a decreased risk of CD and IBD in the European population (75-77), revealing opposing effects of risk loci for IgAN in IBD. Epidemiologic studies with nationwide cohorts and a related meta-analysis primarily from European studies revealed that a tonsillectomy is associated with an increased likelihood of developing CD and IBD (78-80). These results call into question a direct influence of tonsillectomy on GALT. A Danish nationwide cohort study demonstrated that a history of tonsillectomy in first- and second-degree relatives increases an individual’s risk of IBD (78), suggesting shared hereditary or environmental factors.

There is growing evidence of physiological and pathological cross-talk in
IgA immunity between NALT/BALT and GALT (81, 82) or mucosa and non-mucosal tissues (83). After intranasal immunization with inactive cholera toxin (CT), lung dendritic cells stimulate the retinoic acid-dependent up-regulation of α4β7 and CCR9 gut-homing receptors on local IgA-expressing B cells (81). The migration of these B cells to the gut results in IgA-mediated protection against an oral challenge with active CT. Such homing plasticity of IgA+ B cell in NALT/BALT may underlie this cross-talk, although GALT-oriented IgA+ B cells home more efficiently to GALT but not to spleen or NALT/BALT (84, 85).

3) APRIL/BAFF balance in B cell regulation in IgAN

Different GWAS for common infections and infection-associated procedures in patients with a European ancestry demonstrated certain independent genome-wide associations with tonsillectomy. These include HLA and genes of the TNF/receptor superfamily ligands such as TNFSF13B and TNFRSF13B, which encode BAFF and the transmembrane activator and cyclophilin ligand interactor (TACI), respectively (86). BAFF and a proliferation-inducing ligand (APRIL) are members of the TNF superfamily and are essential cytokines to IgA class switch recombination and B cell differentiation and maturation in the mucosa, although pathophysiologic role sharing between APRIL and BAFF largely remains unknown (87). TACI is one of the shared receptors of BAFF and APRIL. Although the overexpression of BAFF leads to the intestinal accumulation of IgA+PC and subsequent murine IgAN (52), several GWAS carried out in IgAN patients identified a strong associated loci at TNFSF13 at 17p13 encoding APRIL, but not TNFSF13B (BAFF) (71, 72). Moreover, APRIL targeted antibodies (88, 89), but not BAFF (paper in revision), dramatically improved kidney injury as evidenced by decreased proteinuria and mesangial IgA deposition in spontaneous murine IgAN models (grouped ddY). Moreover, the serum levels of APRIL were correlated with the serum levels of GdIgA1 and IgAN prognosis (90, 91). Such experimental and clinical results support the idea that IgAN is an APRIL-mediated disease rather than a BAFF-mediated disease.

The tonsillar expression of APRIL in patients with IgAN is significantly higher than in those with chronic tonsillitis (92). Such tonsillar APRIL expression involves germinal center B cells (92). Toll-like receptor (TLR)-mediated microbial sensing plays a critical role in IgA production in the mucosa via APRIL/BAFF activation (87). We previously reported that a specific SNP of TLR9 that recognizes the unmethylated DNA of microbiomes is significantly associated with
the pathologic severity of IgAN (93). The expression of TLR9 in the tonsils is related to reduced serum IgA and GdIgA1 after a tonsillectomy, which represents treatment response (94, 95). Note that the persistent stimulation of TLR9 induces APRIL expression in the B cells themselves, even in tonsillar B cells from non-IgAN patients (92). Indeed, tonsillar APRIL expression is significantly correlated with TLR9 in IgAN patients (92). At least in the spontaneous murine IgAN model, TLR9 activation in NALT, but not GALT, is involved in nephritogenic aberrantly glycosylated IgA production and subsequent renal damage (96). The association between TNFSF13 (APRIL) at 17p13 and HOMAD2(LIF/OSM) at 22q12 in an independent population-based GWAS of the serum levels of IgA is worthy of note (97), as LIF/STAT1 signaling is involved in the overproduction of Gd-IgA1 in IgAN (98). These results suggest an aberrant innate immune activation of mucosal TLR9/APRIL in IgAN. Furthermore, in addition to the risk of tonsillectomy, BAFF is known as a potential biomarker for active IBD and celiac disease (99, 100). Further examinations with translational approaches are required to get a core molecular mechanism, however, assessment from the point of APRIL/BAFF balance in the cross-talk between NALT/BALT and GALT may be one of next challenges to explain the heterogeneity of IgAN.
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**Author Contributions**

Y Suzuki: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing
R Monteiro: Formal analysis; Investigation; Methodology; Project administration; Validation; Writing - review and editing
R Coppo: Methodology; Validation; Writing - review and editing
H Suzuki: Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing - original draft; Writing - review and editing
References
7) Schena FP, Nistor I: Epidemiology of IgA Nephropathy: A Global Perspective. Semin Nephrol 38:435-442, 2018


Sano T, Kobayashi Y: Detection of gender difference and epitope specificity
of IgG antibody activity against IgA1 hinge portion in IgA nephropathy patients
by using synthetic hinge peptide and glycopeptide probes. Nephrology (Carlton) 9:26-30, 2004
Er L, Espino-Hernandez G, Kim SJ, Reich HN, Feehally J, Cattran DC,
International IgA Nephropathy Network: Evaluating a New International Risk-
Prediction Tool in IgA Nephropathy. JAMA Intern Med 179:942-952, 2019
35) Suzuki Y, Tomino Y: Potential immunopathogenic role of the mucosa-bone
marrow axis in IgA nephropathy: insights from animal models. Semin Nephrol
36) Coppo R: The Gut-Renal Connection in IgA Nephropathy. Semin Nephrol
38:504-512, 2018
Turner JR, Fu YX: Dysregulated LIGHT expression on T cells mediates
intestinal inflammation and contributes to IgA nephropathy. J Clin Invest 113:
826-835, 2004
38) Hirano K, Matsuzaki K, Yasuda T, Nishikawa M, Yasuda Y, Koike K, Maruyama
S, Yokoo T, Matsuo S, Kawamura T, Suzuki Y: Association Between
Tonsillectomy and Outcomes in Patients With Immunoglobulin A Nephropathy.
JAMA Netw Open 2: e194772, 2019
Zhao M, Barbour S, Reich H, Cattran D, Glassock R, Levin A, Wheeler D,
Woodward M, Billot L, Chan TM, Liu ZH, Johnson DW, Cass A, Feehally J,
Study Group: Effect of Oral Methylprednisolone on Clinical Outcomes in
Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial.
JAMA 318: 432-442, 2017
40) Liu LL, Wang LN, Jiang Y, Yao L, Dong LP, Li ZL, Li XL: Tonsillectomy for IgA
41) Feehally J, Coppo R, Troyanov S, Bellur SS, Cattran D, Cook T, Roberts ISD,
Verhave JC, Camilla R, Vergano L, Egido J, Wieck A, Karkoszka H, Tesar V,
Maixnerova D, Ots-Rosenberg M, Quaglia M, Rollino C, Magistrone Ri,
Cusinato S, Cravero R, Peruzzi L, Lundberg S, Gesualdo L, Canzarini G,
Feriozzi S, Ferrario F, VALIGA study of ERA-EDTA Immunonephrology


50) Barnes EL, Loftus Jr EV, Kappelman MD: Effects of Race and Ethnicity on Diagnosis and Management of Inflammatory Bowel Diseases. Gastroenterology 160:677-689, 2021


54)Turula H, Wobus CE: The Role of the Polymeric Immunoglobulin Receptor and Secretory Immunoglobulins during Mucosal Infection and Immunity. Viruses 10:237, 2018


63)Moeller S, Canetta PA, Taylor AK, Arguelles-Grande C, Snyder H, Green PH,


76) Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC,


97) Osman W, Okada Y, Kamatani Y, Kubo M, Matsuda K, Nakamura Y: Association of common variants in TNFRSF13B, TNFSF13, and ANXA3 with serum levels of non-albumin protein and immunoglobulin isotypes in


Table 1. Clinical features of patients with IgA nephropathy obtained by questionnaire surveys from European countries and Japan

<table>
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<tr>
<th></th>
<th>Euro</th>
<th>Japan</th>
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<tbody>
<tr>
<td>Numbers</td>
<td>437</td>
<td>470</td>
</tr>
<tr>
<td>Age</td>
<td>43.5</td>
<td>40.1</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 67%, Female 33%</td>
<td>Male 41%, Female 59%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>93% from Caucasian, others from Asian, American and African</td>
<td>all Japanese</td>
</tr>
<tr>
<td>History and persistent macrohematuria</td>
<td>23%</td>
<td>29%</td>
</tr>
<tr>
<td>Time between first detection of hematuria and renal biopsy (&lt; 1 year)</td>
<td>54%</td>
<td>34%</td>
</tr>
<tr>
<td>History of single detection of proteinuria (&gt; 1g/day)</td>
<td>22%</td>
<td>11%</td>
</tr>
<tr>
<td>History of proteinuria (&gt; 300mg/day) in twice detections greater than 3 months apart before renal biopsy</td>
<td>40%</td>
<td>72%</td>
</tr>
<tr>
<td>Nephrotic syndrome before renal biopsy</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>Time between first detection of proteinuria and renal biopsy (&lt;1 year)</td>
<td>72%</td>
<td>40%</td>
</tr>
<tr>
<td>Detection of increase of serum creatinine before renal biopsy</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>eGFR at the time of renal biopsy (&gt; 60 mls/min/1.73m$^2$)</td>
<td>55%</td>
<td>71%</td>
</tr>
<tr>
<td>Significant (&gt;20%) decrease in GFR at time of biopsy over the previous months</td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td>Elevated serum IgA at the renal biopsy</td>
<td>11%</td>
<td>34%</td>
</tr>
<tr>
<td>Family history of kidney disease / family history of IgAN</td>
<td>7% / (IgAN: 2%)</td>
<td>16% / (IgAN: 2%)</td>
</tr>
<tr>
<td>Renal abnormalities were discovered as part of a systematic screening program</td>
<td>10%</td>
<td>74%</td>
</tr>
</tbody>
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Table 2. Complications accompanied by IgA nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Euro</th>
<th>Japan</th>
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<tbody>
<tr>
<td><strong>Gastrointestinal complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>2.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>3.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>4.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Chronic, non-defined</td>
<td>5.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>gastrointestinal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodontitis</td>
<td>0.2%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1.0%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>3.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Time Period</td>
<td>Euro</td>
<td>Japan</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>3 - 6 months</td>
<td>31%</td>
<td>11%</td>
</tr>
<tr>
<td>6 months - 1 year</td>
<td>32%</td>
<td>47%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>2-3 years</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>3-5 years</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Figure legend

Figure 1. The ratio of episodic hematuria coincident with an acute gastrointestinal disorder or upper respiratory tract infection.
There are no clear differences between the ratio of episodic hematuria coincident with an acute gastrointestinal disorder between Europe and Japan. However, the ratio of episodic hematuria coincident with an upper respiratory tract infection was relatively high in both Europe and Japan (22.7% vs. 29.8%, respectively).

Figure 2. History of recurrent tonsillitis and tonsillectomy.
Although recurrent tonsillitis is relatively common in Japanese patients with IgAN, the ratio of tonsillectomy because of recurrent tonsillitis is similar between Europe and Japan. However, tonsillectomy is a common treatment option in Japan, and ~53% of Japanese patients with IgAN underwent a tonsillectomy.

Figure 3. Differences in current status of treatment between Europe and Japan.
Treatment with RAS inhibitors is common in both Europe and Japan. There are major differences in the use of high-dose intravenous corticosteroids and oral corticosteroids between Europe and Japan.
Figure 1-3

Figure 1

Gastro-intestinal disorders

Upper respiratory tract infection

<table>
<thead>
<tr>
<th></th>
<th>Euro (%</th>
<th>Japan (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-intestinal disorders</td>
<td>5.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>22.7%</td>
<td>29.8%</td>
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</tbody>
</table>
History of repeated tonsillitis
Tonsillectomy before renal biopsy
Tonsillectomy because of repeated tonsillitis
Tonsillectomy because of IgAN

Figure 2

Figure 1-3
Figure 1-3

- RAS inhibitors: Euro 66.2%, Japan 53.2%
- High-dose intravenous corticosteroids: Euro 8.0%, Japan 60.0%
- Oral corticosteroids: Euro 12.4%, Japan 61.3%
- Immunosuppressive agents: Euro 8.0%, Japan 1.2%