Soluble interleukin-2 receptor alfa predicts renal outcome in IgA nephropathy

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Abstract

Background. Both systemic and mucosal IgA production are controlled by T lymphocytes and infiltrating T lymphocytes are involved in the progression of interstitial fibrosis in chronic kidney disease (CKD). Since the concentration of soluble interleukin-2 receptor alfa (sIL-2Ra) reflects the degree of T cell activation over time, we studied the impact of interleukin-2 receptor alfa levels on disease progression in patients with biopsy-proven IgA nephropathy (IgAN), a disease in which 20–30% of the patients progress to end-stage renal failure.

Methods. sIL-2Ra plasma levels were measured in 194 patients (median age 39 years, 70% men) and 84 matched controls. One hundred and seventy-nine of the patients, patients (median age 39 years, 70% men) and 84 matched controls. One hundred and seventy-nine of the patients, with an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73m² at baseline (CKD Stages 1–4), were followed for up to 15 years (median 52 months; range 12–188). sIL-2Ra was evaluated as a risk marker for severe renal progression, here defined by the development of CKD Stage 5 (GFR <15 mL/min/1.73m²), a 50% decline in GFR during the follow-up period or a 30% GFR decline within 5 years of follow-up. In 51 patients, upon whom a renal biopsy had been performed within 2 years of IL2-Ra measurement, the biopsies were scored according to the Oxford classification. The correlations between the histopathological findings and the sIL-2Ra levels were examined.

Results. sIL2-Ra levels were significantly higher in patients than in controls (P < 0.001). sIL-2Ra levels in the upper third tertile predicted a severe renal outcome, even after adjustment for the main clinical risk factors: time average albuminuria and GFR at baseline (Relative risk 5.35, P < 0.001). sIL-2Ra levels also correlated significantly to the yearly GFR slope (β = −0.24, P = 0.01). According to the Oxford classification, the presence of >25% tubular atrophy/interstitial fibrosis (T1–2) was associated with higher sIL-2Ra levels, after adjustment for serum creatinine levels, if analysed within 4 months [n = 24, odds ratio (OR) 1.0, P = 0.044] or within 2 years from the kidney biopsy [n = 51, OR 1.0, P = 0.017].

Conclusions. The plasma levels of sIL-2Ra were predictive of long-term renal disease progression in a large cohort of patients with biopsy-proven IgAN. Further studies are warranted to evaluate if sIL-2Ra levels can feasibly contribute in the monitoring of effects of treatment, aimed to prevent the progression of interstitial fibrosis and progressive glomerulosclerosis in IgAN.

Keywords: disease progression; IgA nephropathy; IL-2Ra; risk markers; T-cells

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and ~20–30% of the patients have been shown to progress to end-stage renal failure in long-term follow-up studies [1–3]. The mechanisms involved in mesangial IgA deposition, the initiation and continuation of the inflammatory glomerular injury in IgAN, remain unclear.

Both the systemic and mucosal IgA production appear to be controlled by T lymphocytes [4, 5]. CD4 T lymphocytes (T helper cells, Th cells) play a critical role in the adaptive immune response and promote antibody production and class switching in B cells [6]. Th cells can be divided into four main lineages, Th1, Th2, Th17 and Treg, characterized by the different main signature cytokines, IFNγ, IL-4, IL-17 and TGFβ, respectively. IgAN has been described as a primarily Th2-dependent disease, although the pattern of peripheral T lymphocyte population and renal cytokine expression in IgAN suggests that both Th1 and Th2 may be involved [7–10].

IL-2 is produced by activated T cells and plays a pivotal role in the proliferation of T lymphocytes after antigenic stimulation. Upon activation, the T cell expresses high-affinity receptors for IL-2 (IL-2R), and subsequently, a soluble form of the IL-2R protein (sIL-2R, 45 kDa) is released. The release of sIL-2R appears to be a characteristic marker.
of continuous T lymphocyte activation and is attributed to playing a regulatory function during normal and abnormal cell growth and differentiation [11, 12]. Previous experimental investigations and relatively small cross-sectional studies in IgAN have demonstrated high production of IL-2 and IL-2R [13–15]. However, whether these factors are suitable as prognostic markers has not been validated in longitudinal studies.

A number of clinical, histological and biochemical risk factors have been shown to predict disease progression in patients with IgAN [16–24]. Since T-cell activation seems to be involved in the pathogenesis of IgAN and since the concentration of sIL-2R reflects continuous T-cell activation, we studied the levels of sIL-2Ra in a large cohort of patients with biopsy-proven IgAN who were prospectively followed for up to 15 years. The patient population and follow-up data fulfilled the qualifying criteria described by D’Amico [2]. Our prime aim was to evaluate whether sIL-2Ra could be used as a prognostic marker in IgAN.

Materials and methods

Patients

The population comprised prevalent and incident patients with a renal biopsy-confirmed diagnosis of IgAN who had been treated at the Department of Nephrology at Karolinska University Hospital and Danderyd University Hospital, Stockholm, Sweden. The patients had been consecutively included in a prospective follow-up study between November 1994 and April 2009 (229 patients). From this cohort, we excluded patients with a concomitant diagnosis of malignancy (n = 2), diabetes (n = 7), inflammatory bowel disease (n = 1), rheumatoid arthritis (n = 4), severe ANCA-negative systemic vasculitis (n = 1), anti-phospholipid syndrome (n = 1), traumatic damage to the kidney (n = 1), nephropathia epidemica (n = 1), acute tubular necrosis (n = 2) and pregnancy (n = 1). Patients were also excluded if they had been treated with steroids within 6 months prior to the sample collection (n = 12) or if they were ≥75 years at renal biopsy (n = 2).

None of the patients had any liver disease or had started renal replacement therapy at baseline.

Cross-sectional study cohort (patients and controls)

In all, the cross-sectional patient cohort comprised 194 patients (136 men, 70%), including 18 patients with an initial manifestation of Henoch–Schönlein purpura. Eighty-four control subjects from a population-based cohort were obtained from the Swedish National Register and were matched to the patient group by gender and age. Control individuals with a known diagnosis of renal disease, malignancy, diabetes mellitus, liver disease or chronic rheumatologic or inflammatory disease were excluded.

The study was approved by the local Ethics Committee at the Karolinska University Hospital and Danderyd University Hospital. Stockholm, Sweden and informed consent was obtained from all participants.

Follow-up study cohort

For follow-up analysis, 179 patients with an estimated MDRD (Modification of Diet in Renal Disease) glomerular filtration rate (GFR) of ≥15 mL/min/1.73 m² [chronic kidney disease (CKD) Stages 1–4] at baseline were included. Of the initial 194 patients, 7 had CKD Stage 5 at baseline and another 8 were excluded from follow-up analysis as they had been followed for <12 months.

The cohort consisted of 126 men (70%) and 53 women, the median patient age at baseline was 38 years (range 19–74) and the median time from the renal biopsy was 20 months (range 0–434). The median interval from first clinical signs of renal disease (episode of macroscopic haematuria, discovery of microscopic haematuria or proteinuria or renal insufficiency) to baseline examination was 6 years (range 0–43 years). Patients were followed until the final observation on 1 November 2010, which resulted in a mean follow-up period of 63 ± 40 months and median follow-up period of 52 months (range 12–188). During the follow-up, 1 patient died from cardiovascular disease, 20 patients started dialysis or received a kidney transplant and 13 patients moved away from the district and were therefore lost to follow-up after a median observation period of 43 months (range 13–76).

Clinical data and routine laboratory results

At baseline, plasma samples were drawn and stored at –70°C. Clinical data and routine laboratory results were collected from the patients’ records at the time of inclusion and once yearly thereafter. The healthy controls were asked to fill in a health questionnaire and a blood pressure control was performed in the sitting position after 5 min of rest.

Analyses of serum creatinine (reference <100 μmol/L for men, <90 μmol/L for women) were performed using routine methods. To correct for the different method-related reference values during the period from 1 January 2001 until 1 March 2005, 5 μmol/L were subtracted from the serum creatinine values obtained for standardizing to isotope dilution mass spectrometry (IDMS), according to recommendations from the local laboratory.

For the assessment of albuminuria, patients had either provided a 24-h urine sample or a morning urine sample for analysis of the urine-albumin/creatinine ratio (U-alb/cr, reference <3.0 mg/mmol). From the latter samples, 24-h albuminuria was calculated using the Cockcroft–Gault formula in accordance with Fournier [25] [(U-alb/24-h × U-cr/1000) × (140–age) × weight × 1.77/1000] for men and U-alb/24-h × U-cr/1000 × (140–age) × weight × 1.5/1000 for women. From the healthy subjects, a urine sample was obtained for analysis of the U-alb/cr ratio. U-alb/cr values of <2 mg/mmol were defined as 1 mg/mmol, for calculation of median values. Haematuria on dipstick was recorded in the range of 0–3+. Body mass index (BMI) was calculated by dividing a person’s weight by the square of their height. Mean arterial blood pressure (MAP) was calculated as the sum of diastolic blood pressure and one-third of the difference between systolic and diastolic blood pressure. GFR was estimated by the four-parameter MDRD equation for serum creatinine values standardized to IDMS [26].

Analysis of sIL-2Ra

The analysis of plasma sIL-2Ra concentrations was performed on the Luminex-100 system (Luminex Corporation) using Milliplex-kit (Millipore), according to the manufacturer’s instructions. The lower detection limit was 3 pg/mL and a value of <3 pg/mL was defined as 2 pg/mL for statistical analysis.

Definition of progressive disease

Progressive disease was defined by either reaching CKD Stage 5 [estimated glomerular filtration rate (eGFR) of <15 mL/min/1.73 m²] or a 50% decline of eGFR during follow-up or a 30% decline of eGFR within 5 years of follow-up. The rate of decline in renal function was expressed as the slope of eGFR, which was obtained by fitting a straight line through the calculated eGFR values, using linear regression and the principal of least squares.

Risk factors for progressive disease

For survival analysis, the levels of sIL-2Ra and of BMI were dichotomized with a cut-off point at the upper tertile, eGFR was stratified by 10 mL/min/1.73 m² and age by 10 years. Time average albuminuria (TA albuminuria) and time average MAP (TA MAP) were assessed as the mean of albuminuria or MAP measurements during follow-up. We also assessed the correlations between continuous values of risk factors and eGFR slope.

Histopathologic classification

Patients with primary IgAN, having had baseline blood samples drawn within 2 years from the renal biopsy and sufficient biopsy material (more than eight glomeruli without global sclerosis) (n = 51), were considered for histopathologic scoring of the biopsy specimens according to the Oxford classification. In brief, four histopathological variables were scored: Mesangial hypercellularity (M0/M1), segmental glomerulosclerosis (S0–S1), endocapillary hypercellularity (E0–E1) and tubular atrophy/interstitial fibrosis (T0 if absent, T1 if >25%, T2 if >50%) [17].

Statistical analyses

Results are reported as mean ± SD when normally distributed or otherwise as median and interquartile ranges. Comparisons of continuous variables between two groups were assessed using Student’s unpaired t-test or Mann–Whitney U-test as appropriate. Differences in proportions in different
Results

Baseline characteristics of patients and controls and correlations with inflammatory markers

Serum creatinine, the degree of albuminuria, MAP and BMI were higher in patients compared to controls (Table 1). Also, sIL-2Ra values were higher in patients than in controls (P < 0.001). In patients, sIL-2Ra levels showed a correlation to serum creatinine [rSpearman (rS) = 0.30, P < 0.001] and to 24-h albuminuria (rS = 0.24, P = 0.001). There was no such correlation in the controls (rS = -0.053, P = 0.63 and rS = -0.058, P = 0.57, respectively).

According to the National Kidney Foundation classification of CKD, 44 patients (23%), 84 patients (43%), 47 patients (24%), 12 patients (6%) and 7 patients (4%) were in CKD Stages 1, 2, 3, 4 or 5, respectively. All the control subjects had an eGFR of ≥ 60 mL/min/1.73m².

One hundred and twenty-five patients (64% of the cross-sectional study cohort) were treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) at baseline, 28 patients (14%) used statins and 16 patients (8%) fish oil. None of the control subjects were prescribed any of these medications.

Association of sIL-2Ra levels with renal outcome

In the follow-up cohort, tertiles of sIL-2Ra levels were ≤ 25.3, 25.3–153.1 and 153.2–1549.3 pg/mL. High sIL-2Ra, defined as sIL-2Ra levels in the upper third tertile, were predictive of progression to the combined end point, independent of kidney function at baseline, the degree of albuminuria during follow-up, MAP during follow-up, age or a combination of these variables (Table 2). Estimated GFR and albuminuria at baseline, TA albuminuria and TA MAP were all associated with progressive disease, but not MAP, age or BMI (dichotomized by the upper third tertile of 27 kg/m²) at baseline (Table 2). Also, continuous sIL-2Ra levels were associated with progressive disease (HR = 1.002, 95% CI 1.002–1.003, P < 0.001). Figure 1 shows the impact of sIL-2Ra levels, divided into tertiles, on survival from kidney function loss which can be compared with the impact of TA albuminuria, dichotomized by 1 g/24-h, as visualized in Figure 2.

Thirty of the 179 (17%) patients included in the survival analysis had progressive disease as defined in the Materials and method section. Of these, 20 patients had progressed to CKD Stage 5, 9 patients had a decline in GFR of at least 30% within 5 years of follow-up and 1 patient had a GFR decline of >50% during the total follow-up period. The median sIL-2Ra levels in these groups were 204.6 (range 2–878.5), 199.2 (range 52.5–1549.3) and 162.2 pg/mL, respectively.

Differences in clinical parameters, including medications, between patients with high or low sIL-2Ra levels (defined by the cut-off value of 153.2 pg/mL) are shown in Table 3.

There were no significant differences in age, gender, the percentage of patients with primary IgAN, time from first discovery of signs of renal disease, BMI, MAP, TA MAP during follow-up or use of statins, fish oil or immunosuppressive treatment. In patients with high sIL-2Ra levels, a shorter period had passed from time of diagnosis to baseline evaluation. Patients with high sIL-2Ra levels had a lower eGFR at baseline and a higher degree of albuminuria at baseline and during follow-up.

Compared to the low sIL-2Ra group, more patients in the high sIL-2Ra group had ACEIs or ARBs. Eighteen patients (10 per cent of each group) had been treated with oral prednisolone during the disease course, in three cases combined with methyl prednisolone infusions, in one case combined with oral cyclophosphamide for 12 weeks. In 6 cases, the immunosuppressive treatment had been terminated between 5 years and 9 months before the baseline assessment, in the

Table 1. Baseline clinical parameters and laboratory results in patients compared to healthy controls and correlation to sIL-2Ra

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 194)</th>
<th>Controls (n = 84)</th>
<th>P-valuea</th>
<th>sIL-2Ra</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30%</td>
<td>27%</td>
<td>0.77</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.9 ± 12.5</td>
<td>40.5 ± 12.8</td>
<td>0.79</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>S-cr</td>
<td>97 (80–127)</td>
<td>80 (68–88)</td>
<td>&lt;0.001</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>U-alb/24-h</td>
<td>0.37 (0.10–1.20)</td>
<td>0.0 (0.0–0.01)</td>
<td>&lt;0.001</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>99 ± 10</td>
<td>93 ± 18</td>
<td>0.011</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI</td>
<td>25.8 ± 3.9</td>
<td>24.3 ± 3.0</td>
<td>0.018</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>sIL-2Ra (pg/mL)</td>
<td>101.8 (13.4–199.2)</td>
<td>2.0 (2.0–2.92)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aS-cr, serum creatinine. Normally distributed variables are expressed as mean and SDs, non-normally distributed variables as median and IQ ranges (25th and 75th percentiles). Only correlations with a significant P-value of <0.05 are shown (values represent Spearmen rank r); n.s., non significant.
bMann–Whitney U-test.
remaining 12 cases, the immunosuppressive treatment had been started between 1 day and 3 years after baseline.

Correlations of sIL-2Ra levels and clinical parameters with rate of renal function decline

As shown in Table 4, sIL-2Ra levels at baseline were significantly correlated to the rate of decline in renal function, also after adjustment for either of the best known clinical risk factors TA albuminuria or TA MAP. Age, eGFR and MAP at baseline did not correlate to the rate of renal function decline during follow-up and there was no significant gender difference in the GFR slope (median −0.6 mL/min/1.73m²/year (interquartile, IQ, range −3.2 to +1.5) in men and −1.1 mL/min/1.73m²/year (IQ range −3.4 to +0.4) in women, P = 0.37). The median rate of renal function decline was −5.6 mL/min/1.73m²/year (IQ range −12.2 to −3.9) in patients with progressive disease, as defined in this study, compared to −0.4 mL/min/1.73m²/year (IQ range −1.85 to +1.05) in patients with more stable disease.

Histopathologic classification and correlation to sIL-2Ra and clinical parameters

In 51 tissue samples, scored by the Oxford classification, continuous sIL-2Ra levels were predictive of the presence of >25% of tubulointerstitial fibrosis (T1–2) after adjustment for serum creatinine (logistic regression analysis, odds ratio (OR) 1.007 (CI 1.001–1.013), P = 0.014, data not shown).
In 24 patients, blood samples were available within 4 months of renal biopsy. In these patients, the presence of >25% of tubulointerstitial fibrosis in kidney biopsy specimens (T1–2) was significantly associated with higher sIL-2Ra levels (P = 0.013) and higher serum creatinine levels at baseline (P = 0.003) and with a longer period from onset to diagnosis (P = 0.034). The mesangial proliferation index M1 and the presence of endocapillary proliferation (E1) were associated with the degree of haematuria at baseline (P = 0.029 and P = 0.029, respectively). The presence of segmental sclerosis (S1) was associated with a higher degree of albuminuria (P = 0.044) and a higher MAP at baseline (P = 0.019, Table 5).

**Discussion**

This is the first report evaluating sIL-2Ra levels as a single risk marker for disease progression in IgAN during a long-
The finding of increased levels of sIL-2Ra in IgAN is in agreement with cross-sectional studies performed by other groups [15]. Parera et al. [14] demonstrated an increased percentage of IL-2Ra-positive cells (CD25+) in IgAN patients compared to controls and Schena et al. [13] reported a higher IL-2Ra expression on peripheral blood mononuclear cells in patients with IgAN compared to patients with other forms of chronic glomerulonephritis. In line with these in vivo findings, Lai et al. [27] reported that the cellular IL-2Ra expression paralleled the sIL-2Ra release by cultured lymphocytes, isolated from patients with IgAN, patients with other forms of chronic glomerulonephritis or healthy controls. In systemic lupus erythematosus, serum IL-2Ra levels were higher in patients with lupus nephritis than those without nephritis or healthy controls and also correlated to disease activity [28, 29].

In the present study, renal function was found to influence the serum levels of sIL-2Ra. This has also been reported in patients with different forms of glomerular disease [15] and in patients with end-stage renal disease [30]. Also in IgAN, sIL-2Ra levels correlated with active urinary sediment findings, whereas urinary IL-2Ra levels did not appropriately reflect disease activity [14, 15]. There is increasing evidence for both innate and adaptive aberrant immune regulation in IgAN, biased by genetic background, including Toll-like receptor (TLR) expression, T lymphocyte activation and B cell maturation [5, 31–34]. A disturbed mucosal immune response to environmental factors such as microbial or food antigens may lead to activation of the innate immune system, triggering of inflammatory transcription factors followed by generation of mediators that further impact T and B cell function. These events thereby constitute a link between the innate and adaptive immune systems [32, 35]. The genetic background can influence these mechanisms on different levels, and inherited HLA specificities are considered to play a major role in determining the immune response to endogenous and exogenous antigens. In support of this view is the fact that it has been demonstrated that genetic factors, activation of TLRs and Th2 cytokines contribute to the altered glycosylation of IgA1, which plays a predominant role in the pathogenesis of IgAN [36–43]. It is hypothesized that a skewed Th1/Th2 balance might contribute to the difference in clinical and pathological pictures between individual patients with IgAN. An advantage of measuring sIL-2Ra could therefore be that this molecule mirrors the overall T cell activation over time. This view is supported by the fact that we did not find any significant difference in sIL-2Ra levels between patients with primary IgAN and IgAN with manifestations of Henoch–Schönlein purpura (HSPN). Patients with HSPN typically have more active crescents in kidney biopsy, a pathological picture generally associated with Th1 predominance in experimental studies [44]. In contrast, renal biopsies in patients with primary IgAN often show histopathological changes of a more chronic nature, possibly more closely associated with Th2 predominance. Although no major biological or genetic differences have been found comparing IgAN and HSPN, the classification of the two conditions as different forms of the same disease is not generally accepted [45, 46].

We found an association of a higher degree of tubular atrophy/interstitial fibrosis with higher sIL-2Ra levels in a subgroup of patients evaluated with the new Oxford histopathologic classification. This is in line with the current concept that the progression of tubular injury and renal

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**Table 4.** Univariate and multivariate adjusted associations between sIL-2Ra levels or clinical markers and rate of renal function decline

<table>
<thead>
<tr>
<th>Marker</th>
<th>β</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIL-2Ra (pg/mL)</td>
<td>-0.239</td>
<td>-0.384 to -0.094</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted for eGFR baseline</td>
<td>-0.227</td>
<td>-0.376 to -0.079</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted for TA albuminuria</td>
<td>-0.220</td>
<td>-0.365 to -0.074</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted for TA MAP</td>
<td>-0.166</td>
<td>-0.310 to -0.022</td>
<td>0.024</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.041</td>
<td>-0.108 to 0.189</td>
<td>0.33</td>
</tr>
<tr>
<td>eGFR baseline (10 mL/min/1.73m²)</td>
<td>0.107</td>
<td>-0.041 to 0.255</td>
<td>0.15</td>
</tr>
<tr>
<td>Albuminuria at baseline (g/24-h)</td>
<td>-0.215</td>
<td>-0.362 to -0.069</td>
<td>0.004</td>
</tr>
<tr>
<td>MAP baseline (mmHg)</td>
<td>-0.358</td>
<td>-0.498 to -0.217</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TA MAP (mmHg)</td>
<td>-0.322 to -0.026</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*a* eGFR, estimated GFR by four-parameter MDRD formula.

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**Table 5.** Summary of P-values for differences in laboratory results and clinical findings at baseline with respect to Oxford classification scores in renal biopsies performed within 4 months (n = 24)

<table>
<thead>
<tr>
<th>Marker</th>
<th>M0:M1</th>
<th>E0:E1</th>
<th>S0:S1</th>
<th>T0:T1–2</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIL-2Ra</td>
<td>0.35</td>
<td>0.16</td>
<td>1.00</td>
<td>0.013</td>
</tr>
<tr>
<td>S-creatinine</td>
<td>0.35</td>
<td>0.18</td>
<td>0.33</td>
<td>0.003</td>
</tr>
<tr>
<td>Degree of haematuria</td>
<td>0.029</td>
<td>0.029</td>
<td>0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>0.157</td>
<td>0.210</td>
<td>0.044</td>
<td>0.099</td>
</tr>
<tr>
<td>MAP</td>
<td>0.115</td>
<td>0.157</td>
<td>0.019</td>
<td>0.664</td>
</tr>
<tr>
<td>BMI</td>
<td>0.682</td>
<td>0.494</td>
<td>0.230</td>
<td>0.153</td>
</tr>
<tr>
<td>Time from onset to biopsy</td>
<td>0.682</td>
<td>0.737</td>
<td>0.891</td>
<td>0.034</td>
</tr>
</tbody>
</table>

P-values (two sided) are results of Mann–Whitney U-test, P < 0.05 in bold.

Degree of haematuria on dipstick (0, 1+, 2+, 3+).
fibrosis is associated with the presence of infiltrating mononuclear cells, predominantly T lymphocytes [47–51]. The progression of interstitial fibrosis is partly caused by ischaemia due to atherosclerotic vessel damage with hyalinosus and media hypertrophy, which is frequently observed in renal biopsies of patients with IgAN. In addition, activated T cells are frequently present in human atherosclerotic lesions [52–54].

Interestingly, besides treatment with immunosuppressive, treatment with ACEIs and treatment with statins have shown to influence T lymphocyte activity [55–57], which also may have influenced IL-2Ra levels in our study. Patients respond individually and differently to a given therapy. Genetic polymorphisms of the ACE gene, shown to associate with IgAN disease progression, as reviewed by Hsu et al. [33], could be one explanatory factor. In our patient cohort, the majority of patients had ongoing treatment with ACEIs or ARBs at baseline. Patients with higher IL-2Ra levels were more often on ACEI/ARB treatment than patients with lower IL-2Ra levels, probably due to treatment indication, as the former patient group also had more albuminuria and lower kidney function. The observational character of our study and the limited number of patients on lipid-lowering therapy, or with a history of immunosuppressive treatment, did not allow any statistical analysis of the effect of treatment on either IL-2Ra levels or outcome.

A large number of studies have been published during recent decades describing different ways of predicting renal outcome in IgAN and potential clinical risk markers. The patient population and follow-up data of our study meet the qualifying criteria defined by d’Amico of (i) a relatively patient population and follow-up data of our study; (ii) definite histological qualifying criteria; (iii) small percentage of patients lost to observation and prolonged follow-up, at least 5 years on average and (iv) statistical evaluation including Cox regression models [2]. Moreover, our patient population was recruited from only two different nephrology centres in the same town, with similar clinical practice and only a few different nephrologists taking care of the patients in clinical practice. To define outcome in our study, we chose the well-established criteria of CKD Stage 5 (end-stage renal disease) or a 50% decline of eGFR during follow-up. To minimize the number of misclassified patients according to these criteria due to a limited follow-up time, we also defined patients with an eGFR decline of at least 30% within 5 years of follow-up as having progressive disease.

In the present study, we report for the first time that the plasma level of sIL-2Ra is predictive of renal disease progression in a large cohort of patients with biopsy-proven IgAN, providing further support for the view that IgAN is a T-cell-driven disease. Further studies are warranted to establish whether sIL-2Ra levels are appropriate considerations in the monitoring of effect of treatment, aimed to prevent the progression of interstitial fibrosis and progressive glomerulosclerosis in this patient group.

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