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# Spondyloarthritis-Associated IgA Nephropathy



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**Introduction:** IgA nephropathy (IgAN) can be associated with spondyloarthritis (SpA). The course of SpA-associated IgAN remains largely unknown due to the absence of large cohorts.

**Methods:** This retrospective study included patients with biopsy-proven IgAN and definite SpA. Kidney biopsies were centrally examined and scored according to the IgAN Oxford Classification. Thirty-two patients fulfilled the inclusion criteria, with a male:female ratio of 9:1 and median age of 27 and 37 years at SpA and IgAN diagnosis, respectively. HLA-B27 was positive in 90% of cases, and most patients (60%) presented with ankylosing spondylitis. The mean baseline estimated glomerular filtration rate (eGFR) was  $84 \pm 26$  ml/min per  $1.73 \text{ m}^2$ , and the urine protein-to-creatinine ratio was 0.19 g/mmol.

**Results:** Renal biopsy revealed frequent presence of crescents (33%) and interstitial inflammation (18%). Despite almost constant use of renin-angiotensin system inhibitors, combined with steroids in 13 of 32 patients, renal outcome was particularly poor. After a median follow-up of 5.9 years, 4 patients (12.5%) reached end-stage renal disease and 41% of patients experienced a >50% decrease of eGFR. The mean annual eGFR decline rate was  $-4.3 \pm 6.7$  ml/min per  $1.73 \text{ m}^2$ . The risk of reaching class IV or V chronic kidney disease (CKD) stage during follow-up was associated with the presence of hypertension, level of proteinuria, and baseline S- and T-scores of the Oxford.

**Conclusion:** SpA-associated IgAN is associated with a poor renal outcome, despite frequent use of steroids. Tumor necrosis factor (TNF)- $\alpha$  blockade did not appear to influence the rate of eGFR decline in this setting.

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KEYWORDS: ankylosing spondylitis; IgA nephropathy; NSAIDs; renal failure; spondyloarthritis; TNF- $\alpha$  blockers

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## See Commentary on Page 766

IgAN is an immune complex-driven glomerulonephritis linked to the presence of mesangial IgA deposits. Primary IgAN is characterized by the absence of extrarenal manifestations. Nevertheless, various medical conditions have been associated with this glomerulopathy, defining the so-called secondary forms of IgAN. Knowing the high prevalence of IgAN,<sup>1</sup> most of these

associations are possibly accidental; however, some associations are particularly frequent, such as SpA-associated IgAN.<sup>2</sup> More than 50 cases have been reported to date, suggesting that these 2 diseases share common pathophysiological mechanisms.<sup>3–5</sup> Nevertheless, the description of SpA-associated IgAN is only based on single-case reports and small series. In addition, it remains unknown whether SpA-associated IgAN differs from primary IgAN in terms of clinical presentation, renal pathology, and prognosis. Finally, the renal effects of drugs used for SpA management, such as glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-TNF- $\alpha$  biologics, have not been studied in this situation. Although glucocorticoids seem to be beneficial in the course of primary IgAN,<sup>6,7</sup> the safety of anti-TNF- $\alpha$  agents in this setting remains controversial. The occurrence of rapidly progressive IgAN has been reported after initiation of anti-TNF- $\alpha$ ,<sup>8–11</sup> as well as treatment-induced cases of focal segmental glomerulosclerosis,<sup>12</sup> whereas other reports have described remission of nephropathy following biotherapy initiation.<sup>13,14</sup>

The aim of this study was to obtain a detailed description of clinical presentation, kidney pathology, and outcome of SpA-associated IgAN, but also to evaluate both the efficacy and safety profile of anti-TNF- $\alpha$  agents in this population.

## METHODS

### Study Population

This retrospective study was based on a French nationwide survey conducted between October 2012 and December 2014. Nephrologists, rheumatologists, and internal medicine specialists from all French University Hospitals were contacted through either the French Nephrology Society network or the “Club Rhumatismes et Inflammation,” a permanent committee of the French Society for Rheumatology.

Adult patients were eligible if they met both of the following criteria:

- (i) IgAN proven by kidney biopsy with glomerular mesangial IgA deposits on immunofluorescence and compatible lesions on light microscopy.<sup>15</sup> Cases of Henoch–Schönlein purpura, defined by cutaneous or gastrointestinal involvement of IgA vasculitis, were not included.
- (ii) SpA diagnosis according to the Amor classification criteria.<sup>16</sup>

No specific temporal relationship between the IgAN and SpA diagnosis was required for inclusion.

### Data Collection

After patient identification, both the referring nephrologist and rheumatologist were asked to fill out a

standardized data collection form. Collected information included general demographics, significant comorbidities, and clinical and laboratory data concerning disease activity and treatment.

Rheumatologists were asked to confirm SpA diagnosis and to define the clinical subtype: ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease-associated SpA (IBD-SpA), reactive arthritis, and undifferentiated SpA. The disease activity score (Bath Ankylosing Spondylitis Disease Activity Index) was recorded, when available.

Nephrologists reported the nature and date of the first clinical or biological sign revealing IgAN (e.g., macroscopic hematuria, urine tests abnormalities). This was considered as the onset of renal disease, even if IgAN diagnosis was sometimes confirmed only several years later.

### Definitions

CKD stages were defined according to the current Kidney Disease: Improving Global Outcomes classification.<sup>17</sup> Proteinuria was reported as urine protein-to-creatinine ratio. The eGFR was calculated using the Modification of Diet in Renal Disease Study equation.<sup>18</sup> *The rate of eGFR deterioration was calculated by dividing the difference between the initial eGFR, at nephropathy diagnosis, and the last eGFR available by the duration separating these 2 values.* The renal endpoint was defined as reaching CKD stage 4/5 (eGFR <30 ml/min per 1.73 m<sup>2</sup>) or doubling or serum creatinine during follow-up. The SpA diagnosis was based on the Amor criteria.<sup>16</sup> The AS diagnosis was based on the revised New York classification criteria.<sup>19</sup>

### Renal Pathology

Whenever possible, tissue specimens from the first kidney biopsy that established the diagnosis of IgAN were retrieved for centralized examination by an experienced renal pathologist who was blinded to the clinical data and renal outcome. Renal biopsies were scored according to the Oxford Classification<sup>15,20</sup> as follows: mesangial hypercellularity, M0/M1 (if <50% or >50% of glomeruli showed >4 mesangial cells/area, respectively); endocapillary hypercellularity, E0/E1 (present/absent); segmental glomerulosclerosis, S0/S1 (present/absent); tubular atrophy/interstitial fibrosis, T0/T1/T2 ( $\leq$ 25%, 26%–50%, >50% of cortical area, respectively) and crescents, C0/C1/C2 (no crescents, <25%,  $\geq$ 25%). In addition, the percentage of sclerotic glomeruli, as well as the presence of arterial intimal thickening, thrombotic microangiopathy and tubulo-interstitial inflammation was recorded.

## Statistical Analysis

Statistical analysis was performed using JMP8 software (SAS Institute, Cary, NC). Comparisons between discrete variables were made using the Fisher exact test. For continuous variables, comparisons were performed using an unpaired 2-tailed Student's *t* test or Mann-Whitney *U* test as appropriate. To determine prognosis factors of IgAN, patients were divided into 2 groups according to their renal outcomes at the end of follow-up. The proportion of patients exhibiting a given risk factor was then compared between groups using the Fisher exact test. Renal prognosis was also evaluated with a Cox time-to-event analysis. Survival analysis was performed with the Kaplan-Meier method. Patients were censored if lost to follow-up. *P* values < 0.05 were considered significant.

## RESULTS

### Study Population

Forty patients were reported to the investigators via the survey and were subsequently reviewed to check the inclusion criteria. Twenty-one patients were referred by a nephrologist and 11 by a rheumatologist. Seven patients were not included because IgAN had not been confirmed by a kidney biopsy or because rheumatic disease did not fulfill the Amor criteria. One more patient with systemic IgA vasculitis was excluded. Final analysis was performed on 32 patients with SpA-associated IgAN.

### Characteristics of SpA

The SpA subtypes included AS (*n* = 20), undifferentiated SpA (*n* = 7), psoriatic arthritis (*n* = 3), and IBD-associated SpA (*n* = 2) (Table 1). One patient with ulcerative colitis met the criteria for both IBD-SpA and AS.

Most patients had both axial and peripheral symptoms (*n* = 18; 56%), although purely axial (*n* = 12; 37%) or peripheral (*n* = 2; 6%) forms also were reported. Seventeen patients presented with extra-articular symptoms associated with SpA, including 10 patients with ocular manifestations (uveitis *n* = 8; scleritis *n* = 1, episcleritis *n* = 2), 6 patients with cutaneous psoriasis, and 2 patients with IBD (1 Crohn's disease and 1 ulcerative colitis).

First-line treatment for SpA included salazopyrine (*n* = 14), methotrexate (*n* = 9), azathioprine (*n* = 1), or ciclosporin (*n* = 1). In addition, several patients received prolonged (> 3 months) treatment with NSAIDs (*n* = 12) or prednis(ol)one (*n* = 7, 5 to 20 mg/d). Twenty-two patients (69%) received at least 1 anti-TNF- $\alpha$  agent during their disease. The median delay between SpA onset and anti-TNF- $\alpha$  initiation was 6.1 years. Evaluation of anti-TNF- $\alpha$  efficacy was provided

**Table 1.** Demographics and spondyloarthritis characteristics

Characteristics	Value	
Age at spondyloarthritis onset, yr, median (range)	27 (9–59)	
Male sex, <i>n/N</i> (%)	27/32 (84)	
HLA B27 positivity, <i>n/N</i> (%)	26/29 (90)	
Spondyloarthritis subtype, <i>n</i> (%)		
AS	20 (62)	
PsA	3 (9)	
IBD-AA	2 (6)	
USP	7 (22)	
Topography of articular symptoms, <i>n</i> (%)		
Axial and peripheral	18 (56)	
Pure axial form	12 (37)	
Pure peripheral form	2 (6)	
Radiologic sacroiliitis	26 (81)	
Extra-articular symptoms, <i>n</i> (%)		
Psoriasis	6 (19)	
Uveitis/Scleritis/Episcleritis	8/1/2 (25/3/6)	
Inflammatory bowel disease	2 (6)	
Disease activity indices		
CRP max, mg/l, median (IQR)	35 (10–126)	
BASDAI max, median (IQR)	55 (40.7–60)	
<b>Treatments</b>	<b>Any time, <i>n</i> (%)</b>	<b>After nephropathy onset, <i>n</i> (%)</b>
NSAIDs	12 (38)	7 (22)
Corticosteroids	6 (19)	6 (19)
Methotrexate	9 (28)	2 (6)
Salazopyrin	14 (45)	7 (21)
Anti-TNF $\alpha$	22 (69)	20 (62)
Infliximab	9 (28)	9 (28)
Adalimumab	13 (41)	10 (31)
Etanercept	12 (38)	11 (34)

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; IBD-AA, inflammatory bowel disease-associated arthritis; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; USP, undifferentiated spondyloarthritis.

Corticosteroid use for treating IgA nephropathy is not reported here. For NSAIDs, only prolonged use (daily consumption for at least 3 mo) is reported.

in 20 cases. A complete (*n* = 12 of 20) or partial (*n* = 6 of 20) response of articular manifestations to anti-TNF- $\alpha$  was observed in most cases. The main causes of modification or discontinuation of anti-TNF- $\alpha$  treatment were lack/loss of efficacy (*n* = 11) and side effects (*n* = 5), including cutaneous vasculitis, worsening of psoriasis, pericarditis, renal cancer, and local reaction at the injection site.

### Characteristics of Nephropathy at Disease Onset

For most patients (*n* = 23 of /32), rheumatic disease preceded nephropathy, whereas in 5 cases, renal and rheumatic disease onset was concomitant (<1 year) (Table 2). Overall, the delay between SpA and IgAN diagnosis ranged from –17 to +28 years. There was a significant correlation between the age at the first sign of rheumatic and kidney disease ( $\rho = 0.75$ ,  $P < 10^{-6}$ ).

In most cases, kidney disease was asymptomatic, with fortuitous discovery of proteinuria and/or microhematuria (*n* = 18). At initial kidney evaluation, 9 (28%) reported previous episodes of macrohematuria

**Table 2.** IgA nephropathy characteristics

Characteristics	Value	
Initial presentation		
Age at nephropathy onset, yr, median (range)	37 (10–71)	
Hypertension, <i>n</i> (%)	11 (34)	
Nephrotic syndrome, <i>n</i> (%)	4 (12)	
Macroscopic hematuria, <i>n</i> (%)	9 (28)	
Acute or rapidly progressive renal failure, <i>n</i> (%)	5 (16)	
Mean eGFR, ml/min per 1.73 m <sup>2</sup>	84 $\pm$ 26	
Mean uPCR, g/mmol	0.19 $\pm$ 0.18	
Progression of nephropathy		
Follow-up, yr, median (range)	5.9 (0.4–24)	
Delay until combined renal endpoint, yr, mean $\pm$ SD	9.2 $\pm$ 0.9	
Rate of eGFR decline, ml/min per 1.73 m <sup>2</sup> per year	–4.3 $\pm$ 6.7	
Presence of hypertension at last follow-up, <i>n</i> (%)	15 (63)	
Chronic kidney disease stage		
	At presentation, <i>n</i> (%)	At last follow-up, <i>n</i> (%)
1. eGFR > 90 ml/min	15 (48)	12 (38)
2. 60 < eGFR < 90 ml/min	12 (39)	7 (22)
3. 30 < eGFR < 60 ml/min	2 (6.5)	5 (16)
4. 15 < eGFR < 30 ml/min	2 (6.5)	4 (12)
5. eGFR < 15 ml/min per ESRD	0	4 (12)

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease, uPCR, urine protein-to-creatinine ratio.

and 11 patients (34%) had hypertension. The initial mean eGFR was 84  $\pm$  26 ml/min per 1.73 m<sup>2</sup> with only 4 patients less than 60 ml/min per 1.73 m<sup>2</sup>. The mean urine protein-to-creatinine ratio at IgAN diagnosis was 0.19  $\pm$  0.18 g/mmol, and serum IgA concentration was above normal levels in 17 of 22 (77%) cases.

## Renal Pathology

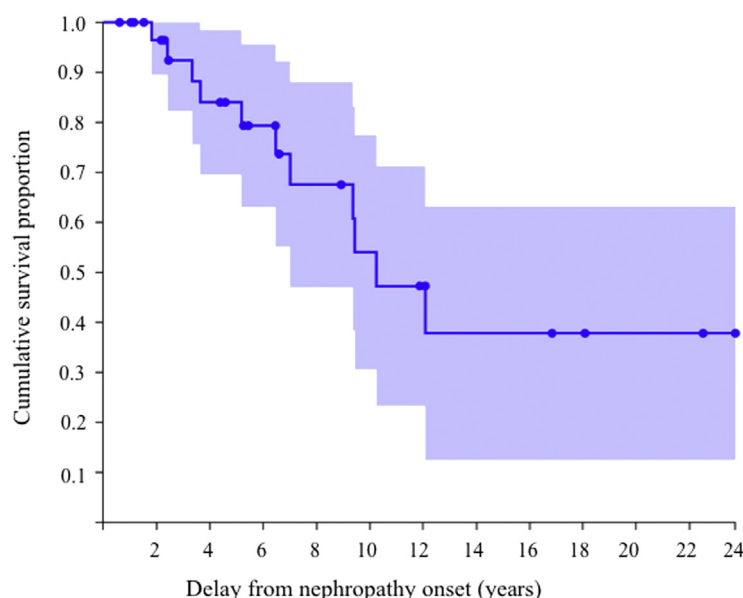
A kidney biopsy was performed after a median delay of 7 months following the initial renal symptoms. Overall,

37 kidney biopsies were performed during the follow-up of these 32 patients. We collected 35 biopsy specimens for a centralized histopathological review. Five inadequate biopsies, containing fewer than 8 glomeruli, and 3 repeat biopsies were excluded from analysis.

Examination of the 27 biopsies performed at diagnosis revealed that the renal lesions were usually mild. The median total number of glomeruli was 13 (interquartile range, 11–25), and the median percentage of sclerotic glomeruli was 12% (interquartile range, 0–28). The M-score was 0 in 18 of 27 (67%) cases, the E-score was 0 in 18 of 27 (67%) cases, and the S-score was 0 in 8 of 27 (29%) cases. The T-score was 0 in 18 of 27 (67%) cases, 1 in 7 of 27 (26%) cases, and 2 in 2 of 27 (7%) cases. Cellular or fibrocellular crescents were found in 9 of 27 biopsies (33%), with a C1 score in 7 cases and a C2 score in 2. Thrombotic microangiopathy was observed in only 1 case, but arterial intimal thickening was common, which scored 1 (<25% of luminal surface) in 5 of 27 (18%) cases, 2 (26% to 50% of luminal surface) in 3 of 27 (11%) cases, and 3 (>50% of luminal surface) in 3 of 27 (11%) cases. Finally, significant interstitial inflammation, occupying >10% of the cortical area, was found in 5 of 27 (18%) cases.

## Treatment and Outcome of Nephropathy

In most cases, nephropathy was treated according to commonly accepted recommendations.<sup>21</sup> Except for 6 patients with a mild proteinuria (<0.1 g/mmol of creatinine) and no hypertension, almost all patients received renin-angiotensin system inhibitors (*n* = 26; 81%), such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Hypertension



**Figure 1.** Survival without reaching the combined renal endpoint (chronic kidney disease stage 4 or 5 and/or doubling of serum creatinine). Circles represent censored data. The shaded zone represents the 95% confidence interval.

occurred during the course of nephropathy in 20 patients (62%), requiring prescription of up to 6 anti-hypertensive drugs (median value = 3). NSAIDs were completely stopped in 6 patients, but 12 patients reported permanent or transient use of these drugs despite kidney disease.

Seven patients presenting with rapidly progressive renal dysfunction ( $n = 4$ ), nephrotic syndrome ( $n = 1$ ), or the presence of crescents on renal biopsy ( $n = 2$ ) received corticosteroids for IgAN. The modalities of the corticosteroid regimen were highly variable between centers, ranging from daily oral prednisone (0.5 mg/kg) to sequential perfusions of i.v. methylprednisolone associated with oral corticosteroids, according to the Pozzi protocol.<sup>6</sup> Only 1 patient received concomitant cyclophosphamide treatment. Of note, 6 more patients received prolonged low-dose corticosteroids (daily prednisolone dose ranging from 5 to 20 mg) for SpA symptoms, and 1 received i.v. methylprednisolone during SpA flares.

After a median follow-up of 5.9 years (range 0.6 to 23.7), four patients developed end-stage renal disease. In the entire study population, 13 (39%) experienced a doubling of serum creatinine level during follow-up and 9 (27%) reached class 4 or 5 CKD. The distribution of patients into different CKD stages at presentation and at final follow-up is shown in Table 2. The average annual eGFR decline rate was  $-4.3 \pm 6.7$  ml/min per  $1.73 \text{ m}^2$ . The duration of survival without reaching the combined renal endpoint (stage 4/5 CKD stage and/or doubling the serum creatinine) was 9.9 years by Kaplan-Meier analysis (Figure 1).

### IgAN Prognostic Factors

Considering the great variability in IgAN prognosis, we studied the risk factors influencing long-term renal outcomes. Patients with a minimum 2-year follow-up ( $n = 28$ ) were separated into 2 groups according to the last available eGFR value. Patients reaching stage 4 or 5 CKD ( $<30$  ml/min per  $1.73 \text{ m}^2$ ) were classified as renal progressors ( $n = 9$ ) and compared with patients with favorable renal outcome, considered as non-progressors ( $n = 19$ ) (Table 3).

The renal prognosis was not associated with the median length of follow-up (6.5 vs. 7.3 years,  $P = 0.32$ ). Of note, initial eGFR was not significantly lower in the progressor group (median eGFR of 65 vs. 97 ml/min per  $1.73 \text{ m}^2$ ,  $P = 0.08$ ), but the annual rate of eGFR decline was higher ( $-9.3$  vs.  $-0.4$  ml/min per  $1.73 \text{ m}^2$ ,  $P = 0.0001$ ). None of the factors related to rheumatic disease (age at diagnosis, C-reactive protein value or Bath Ankylosing Spondylitis Disease Activity Index score, HLA-B27 status, presence of extra-articular symptoms) were associated with IgAN prognosis. On

**Table 3.** Prognostic factors for IgA nephropathy

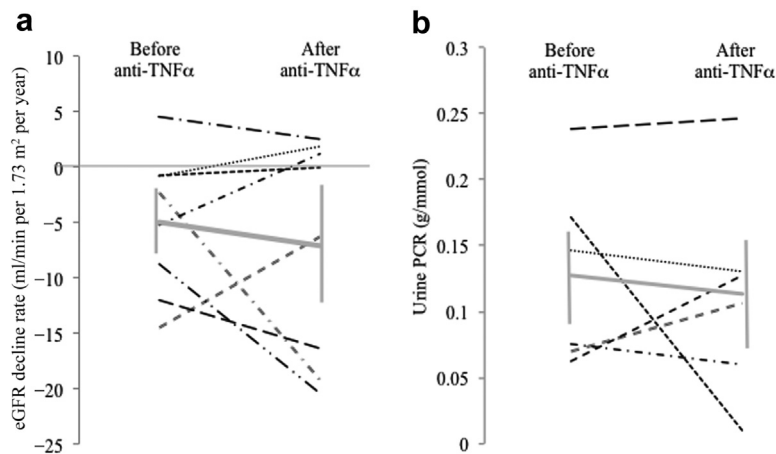
Characteristics	Progressors ( $n = 9$ )	Nonprogressors ( $n = 19$ )	$P$
Demographics and SpA characteristics			
Age at nephropathy, yr	37 (27–49)	37 (26–49)	0.48
Age at spondyloarthritis, yr	30 (23–49)	27 (21–35)	0.07
Female sex	2/9	2/19	0.42
HLA B27 positivity, %	89	93	0.26
Maximal value of CRP, mg/l	31 (7–159)	43 (12–138)	0.26
Maximal value of BASDAI	30 (12–58)	60 (50–71)	0.04
Peripheral arthropathy, %	78	63	0.43
IgA nephropathy characteristics			
Annual rate of eGFR decline, ml/min per $1.73 \text{ m}^2$ per year	−9.3 (−13.3 to −3.7)	−0.4 (−0.9 to +1.6)	0.0007 <sup>a</sup>
Follow-up duration, yr	7.3 (3.7–9.5)	6.5 (3.5–13.8)	0.32
Initial uPCR, g/mmol	0.25 (0.16–0.47)	0.11 (0.04–0.22)	0.0079 <sup>a</sup>
Initial uPCR >0.1 g/mmol, %	100	55	0.0066 <sup>a</sup>
Presence of hypertension, %	89	52	0.047 <sup>a</sup>
Number of antihypertensive treatments	3 (2–4)	1 (1–2)	0.017 <sup>a</sup>
Initial eGFR, ml/min per $1.73 \text{ m}^2$	65 (57–96)	97 (84–105)	0.08
Use of ACEi or ARB, %	100	79	0.07
SP treatments, %			
Use of anti-TNF $\alpha$ agents	67	52	0.48
Use of NSAIDs	22	47	0.19
Use of glucocorticosteroids	55	36	0.35
Renal pathology, %			
Percentage of sclerotic glomeruli	17% (9–66)	11% (0–23)	0.012 <sup>a</sup>
M-score =1	14	33	0.32
E-score =1	28	38	0.62
S-score =1	100	61	0.018 <sup>a</sup>
T-score $\geq 1$	85	16	0.004 <sup>a</sup>
Presence of crescents	57	28	0.15
Presence of interstitial inflammation	43	11	0.088

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis; uPCR, urine protein-to-creatinine ratio.

<sup>a</sup>Statistically significant ( $P < 0.05$ )

For continuous variables, the median (interquartile range) is indicated. Corticosteroid use for treatment of IgA nephropathy is not reported here. For NSAIDs, only prolonged use (daily consumption for at least 3 mo) is reported.

the other hand, presence of hypertension (89% vs. 52%,  $P = 0.04$ ), number of antihypertensive drugs, and level of proteinuria at diagnosis (0.25 vs. 0.11 g/mmol,  $P = 0.0079$ ) were significantly associated with a poor renal prognosis in univariate analysis (Table 3). Among the items of the Oxford classification score, the baseline S-score and T-score were associated with progression to CKD IV/V, as well as the initial percentage of globally sclerotic glomeruli. The M-score, E-score, C-score, the percentage of crescentic glomeruli, the presence of tubulo-interstitial inflammation, thrombotic microangiopathy, or arterial intimal



**Figure 2.** Effect of anti-tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) treatment on estimated glomerular filtration rate (eGFR) decline rate (a) and proteinuria (b). When possible ( $n = 8$  patients), the eGFR decline rate and urine protein-to-creatinine ratio (PCR) were calculated before and after anti-TNF $\alpha$  treatment. Dashed lines represent individual patients. Solid gray line represents the average value. Vertical bars represent the SE.

thickening were not identified as significant prognostic factors in this study.

The persistent use of NSAIDs was not associated with renal prognosis. The proportion of patients who received anti-TNF- $\alpha$  medication, before or after IgAN onset, was not different between the 2 renal prognosis groups (67% vs. 52%,  $P = 0.48$ ). The same results were obtained when infliximab, etanercept, and adalimumab treatments were considered individually. No difference was found when the renal pathology characteristics were compared considering the presence or absence of previous exposure to anti-TNF- $\alpha$  agents.

Renal prognosis was also evaluated by a Cox time-to-event analysis. On univariate analysis, the renal outcome was associated with presence of renal failure (eGFR <60) at initial presentation ( $P = 0.008$ ), initial level of proteinuria ( $P = 0.04$ ), and T-score ( $P = 0.002$ ), percentage of sclerotic glomeruli on renal biopsy ( $P = 0.01$ ), as well as with the annual eGFR decline rate ( $P = 0.08$ ). Presence of hypertension was not significantly associated with the outcome with this test. On multivariate analysis, the only parameter associated with renal prognosis was the presence of a renal dysfunction at diagnosis ( $P = 0.018$ ).

When studying the cases of patients who received anti-TNF- $\alpha$  agents after IgAN onset, we found no significant difference in the eGFR decline rate, before or after anti-TNF- $\alpha$  initiation ( $-5.0$  vs.  $-7.1$  ml/min per 1.73 m<sup>2</sup> per year,  $P = 0.51$ ). The individual effect of anti-TNF- $\alpha$  on eGFR decline rate and proteinuria is shown in Figure 2.

Glucocorticoids were given in 55% of cases in the progressor group versus 36% in the nonprogressor group ( $P = 0.35$ ). Glucocorticoids were mostly given for nephropathy in the progressor group (80%) and for SpA in the nonprogressor group (71%). No difference was found in the prevalence of disease-modifying

antirheumatic drugs or salazopyrine use between the 2 groups.

## DISCUSSION

This study describes the largest series of patients with SpA-associated IgAN. Our findings reveal a severe disease, characterized by rapid decline of renal function and frequent progression to stage 4/5 CKD, despite frequent prescription of corticosteroids.

To date, 51 cases of SpA-associated IgAN have been reported in the literature, mostly as case reports or small (fewer than 5 patients) case series.<sup>2</sup> As no large-scale studies have been performed in SpA populations to date, the prevalence of this association remains unknown, although we can hypothesize that nephropathy is probably underdiagnosed. The only epidemiological study was conducted in Canada, using longitudinal patient-level population-based administrative databases. This study showed that the all-cause CKD prevalence among male patients with SpA is 2.5%,<sup>22</sup> and that the standardized prevalence ratio was 1.7 when compared with CKD prevalence in the general population.

The clinical presentation of the rheumatic disease in our study is not significantly different compared with similar cohorts of SpA. The sex ratio, age at initial diagnosis, and percentage of HLA B27 positivity are consistent with the usual epidemiological data, as well as the distribution among different SpA subtypes and the prevalence of extra-articular symptoms. Our study demonstrates that IgAN can occur in patients with mild rheumatic symptoms as well as in patients with all types of SpA, such as psoriatic arthritis and IBD-associated arthritis.

The prognostic factors associated with renal outcomes in our study reflect the findings reported in larger, primary IgAN cohorts. The presence of hypertension or

high-grade proteinuria ( $>1$  g/d) are well-recognized risk factors associated with progression in most glomerular diseases, especially in IgAN.<sup>23</sup> Although our study failed to validate the prognostic value of the M or E items of the MEST-C score, we confirm that glomerular and interstitial fibrosis can predict deterioration of renal function in SpA-associated IgAN.

Importantly, the renal prognosis of our study population seems to be significantly poorer than previously described in primary IgAN cohorts. The mean annual decline rate in our study was  $-4.3 \pm 6.7$  ml/min per  $1.73$  m<sup>2</sup>, which is higher than that reported in the Oxford Classification Cohort<sup>15</sup> ( $-3.5 \pm 8.4$  ml/min per  $1.73$  m<sup>2</sup>) or in the VALIGA (European Validation Study of the Oxford Classification of IgAN) cohort<sup>7</sup> ( $-1.8 \pm 7.5$  ml/min per  $1.73$  m<sup>2</sup>). After a median follow-up of 5.9 years, 41% of the patients with SpA-associated IgAN experienced a  $>50\%$  decrease in renal function versus 14% of primary IgAN cases in the VALIGA study (median follow-up, 4.7 years) and 22% in the Oxford cohort (median follow-up, 5.7 years). This difference cannot be explained by a more severe initial clinical presentation. The initial eGFR was  $84 \pm 26$  ml/min per  $1.73$  m<sup>2</sup> in our study versus  $73 \pm 30$  ml/min per  $1.73$  m<sup>2</sup> in the VALIGA study and  $83 \pm 36$  ml/min per  $1.73$  m<sup>2</sup> in the Oxford cohort. In addition, initial proteinuria was not significantly higher in our cohort ( $0.19$  g/mmol  $\approx 1.9$  g/d vs.  $1.3$  g/d in the VALIGA study and  $1.7$  g/d in the Oxford cohort). When comparing the MEST-C scores, there was no major difference between our cohort and the VALIGA study cohort: M1 in 33% versus 28%, E1 in 33% versus 11%, S1 in 71% versus 70%, and T1/T2 in 33% versus 25%. Finally, the poor outcome of the patients in our series is not due to less-intensive treatment of IgAN. Regarding nonimmunosuppressive antiproteinuric treatment, 81% of our patients were on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker treatment versus 74% in the Oxford cohort and 86% in the VALIGA study. In terms of immunosuppressive therapy, 43% of our study population received corticosteroids during follow-up versus 29% in the Oxford cohort and 86% in the VALIGA study. Nevertheless, corticosteroids were usually given at low daily doses, just to control the rheumatic disease in most cases. This dose is significantly lower than the usual initial 1 mg/kg dose, given in IgAN therapeutic trials, a discrepancy that may explain the absence of renal benefit for the patients of our study.

One possible explanation concerning the particularly poor renal prognosis in this cohort is the systemic inflammatory response due to SpA. Although the peak C-reactive protein level is not associated with renal outcome, the presence of interstitial infiltration or

glomerular crescentic proliferation is particularly frequent in the kidney biopsies of our patients. For instance, crescents were observed in 33% of our renal biopsies versus 11% in the VALIGA cohort. Another hypothesis is that the treatment given for SpA has some nephrotoxic effects in this specific situation.<sup>10,24</sup> However, we show here that the use of NSAIDs, disease-modifying antirheumatic drugs, or salazopyrine was not associated with a more rapid decline of renal function.

Of note, preclinical data have suggested that TNF- $\alpha$  blockade could have beneficial effects on the IgAN course. TNF- $\alpha$  seems to play a key role in the pathophysiology of IgAN, and the renal expression of TNF- $\alpha$  has been associated with the level of proteinuria and the disease severity.<sup>25,26</sup> In vitro studies have revealed that mesangial cells proliferate and produce TNF- $\alpha$  when exposed to IgA, this effect being suppressed by concurrent use of anti-TNF- $\alpha$  antibodies.<sup>27,28</sup> Finally, several studies have reported that TNF- $\alpha$  gene polymorphisms are associated with increased susceptibility to IgAN.<sup>29,30</sup> Nevertheless, our study failed to demonstrate any improvement in the IgAN course with anti-TNF- $\alpha$ , but also found no renal adverse event associated with this therapeutic option.

In conclusion, this retrospective study reveals that SpA-associated IgAN is a particularly severe condition with poor renal outcome in many cases. Despite similar prognostic factors, frequent use of corticosteroids and no specific renal pathology features, except frequent presence of glomerular crescentic lesions, the eGFR decline is more rapid than in primary IgAN. TNF- $\alpha$  blockers do not influence renal prognosis in this specific population.

## DISCLOSURE

All the authors declared no competing interests

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Our study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the Paris-Ouest University Hospitals Ethics Committee (CERHUPO). The informed consent of patients was obtained retrospectively.

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