

Toward a Clearer Picture of IgA Nephropathy in Spondyloarthritis



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Among the many conditions that have been found to be associated with IgA nephropathy (IgAN), a variety of autoimmune arthropathies are frequently noted, particularly spondyloarthritis (SpA). SpA comprises a family of disorders that produce various types of musculoskeletal inflammation.¹ The prototype is ankylosing spondylitis (AS), which produces chronic inflammatory back pain, particularly sacroiliitis. Related disorders include SpA associated with psoriasis or inflammatory bowel disease, among others. When IgAN co-occurs with SpA, the IgAN will often be termed *secondary* because of the coexistence of a systemic disease. Such terminology is inherently problematic, because it implies that the systemic disease has a causal role in the development of IgAN. The existence of causality has been largely unproven, however. It may be that IgAN and SpA share some independent causal pathways, and that they occur among

demographically similar groups of patients, implying a shared genetic or environmental predisposition to the 2 conditions. Indeed, some authors have gone so far as to question the association outright.² This is a plausible assertion, because the IgAN is typically diagnosed after the patient has come under medical scrutiny for SpA, and certain populations have a remarkably high prevalence of subclinical IgA deposits that might not otherwise be discovered.³ These distinctions are clinically important, because a causal relationship would imply that successful treatment of SpA would result in amelioration of IgAN. Until recently, there have been sparse and conflicting data in this regard, largely limited to case reports.

On this background, Champ-tiaux and colleagues⁴ recently assembled a large retrospective cohort of patients with IgAN and SpA to characterize the clinicopathological features and renal outcomes of these patients. The authors contacted nephrologists and rheumatologists from all university hospitals across France to identify patients diagnosed with both diseases. In this way, they identified 32 patients meeting accepted diagnostic

criteria for SpA and a kidney biopsy definitively showing IgAN. After characterizing their clinical and pathological features at baseline, they studied longitudinal renal outcomes among 28 patients with at least 2 years of follow-up and divided them between “progressors” and “non-progressors” based on an outcome of reaching an estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m².

What did the authors find among these patients? First, in most (28 of 32, 88%) patients, the rheumatologic diagnosis preceded or was made concomitantly with the diagnosis of IgAN. Demographics were typical of SpA, with most being male (84%) and young (median age at SpA onset, 27 years), and AS being the dominant subtype of SpA (62%). HLA-B27 was present in 90%. Treatments included prolonged (>3-month) courses of nonsteroidal anti-inflammatory drugs in 38%, corticosteroids in 19%, sulfasalazine in 45%, and anti-tumor necrosis factor- α (TNF α) agents in 69%. The renal features at presentation were, with the exception of the male sex predominance, fairly typical for IgAN, with relatively preserved eGFR (84 ± 26 ml/min per 1.73 m²) and proteinuria with mean urine protein-creatinine ratio of 1.7 g/g. Biopsy features, scored according to the Oxford *MESTC* classification, were similarly typical for IgAN, with most (67%) having a T score of 0, implying tubular atrophy and interstitial fibrosis in $\leq 25\%$ of the renal parenchyma, and 33% having at least 1 cellular or fibrocellular crescent. Less typical appear to be the renal outcomes, which are presented as being rather poor: over a median follow-up of 5.9 years, 4 reached end-stage renal

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disease and 13 doubled the serum creatinine, and the average annual decline in eGFR was 4.3 ± 6.7 ml/min per 1.73 m^2 . Although the authors accurately point out that this average loss of eGFR is worse than that described in the Oxford and VALIGA (Validation Study of the Oxford Classification of IgAN) cohorts of IgAN, it is not dissimilar from the average loss of eGFR across patients enrolled in the TESTING (Therapeutic Evaluation of STeroids in IgA Nephropathy Global) study of glucocorticoids for IgAN (mean annual decline of eGFR 4.3 ml/min per 1.73 m^2 , with 1.7 in the treatment group and 6.95 in the control group).⁵ Use of renin-angiotensin blockers among the patients with SpA + IgAN was lower than that in both the VALIGA and TESTING studies, which may have contributed to worse outcomes. Thus, the authors' claim that for patients with SpA + IgAN "the eGFR decline is more rapid than in primary IgAN" seems plausible but far from certain.⁴

Data presented on the treatment outcomes are intriguing, although limited. In a simple 2-way comparison between "progressors" and "nonprogressors," the authors found no difference in the proportion treated with nonsteroidal anti-inflammatory drugs, glucocorticoids, and anti-TNF α agents. Although a longitudinal Cox analysis was done, no mention of immunosuppression is made in its description. Caution should be used in interpreting the data on glucocorticoids, because relatively few patients were treated for renal indications and the typical doses given for IgAN are much higher than the typical doses used for SpA. Perhaps more informative are the descriptions of average eGFR decline and proteinuria before and after anti-TNF α therapy, which appeared unchanged. Because

anti-TNF α agents are well-validated to improve symptoms in SpA, the implication is that effective disease-specific therapy for SpA may be ineffective for IgAN. This bolsters the concept that the IgAN associated with SpA is *not* secondary in a causal sense.

An important strength of the study is its attempt to collect patients from a country-wide health system. In a large and relatively diverse population such as France, this helps to maximize the chance that the findings are both representative of this patient population and generalizable to cohorts in other countries. However, survey may not be an optimal case-finding approach, and there is a chance for selection bias in that the most symptomatic patients may be those most easily identified by their clinicians. The use of a robust pathology or electronic medical record-based database to screen patients might have resulted in a broader population. Nevertheless, the authors should be commended for performing a truly transdisciplinary project among nephrologists and rheumatologists, leveraging the insights of both groups for the sake of their shared patients.

How does this study add to the available literature? Although the size and design of the cohort presented by Champtiaux *et al.*⁴ is a major improvement over the existing literature, the overall number of patients included (32) remains small, and so findings must be interpreted with caution. Particularly important is the possibility of type II errors. For example, finding that nonsteroidal anti-inflammatory drugs did not seem to be related to progression of renal disease should not, in my opinion, imply that clinicians may start using nonsteroidal anti-inflammatory drugs indiscriminately in patients with IgAN.

Likewise, and as mentioned earlier, conclusions about the effect of glucocorticoids on IgAN in this setting are limited, and it would be better to defer to other literature on their relative risks and benefits, such as the aforementioned TESTING study.⁵ Although Champtiaux *et al.*⁴ present their study as the largest series of patients with SpA-associated IgAN, another recent study from China was larger, comparing 46 patients with IgAN associated with AS with 26 patients with IgAN associated with rheumatoid arthritis.⁶ This study, by He and colleagues,⁶ found a substantially higher prevalence of IgAN in AS compared with rheumatoid arthritis (167 vs. 51 per 1000, respectively), lending credence to the presence of a true association between IgAN and SpA. Although this study also described a histopathology similar to primary IgAN, relatively few data were provided on treatment.

The sum of this evidence argues against IgAN being truly secondary to SpA. Indeed, another recent publication in this journal found no differences in levels of plasma galactose-deficient IgA1, circulating IgA-IgG immune complexes, and glomerular galactose-deficient IgA1 deposits between primary and secondary forms of IgAN, the latter of which included 9 patients with AS, 1 with inflammatory bowel disease, and 25 with psoriasis.⁷ Likewise, it has been shown that in IgAN related to IgA vasculitis (also called Henoch-Schonlein purpura), another presumed secondary form of IgAN, that serum galactose-deficient IgA1 levels had similar elevations and heritability to pediatric primary IgAN cases.⁸ Nevertheless, it remains plausible that some immunologic features of SpA accelerate the pathophysiology of IgAN, whether through broad

inflammatory mechanisms or specific modifications of IgA levels.⁹

How should clinicians proceed based on these new data? Clearly, we should be cautious not to be wooed into thinking that a disease-specific treatment for SpA, such as anti-TNF α agents, might have any beneficial effect on coexisting IgAN. Likewise, I do not think we can eliminate the possibility that traditional treatments for IgAN, whether renin-angiotensin blockade or glucocorticoids, should be any less valuable in the setting of SpA. For now, we must continue to treat the diseases independently, while personalizing treatment in any given patient. Finally, one glaring truth that is hard to ignore when looking at the literature of SpA and IgAN is the disparity in available treatments for the 2 conditions. Our rheumatological colleagues have the luxury of anti-inflammatories, disease-modifying antirheumatic drugs, and biologics in treating SpA,

whereas the nephrologist's arsenal for treating IgAN remains woefully spare. This should cause us to redouble our efforts to find effective, biologically sound, disease-specific treatments that are so desperately needed for all varieties of patients with IgAN.

DISCLOSURE

The author declared no competing interests.

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