Systemic autoimmune diseases and the kidney

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Since its inception, *Kidney International* has published seminal articles describing the effects of systemic autoimmune diseases on the kidney. These manuscripts have characterized the pathology and clinical course of these diseases and perhaps most importantly have provided guidance to the nephrology community about how to treat these complex conditions using the best possible evidence available at the time. To illustrate the wealth of information contained within the *Kidney International* archives, consider the following papers.

The glomerular basement membrane as antigen: Goodpasture's syndrome and anti-GBM glomerulonephritis

Wilson CB, Dixon FJ. Anti-glomerular basement membrane antibody-induced glomerulonephritis. Kidney Int. 1973;3:74–89. In 1973, Curtis Wilson and Frank Dixon described in detail 63 patients with severe glomerulonephritis (GN) and linear immunofluorescence along the glomerular basement membrane (GBM), often with pulmonary hemorrhage.[1] Although Goodpasture's syndrome had been described in the mid to late 1960s, this series was more extensive and examined cases with and without lung involvement, aspects of treatment, outcomes, and how patients did after receiving a kidney transplant. In those days, to supplement kidney biopsy immunofluorescence studies, Wilson and Dixon eluted antibodies from affected kidney tissue when available and showed that the eluates could bind to frozen sections of normal human and primate kidneys. Going one step further, the investigators perfused patient blood through normal human or primate kidneys to detect the presence of circulating anti-GBM antibodies. This investigation showed how devastating anti-GBM disease is; 62% of their cases required permanent renal replacement therapy, and the Goodpasture's group had an early mortality of 37%. No patients were treated as is done now, but as an interesting historical note, nephrectomy was used in patients with pulmonary hemorrhage to manage the bleeding. Finally, the authors noted recurrent glomerular disease in the allografts of patients who had circulating anti-GBM antibodies at the time of transplantation and suggested that kidney transplantation not be done until anti-GBM antibodies are gone—advice that is followed to this day.

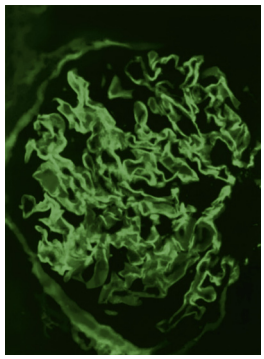

Figure 1 | Figure 1 is adapted with permission from Wilson CB, Dixon FJ. Anti-glomerular basement membrane antibody-induced glomerulonephritis. *Kidney Int.* 1973;3:74–89.[1] Copyright © 1973, International Society of Nephrology.

The use of plasma exchange plus immunosuppression for anti-GBM disease began in 1976[2] and had a positive impact on disease management.[3] Although the therapy for anti-GBM disease has remained essentially unchanged for the past 40 years, a new approach to eliminate pathogenic anti-GBM autoantibodies was recently described in *Kidney International*.[4] A streptococcal endopeptidase, imlifidase, was used to treat 3 patients with refractory anti-GBM nephritis. This enzyme degrades all human IgG subclasses into $F(ab')_2$ and Fc fragments. One dose of the enzyme completely cleared circulating anti-GBM antibodies in all of the patients. Imlifidase is now being tested in a phase II clinical trial in patients with anti-GBM GN (NCT03157037).

Editor's Note

This article is part of the *KI* ISN 60th anniversary series. This month's topic is glomerulonephritis and autoimmunity.

Brad H. Rovin[1]
[1]*Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA*

Correspondence: *Brad H. Rovin, Division of Nephrology, The Ohio State University Wexner Medical Center, 395 West 12th Avenue, Ground Floor, Columbus, Ohio 43210, USA. E-mail: brad.rovin@osumc.edu*

Severe GN but few glomerular antibodies: pauci-immune GN

Pusey CD, Rees AJ, Evans DJ, et al. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int. 1991;40:757–763. Based on the success of plasma exchange in anti-GBM disease, Pusey and co-workers investigated plasma exchange added onto immunosuppression for other forms of rapidly progressive GN and specifically examined what is now called antineutrophil cytoplasmic antibody (ANCA) associated nephritis.[5] They added at least 5 plasma exchanges to prednisone, cyclophosphamide, and azathioprine in patients with impaired kidney function who had a diagnosis of Wegner's granulomatosis, microscopic polyarteritis, or idiopathic rapidly progressive GN. They looked for an improvement in kidney function of at least 25% a month after starting treatment. Although the investigators did not find that the addition of plasma exchange improved the outcomes of patients who did not require dialysis, they found that significantly more patients who initially needed dialysis recovered kidney function in the plasma exchange group (Table 1[5]). This work inspired several additional studies of the role of plasma exchange in the management of vasculitis, culminating in the 2007 Methylprednisolone Versus Plasma Exchange for Renal Vasculitis (MEPEX) trial.[6] MEPEX was a large study of plasma exchange in patients with ANCA-associated nephritis and severe kidney injury. MEPEX also showed that adding plasma exchange to immunosuppression facilitated dialysis independence. Unfortunately, overall mortality was not improved in the plasma exchange group. A meta-analysis of plasma exchange studies for vasculitis that was done using a composite end point of death and end-stage kidney disease concluded the data were not sufficient to support the use of plasma exchange for ANCA-associated nephritis.[7] However, the Plasma Exchange and Glucocorticoids for Treatment of ANCA-Associated Vasculitis (PEXIVAS; NCT03919825) trial, another large study of plasma exchange in persons with severe ANCA vasculitis, has just been completed. The results are eagerly anticipated to settle the question of plasma exchange in persons with vasculitis.

Table 1 | Improvement in renal function at 1 month

Renal function	Plasma exchange (n = 25)	Control (n = 23)
Serum creatinine <500 μmol/l	9/9	7/8
Serum creatinine >500 μmol/l	5/5	7/7
Dialysis-dependent[a]	10/11	3/8

[a]P = 0.041, Fisher's exact test.

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Assessing the prognosis of lupus nephritis: the role of the kidney biopsy

Austin HA III, Muenz LR, Joyce KM, et al. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int. 1984;25:689–695.

Austin HA III, Boumpas DT, Vaughan EM, et al. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney Int. 1994;45:544–550. Several significant articles on lupus nephritis (LN) have appeared in *Kidney International* over the years. One of the most controversial areas in the management of LN is how to use the kidney biopsy to determine the outcome of the kidneys over time. Howard Austin III, Jim Balow, and their colleagues at National Institutes of Health, who have been working on this problem since the 1980s, have produced several manuscripts and contributed 2 important papers to *Kidney International*. In 1984 the team conducted a retrospective analysis of the biopsies of 102 patients with LN seen at the then National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases who participated in therapeutic trials.[8] The investigators observed that all instances of kidney failure occurred in patients with diffuse proliferative LN (World Health Organization class IV). Using the components of the activity and chronicity indices, also developed by this team, the investigators demonstrated that in class IV LN the composite activity index and chronicity index were significantly associated with future renal failure. In fact, the probability of renal failure increased in a graded fashion with the degree of chronic damage. When the individual components of the activity index were

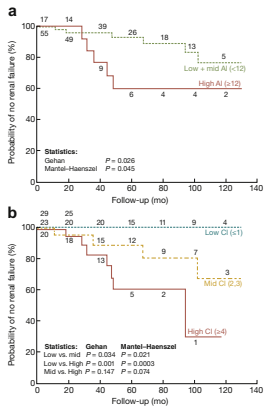

Figure 2 |

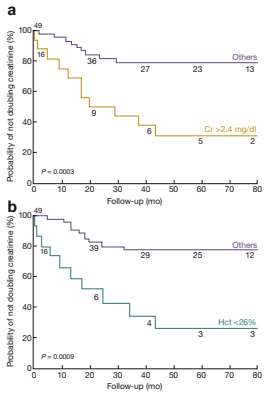

Figure 3|

examined, none was significantly associated with outcome. In contrast, almost all of the individual components of the chronicity index were significant, especially tubular atrophy. Every patient who experienced renal failure had evidence of tubular atrophy. The predictive value of tubular atrophy was enhanced by also considering the presence of cellular crescents and glomerular sclerosis. In 1994 the investigators undertook a prospective trial to identify histologic predictors of progressive kidney disease.[9] The patients included were not typical of current trials, nor was the design of the trial typical. In many ways this trial was more rigorous than current studies. All patients had severe LN with impaired kidney function and cellular crescents and/or fibrinoid necrosis in at least 25% of their glomeruli on biopsies taken within 6 weeks of trial entry. Current trials recruit patients with mild to modest disease and routinely include patients with biopsies done months before entry, which is a problem considering how rapidly LN may change. Study patients (n = 65) were randomized to 3 different treatment regimens and followed up for a mean of about 5 years. The end point was doubling of serum creatinine sustained for a month. Current trials tend to evaluate end points once. Independent clinical variables associated with a poor renal outcome were race, baseline serum creatinine, and hematocrit. Histologically, just like their earlier study, almost all cases of renal insufficiency were in patients with class IV LN. Cellular crescents and interstitial fibrosis emerged as independent histologic predictors of poor outcome. This outcome is fairly consistent with the group's earlier paper because tubular atrophy and interstitial fibrosis are related. When the histologic biomarkers were combined with the clinical biomarkers, the prediction model was significantly improved. In their discussion, the authors pointed out that baseline prognostic biomarker performance will be affected by treatment, implying that more accurate prognostic information may be obtained if a second biopsy is taken to evaluate the effects of therapy on renal histology, a theme subsequently developed in *Kidney International*.[10,11] Despite several LN histologic classification systems, considerable controversy remains around the clinical utility of the current histologic classifications of LN, a problem that is being addressed by members of the Renal Pathology Society, as described in *Kidney International*.[12]

Figure 2 is adapted with permission from Austin HA III, Muenz LR, Joyce KM, et al. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. *Kidney Int.* 1984;25:689–695.[8] Copyright © 1984, International Society of Nephrology.

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Personalizing immunosuppressive treatment in LN

Dooley MA, Hogan S, Jennette JC, et al. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. Kidney Int. 1997;51:1188–1195. Finally, in 1997, Dooley and colleagues from the Glomerular Disease Collaborative Network raised an important concern about the efficacy of standard therapies for LN in patients of different races.[13] It has been known for some time that LN develops more frequently and is often more severe in patients of African descent than in patients of European ancestry. Dooley retrospectively studied a real-world cohort of 89 patients with World Health Organization class IV LN who were treated with high-dose corticosteroids and monthly i.v. cyclophosphamide. More than half the cohort was African American. End-stage kidney disease developed in 19 patients, 17 of whom were African American. Half of these 17 patients reached end-stage kidney disease within 8 months of their diagnostic kidney biopsy. The 5-year kidney survival for African Americans was 57% compared with 95% for the rest of the cohort, who were mainly white. At baseline there were no clinical

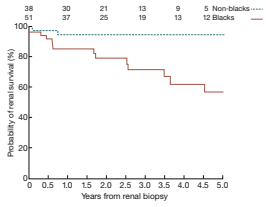

Figure 4|

differences between the African Americans and other patients, blood pressure was controlled to the same degree in each group, and both groups received similar therapy. The authors concluded that African American patients had an inferior response to cyclophosphamide compared with white patients. The idea that different therapies may be needed for patients of different races and ethnicities continues to resonate today. The Aspreva Lupus Management Study (ALMS) trial comparing mycophenolate to cyclophosphamide for the treatment of LN found evidence that mycophenolate mofetil was superior to cyclophosphamide for patients of African ancestry and also Hispanic ethnicity.[14] Such studies highlight the urgency of efforts to improve recruitment of clinical trials of novel LN therapeutics to more closely resemble the racial and ethnic mix of patients affected by the disease. Despite warnings from as far back as 1997, patients of European ancestry continue to be overrepresented in most current LN clinical trials.

These manuscripts, some published more than 4 decades ago, shaped our current understanding of the kidney in systemic autoimmunity. The concepts they presented were novel when the articles appeared in print but have remained relevant to this day. Looking back through this historical lens provides perspective on how our current approaches to glomerular diseases have evolved and will continue to evolve as the kidney is studied by the international nephrology community.

Figure 4 is adapted with permission from Dooley MA, Hogan S, Jennette JC, et al. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int.* 1997;51:1188–1195.[13] Copyright © 1997, International Society of Nephrology.

DISCLOSURE

The author declared no competing interests.

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