JASN Begins Anew

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Welcome to the new JASN. This is the launch issue for a new editorial team, and all of us are honored to edit the finest kidney journal in the world. We accepted this exciting opportunity knowing Bill Couser and his associate editors have done a remarkable job in advancing the quality and substance of your journal during the past several years. We are grateful for their past leadership and recent guidance through our transition. They have left us big shoes to fill.

Going forward, JASN is committed to publishing the very best work in renal science and clinical nephrology. Everything that we take for granted in kidney medicine today had its start somewhere in the laboratory, and as our science grows, so does the clinical success of the subspecialty. We instinctively believe this dynamic is an important value to preserve in the pages of your journal.

JASN has built such a fine reputation that it now receives far more submissions than it can publish. This is both good and bad. At a final acceptance rate of less than 20%, we are able to offer really outstanding original contributions to our readers. Unfortunately, this also means the journal is unable to publish much of the great work coming from other laboratories and clinical investigators. The growing numbers of submissions also increases the pressure on our reviewers, and we must therefore return a larger fraction of our submissions without formal review, while at the same time working to expand our reviewer pool (you can help us by updating your keywords at the JASN submission site). We truly regret these difficulties.

In planning our launch, we have added many new features to JASN to appeal to an ever-expanding readership. The journal has been redesigned inside and out, in print and online, which we hope will make the journal more appealing to browse and use. The cover has been updated, and we invite all members to submit interesting pictures as potential cover candidates. You can do this by going to the JASN submission site, choosing COVER as your manuscript type, and uploading your kidney-related image and figure legend. We hope that this collection of classic pictures will vividly represent the art in renal medicine.

By shortening the page length of our articles, we will be able to publish a variety of new features in the front section of the journal. These include Brief Reviews, Occasional Observations, JASN Debates, Science in Renal Medicine, Pathophysiology of the Renal Biopsy, Clinical Commentaries, and Editorials. The Original Contributions section is divided into Basic Research, Clinical Epidemiology, and Clinical Research. These will feature the very best of both Regular Articles and Brief Communications, the latter in a new letter format.

Bonnie O’Brien continues as our indispensable managing editor, and JASN’s new associate editors include Lloyd Cantley, Yale University (cell biology/signaling/pathophysiology); Robert Colvin, Harvard Medical School/Massachusetts General Hospital (pathology/pathophysiology/transplantation); Alfred George, Vanderbilt University (genetics/physiology); T. Alp Ikizler, Vanderbilt University (clinical nephrology/dialysis); Mary Leonard, Children’s Hospital of Philadelphia (renal osteodystrophy/translational health services/epidemiology and outcomes); Neil Powe, Johns Hopkins University (clinical epidemiology/translational health services); Susan Quaggin, University of Toronto (developmental biology); Andrew Rees, Medical University Vienna (glomerular injury/pathophysiology/immunology); and Terry Strom, Harvard Medical School/Beth Israel Hospital (transplantation/immunology).

We welcome your suggestions as we work together to make the finest kidney journal in the world even better.

Removing Antibody and Preserving Glomeruli in ANCA Small-Vessel Vasculitis

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If anti-neutrophil cytoplasmatic autoantibodies (ANCA) participate in the pathogenesis of small-vessel vasculitis, then it would stand to reason that removal of these antibodies should ameliorate disease. There is substantial evidence that...
ANCA are capable of activating leukocytes \textit{in vitro}.\textsuperscript{1,2} In at least two experimental models, anti-myeloperoxidase antibodies induce necrotizing glomerulonephritis and widespread systemic vasculitis.\textsuperscript{3,4} There is also one clear example of placent al transfer of ANCA to a newborn infant who developed small-vessel vasculitis.\textsuperscript{5} Why, then, is plasmapheresis not the world-wide standard for induction therapy? Conventional treatment includes intravenous pulses of glucocorticoids followed by oral administration in association with cyclophosphamide. This induction followed by maintenance therapy results in long-term remission rates of between 75 and 90%. Speed in making a diagnosis and instituting therapy for ANCA small-vessel vasculitis is essential, especially in the face of life-threatening pulmonary hemorrhage or rapidly progressive glomerulonephritis.\textsuperscript{6}

One of the important predictors of death is diffuse alveolar hemorrhage,\textsuperscript{7} with the risk for death almost nine times higher in those with pulmonary hemorrhage. The prompt prescription of plasmapheresis in patients with pulmonary hemorrhage is of significant benefit in that 20 of 20 individuals with massive pulmonary hemorrhage in this disease survived when compared with 50% of historical controls.\textsuperscript{8} Similarly, the entry serum creatinine is a strong predictor of long-term outcome in kidney function.\textsuperscript{9} Pulses of methylprednisolone quickly diminish glomerular and tubulointerstitial inflammation and have been efficacious for decades in the treatment of rapidly progressive glomerulonephritis.\textsuperscript{9,10}

What are the historical data pertaining to plasmapheresis and rapidly progressive glomerulonephritis? In two randomized, controlled trials in patients who were not on dialysis, there was no therapeutic advantage of plasma exchange in pauci-immune, rapidly progressive glomerulonephritis.\textsuperscript{11,12} It was only in dialysis-dependent patients that plasma exchange was beneficial. Renal function was more likely to recover when patients were treated with plasma exchange plus cytotoxic agents, rather than with cytotoxic agents alone.\textsuperscript{13}

Perhaps, then, it is only at the extremes of illness, such as dependence on dialysis, that the salutary role of plasmapheresis is most demonstrable. In this issue of \textit{JASN}, a European Vasculitis Study Group study supports the long-held belief of the senior author, Dr. Charles Pusey, that plasma exchange when compared with intravenous methylprednisolone is superior induction therapy in patients who have ANCA small-vessel vasculitis and in whom the serum creatinine is >5.8 mg/dl.\textsuperscript{14} The primary end point was dialysis independence at 3 mo, and the secondary end points were renal and patient survival at 1 yr. In this important study, plasmapheresis won the day compared with induction therapy with methylprednisolone. Both groups were placed on oral cyclophosphamide and prednisolone for maintenance therapy.

There are, however, certain caveats to this study. Patients with life-threatening pulmonary hemorrhage or those who had been on dialysis for at least 2 wk were excluded from the trial. Furthermore, both treatment groups suffered a very high mortality rate of 25% over 12 mo. This percentage should give the treating physician pause and begs the question of whether aggressive induction therapy accompanied by 3 mo of oral cyclophosphamide adds undue risk for death late in disease. This question must be resolved. If plasmapheresis is used in this setting, then perhaps immunomodulating therapy with intravenous rather than oral cyclophosphamide should be considered. Intravenous cyclophosphamide is likely as efficacious as oral cyclophosphamide and results in only half of the cumulative dosage.\textsuperscript{15} Another limitation of this study pertains to potential differences in plasma exchange protocols among the participating centers. Uncertainty exists as to whether plasma filtration, centrifugation, concomitant coagulation therapy, or daily or alternate-day sessions of plasmapheresis were used and what role, if any, this plays in the outcome of treated patients. It is reasonable that plasmapheresis sessions should be aimed at removing pathogenetic antibodies early and then continuing plasmapheresis until remission therapy is capable of suppressing the potential rebound of ANCA once plasmapheresis is stopped.

A common clinical conundrum is the risk versus benefit of therapy to a patient who arrives with ANCA small-vessel vasculitis and severe kidney dysfunction approaching end stage. Do the risks of therapy outweigh the benefits of possible recovery of kidney function? What are the best measures that are indicative of improved long-term prognosis? In a recent study based on a plasmapheresis trial, de Lind van Wijngaarden et al.\textsuperscript{16} noted that chronic and acute tubulointerstitial lesions predict the GFR at 12 mo, yet it is the use of plasma exchange and the number of normal glomeruli on biopsy that remained positive predictors of dialysis independence in the same time interval. This finding is important because it suggests that unaffected glomeruli determine long-term renal outcome at 1 yr. In this issue of \textit{JASN}, this same group of investigators, in a second study, extended their work in determining the rate of renal recovery.\textsuperscript{17} In 69 dialysis-dependent patients who were part of the plasmapheresis trial, plasma exchange was superior to pulse methylprednisolone with respect to the chance of coming off dialysis. The outcome measure depended on the relative number of normal glomeruli. One of the intriguing facets of ANCA small-vessel vasculitis is the focality of the glomerular lesions. In fact, it is common to see an example of focal necrotizing glomerulonephritis adjacent to a segment of a glomerulus that is completely unaffected. Therefore, it is possible that many segments of glomeruli or whole glomeruli may be spared from the disease, thereby allowing for long-term preservation of kidney function. These studies raise an important pathophysiologic question. Is induction therapy aimed at treating inflamed glomeruli, preserving normal glomeruli, or both?

What is next on the horizon? First, early detection of ANCA small-vessel vasculitis may reduce the number of patients who

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have advanced disease and require such aggressive induction therapy. In a series published by Hogan et al.,22% of patients in their cohort were treatment resistant largely as a consequence of advanced glomerular and interstitial scarring. Nephrologists must educate primary care physicians to recognize and quickly refer these patients. Second, if the antibody removal is useful, then it stands to reason that diminishing circulating B cells and therapy to reduce circulating ANCA titers may be of therapeutic advantage. A number of anecdotal experiences have been reported using rituximab or the anti-CD20 mAb that depletes B cells in ANCA small-vessel vasculitis. Many of these patients have had treatment-resistant disease. The use of this expensive therapy, although of potential interest, must be critically tested to determine whether it, too, can preserve normal glomeruli.

When the practicing physician confronts patients with ANCA small-vessel vasculitis and kidney injury that is complicated by life-threatening pulmonary hemorrhage, prompt induction of therapy with plasmapheresis is essential. On the basis of current reports, physicians should also add plasmapheresis to induction therapy in patients who have advanced renal insufficiency and dialysis dependence. The complications of this therapy, particularly the high mortality of plasmapheresis and oral cyclophosphamide, should limit this therapy only to dialysis patients with severe disease.

DISCLOSURES

None.

REFERENCES


See the related articles, “Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis,” on pages 2180–2188, in “Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis,” on pages 2189–2197.

Renin and Its Putative Receptor Remain Enigmas

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In this month’s issue of JASN, Takahasi et al.1 report that prorenin receptor blockade causes diabetic nephropathy to regress. The authors performed uninephrectomy in mice; induced diabetes with streptozotocin; and treated these mice with a prorenin receptor blocker (PRRB), an angiotensin converting enzyme (ACE) inhibitor, or vehicle. PRRB was nigh to curative, whereas ACE inhibition was solely ameliorative. This