Editorial

Renal Biopsy at the Onset of Clinical Lupus Nephritis: Can It Yield Useful Information?

Lupus nephritis affects approximately 50% of patients with systemic lupus erythematosus, and progression to endstage renal disease (ESRD) can occur in up to 48% of those with nephritis at 5 years[1]. The goal of clinicians is to identify individuals with clinical nephritis who are at risk for renal damage so that appropriate treatment can be initiated to prevent inflammatory lesions from progressing to sclerotic ones.

The value of the renal biopsy to identify individuals at risk has been debated. Most reports finding lack of prognostic value of renal biopsy are biased by the treatment patients receive after diagnosis made by renal biopsy. Many such reports have been published since it became routine to use steroid-sparing agents such as cyclophosphamide and mycophenolate mofetil.

In a 1904 report by Sir William Osler, 5 of 14 cases of nephritis died, one within a week of diagnosis[2]. When corticosteroid therapy became available for proliferative lupus nephritis, short-term remissions were achievable, but 2-year survival rates were close to 30%[3]. After pulse cyclophosphamide became the gold standard for treatment of proliferative disease, the effect of proliferative lesions on outcomes became less clear[3]. Even with the use of cyclophosphamide therapy for World Health Organization (WHO) class III and IV disease, those with segmental proliferative lesions continued to experience a greater rate of ESRD than those with global proliferative lesions[4]. Thus, now that therapy is more timely and effective, the outcomes of different classes of nephritis may differ less.

Studies reporting lack of association between renal biopsy and outcomes observe poor outcomes such as ESRD to be associated with clinical factors that include serum creatinine at baseline, older age, male gender, smoking, hypertension, low complement levels, and marked proteinuria. Some studies advocate hypocomplementemia as an important variable predicting poor outcome in patients with proliferative disease[3]. As mentioned above, utility of hypocomplementemia as a predictor of outcome may be diminished by more aggressive therapy given to those with proliferative disease. Another factor is that hypocomplementemia may not reliably identify segmental, pauciimmune lesions[5].

Among the biopsy findings felt to be prognostic in some studies are the presence of crescentic and segmental lesions, global proliferative lesions (either diffuse or focal), interstitial fibrosis, and high activity and chronicity indices[3]. Several studies, including a recent article by Faurschou, *et al*[6], report that a delay in renal biopsy (and therapy) is a strong independent predictor of poor outcome[7-9]. Others have advocated a more conservative approach to renal biopsy, and instead recommend induction therapy followed only by biopsy in the event of incomplete treatment effect. This approach is based on the assumption that those with mild or no hematuria, urine protein/creatinine of < 1.0, and normal serum creatinine have WHO class II disease[10].

The report of Christopher-Stine, *et al* in this issue of *The Journal* challenges this notion[11]. The authors report findings from a subset of patients receiving renal biopsies in their cohort in whom the level of proteinuria at the time of biopsy was less than 1.0 g in 24 hours in the setting of new or rising proteinuria or hematuria but stable renal function. In their study, 13 of the 21 patients had WHO class III, IV, or V nephritis. Three patients had biopsy findings that would not have required immunosuppressive therapy. One of these had thrombotic microangiopathy that would have required anticoagulation rather than immunosuppressive therapy. This is an important observation, because thrombotic microangiopathy is an independent risk factor for renal compromise[12,13]. Finally, 5 patients had diagnoses that are often treated initially with corticosteroids that are tapered after effect. Important is the finding that the biopsies from 3 of the patients in this study had significant chronicity indices on biopsy even with low levels of proteinuria.

Should early biopsy be performed to improve outcomes

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in lupus nephritis as advocated by Christoper-Stine, *et al*? First, their study cannot adequately address this question due to its retrospective, cross-sectional design and to limited numbers of patients. Studies randomizing early versus late biopsy and treatment have not, and likely will not, be performed in the future due to ethical concerns. However, several retrospective studies strongly suggest that delay of biopsy and treatment from the time of clinical onset of nephritis is an independent risk factor for poor outcome[7-9]. Second, would the findings of this study change the manner in which one would diagnose and treat patients with lupus nephritis? There are several perspectives on the utility of renal biopsy in guiding the choice of induction therapy, so each will be discussed separately.

If one is of the opinion, as the authors advocate, that diagnosis by renal biopsy is essential to guide treatment decisions, then their report strongly supports the notion that early renal biopsy should be performed. Thirteen of the 21 patients in this study had diagnoses that would have required steroid-sparing therapy. Thus, treatment delay may have increased the risk for progression of glomerulosclerosis in these patients. If one asserts the more conservative approach of performing biopsy only after a lack of response to induction therapy, then this report argues for initiation of therapy early, rather than waiting for what is traditionally felt to be significant proteinuria (urine protein/creatinine > 1.0). If empiric steroid-sparing therapy were given to all in this group of patients with new onset or rising proteinuria or hematuria with normal serum creatinine, then only 13 of the 21 would have received appropriate therapy. This approach would have resulted in 5 of 21 patients receiving inappropriately aggressive induction therapy and 3 of 21 patients inappropriately receiving immunosuppressive therapy. Some have suggested that steroid-sparing immunosuppressive therapy be given only to those with proteinuria or hematuria associated with hypocomplementemia as a marker of immune complex-mediated proliferative disease. This approach would have resulted in a missed diagnosis and inappropriately delayed therapy in 2 patients with aggressive disease as marked by already elevated chronicity indices (averaging 4).

Thus, when deciding whether early biopsy or early empiric treatment is in the best interests of the patient, one must weigh the risk of renal biopsy against that of the consequences of misdiagnosis and mistreatment. The literature regarding the number needed to harm (serious complication rate) with renal biopsy is variable, and each institution and operator has a different adverse event rate. Taking data from the recent cyclophosphamide versus mycophenolate mofetil trial, the number needed to harm (serious infections) was 12 with cyclophosphamide versus 83 with mycophenolate mofetil therapy[14]. Regarding the approach of delaying therapy, the number needed to harm is more difficult to estimate, given the lack of prospective data. However, this factor should always be considered. Thus, in centers with much higher serious adverse event rates for renal biopsy, empiric therapy with mycophenolate mofetil for all patients with new or rising proteinuria or hematuria in the face of low complement may be a reasonable approach, providing biopsy follows when there is lack of treatment response or worsening of disease within 3 months. One could also refer patients for biopsy to centers with lower adverse event rates. A conservative approach to biopsy may also be reasonable in patients with stable renal function and risk factors for complications from renal biopsy such as prolonged partial thromboplastin time (in the absence of signs of antiphospholipid syndrome), low platelet count, or hypertension[15,16].

Christoper-Stine, *et al* achieved their first objective, i.e., to determine if those in their clinic population with low levels of proteinuria had significant findings on biopsy. Whether they achieved their second objective — to determine if renal biopsy is warranted to prevent renal damage in those with low levels of proteinuria — can be debated but is strongly supported by the data presented. Whether one takes an early biopsy or early treatment approach to lupus nephritis, this study demonstrates clearly that significant disease can be observed on renal biopsy in early clinical disease and that delay in treatment until the onset of more clinically apparent disease is not justified. Thus, any lupus patient with new-onset proteinuria, hematuria, or rising proteinuria, even in the absence of impaired renal function or a urine protein/Cr > 1.0, should receive either (1) a biopsy to guide therapy, or (2) empiric therapy based on clinical predictors of outcome if the risk of biopsy is unacceptably high.

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