Update on scoring and providing evidence basis for assessing pathology in lupus nephritis

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Like the majority of renal histopathologic classifications, the 2004 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (LN) (ISN/RPS 2004)[1,2] is the result of expert consensus opinion based on literature available at the time; indeed, the only truly evidence-based classification is the Oxford (MEST-C) classification for IgA nephropathy.[3–5] In this way, ISN/RPS 2004 resembles early iterations of the Banff classification for kidney allograft pathology (reviewed[6]); the latter has undergone periodic revision based in large part on new evidence from single-center and multicenter studies. ISN/RPS 2004 denotes 3 general patterns of glomerular injury that alone or in combination are present in the overwhelming majority of kidney biopsies with LN and have formed the basis of numerous clinical trials and investigations, as follows: mesangial (class II); endocapillary/extracapillary (classes III and IV); and membranous (class V). During phase I of the LN classification project, we updated ISN/RPS 2004 by refining lesion definitions, including incorporation of consensus definitions,[7] and emphasizing the role of the previously established National Institutes of Health activity index (AI) and chronicity index (CI).[8]

Comparing old and new

Three studies have investigated the modified LN classification in comparison to ISN/RPS 2004, concluding that the modified version can predict clinical outcomes more precisely,[9] is more useful,[10] and has utility for prediction of clinical renal outcomes.[11] Recommendations from other publications for modifying the LN classification have focused on histologic lesions that are inadequately addressed by ISN/RPS 2004. Of these, vascular lesions[12] were mentioned most often, in particular microvascular lesions resulting from immune complex deposits and lesions characteristic of vasculitis and noninflammatory necrotizing vasculopathy,[13] but also arteriosclerosis[14] and changes indicative of thrombotic microangiopathy (TMA).[15] A few studies focused on the significance of nonvascular lesions, such as Bowman's capsule rupture,[16] and lupus podocytopathy.[17] A common drawback of these studies is the use of univariate analyses to investigate correlations between histologic parameters and clinical outcome measurements, although how effectively these parameters predict outcome in multivariable analyses, including clinical and histologic parameters most often encountered in LN, remains unknown. Focusing on the roles of the AI and the CI, Moroni *et al.*[18] showed that the CI and its separate components were directly related to clinical outcomes, in particular serum creatinine levels. They also showed that a delay in the performance of a kidney biopsy predicted kidney function impairment, likely related to delay of diagnosis and appropriate treatment, with the associated development of irreversible, chronic lesions. Time is an important factor that influences the AI and the CI, suggesting that chronologic parameters should be incorporated into future classification system.

The phase II study: plans and goals

We embark on phase II with 2 major goals. First, given that the AI and CI form a major component of the updated classification, replacing in a more granular way the (A), (A/C), and (C) designations in ISN/RPS 2004, examination of their interobserver variability is important. As high interobserver variability was a recognized issue with the original National Institutes of Health indices, the definitions for the specific lesions comprising these indices were clarified in phase I, although the extent to which this clarification will improve such variability remains uncertain. Given the availability of digital pathology by which whole slide images can be distributed to renal pathologists worldwide (i.e., the full membership of the RPS and other renal pathology working groups), this factor can be easily assessed. If agreement is unsatisfactory, online case-review

sets (e.g., linked to the RPS website) can be used as an improvement tool.

The second aim of phase II is to identify histologic parameters that best predict kidney outcome in patients with LN and modify the classification accordingly. Our aim is not to substantially modify the existing ISN/RPS classes that are recognized worldwide. However, we aim to improve the value of the ISN/RPS classes with respect to prognosis and guiding therapy, by adding specific detailed assessment of risk modifiers, in part focused on extending the usefulness and reproducibility of the AI and the CI, but also introducing additional parameters (e.g., vascular lesions). Modifications of the classification also could be introduced for repeat kidney biopsies, which have proven useful in assessing therapeutic response and providing guidance on how long immunosuppression should be continued. Indeed, the second, posttreatment biopsy may be more valuable than the initial biopsy in predicting kidney outcomes.[19] Biopsies in patients with ongoing proteinuria may indicate persistence/new development of membranous lupus nephritis or, despite years of treatment, may show continued inflammatory activity but often only chronic injury with secondary focal segmental glomerulosclerosis; in such patients, the risk of continuing immunosuppression may outweigh its benefit. In contrast, LN patients with clinical resolution who undergo a protocol biopsy often show persistent inflammation,[20,21] and withdrawal of immunosuppression in such patients is associated with a high relapse rate, an outcome to be avoided as LN flares create predisposition to progressive kidney failure.[21,22] Specific modifications to the classification, focused on comparing findings in initial and repeat biopsies, and possibly incorporating results of studies such as ReBiolup, a prospective repeat biopsy study, could greatly expand the clinical value of the classification.

In light of such ongoing studies, our aim is also to develop a classification that is fluid, that is, readily modifiable in response to new and important findings regarding pathophysiology and especially treatment of LN. This fluidity is crucial, noting the emergence of new therapies for LN that have shown improved kidney response with reduced adverse effects. This type of fluidity is an important strength of the Banff classification for assessing transplant biopsies, which while not being fully evidence-based has been updated every 2–3 years to incorporate new findings that have potential to impact care of individual patients.[6]

Beyond morphology: molecular approaches and biomarkers

Newer methodologies, which elaborate on the pathophysiology and underlying pathogenic mechanisms, are likely to contribute to the development of a more personalized approach to LN management. Studies of expression of gene transcripts and pathogenesis-based transcript sets, using microarray analysis of RNA derived from fresh biopsy tissue or the NanoString platform, that can utilize formalin-fixed, paraffin-embedded tissue and thus be correlated directly with histologic findings,[23] may be an important adjunct to histologic and clinical studies. The potential value of such approaches has been demonstrated in characterizing different rejection subtypes in kidney allografts.[24,25] Histologic, clinical, serologic, and other data also can be input into computer models to generate predictors of clinical outcomes beyond what can be determined from clinical and morphologic data alone, as well as in defining endpoints for clinical studies beyond those currently used (e.g., kidney failure, >50% decline in estimated glomerular filtration rate).[26–28] Although the main aim of phase II is to provide detailed and reproducible assessment of histologic lesions that correlates with outcome and response to available treatments, a possible phase III might then further assess subvisual elements of pathogenic pathways, using molecular diagnostics, artificial intelligence, and spatial transcriptomic pathway analysis, and match these with specific pathway-directed therapies.

Since 2018, numerous biomarker studies have pointed toward the need to identify reliable, noninvasive, sensitive, and specific biomarkers that reflect histologic changes of LN, facilitate diagnosis and assessment of disease activity, and predict kidney damage and therapeutic response. Biomarkers should be validated and should be predictive in populations of interest. Almost invariably, studies emphasize the importance of future identification of biomarkers in reducing the need for kidney biopsies in LN. We envision that future biomarker studies would be validated using the latest phase of the LN histologic classification, ensuring reproducibility of correlates. An important concern is use of nonstandardized approaches to histologic subtypes. An evident

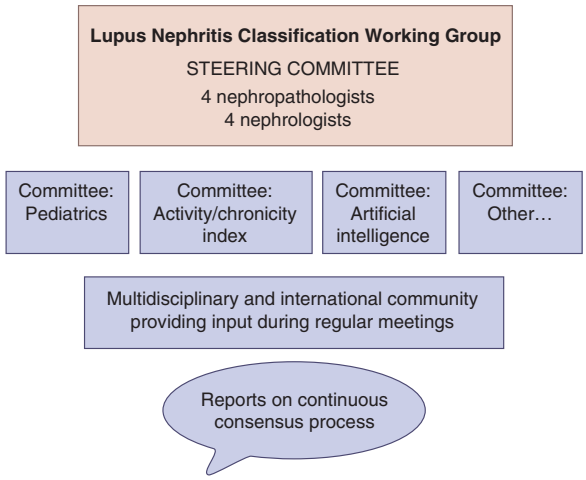

Figure 1 | Organizational structure of working group for lupus nephritis classification.

point is that impactful biomarker studies need to include a thorough understanding of the diversity of histologic changes observed in LN.

Summary

In an effort to match the needs of clinicians caring for LN patients in an evolving therapeutic landscape, the Working Group for Lupus Nephritis Classification, in phase I of this project, has proposed improvements in the definitions of individual lesions that could impact assessment of prognosis and treatment. Indeed, a study by the RPS has demonstrated improvement in interobserver agreement in defining specific glomerular lesions using consensus definitions developed in phase I.[7,29]

Phase II involves tests of interobserver reproducibility to evaluate and validate the value of the newly proposed definitions, and the use of findings of new clinicopathologic studies and clinical trials to make adjustments to the classification system. Following the lead of the Banff initiative for kidney allograft pathology, we plan to organize meetings on a regular basis to discuss implications of recent developments for the classification scheme, incorporating new knowledge from nephropathologists, nephrologists, rheumatologists, immunologists, and basic/translational scientists. Updates to the classification, and the rationale for these, will be reflected in meeting reports. Specific topics will be the focus of committees that will report their updates at the meetings and in the meeting reports. Following the long-standing consensus process of Banff, revisions of the LN classification will be embedded in a multidisciplinary and international community, so these can be incorporated swiftly into routine practice, research studies, and clinical trials.

In Figure 1, we present a working scheme for our endeavor.

DISCLOSURE

All the authors declared no competing interests.

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