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EDITORIAL

Lupus Nephritis: Breaking the Lull

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Systemic lupus erythematosus (SLE) has a prevalence of 241 per 100,000 people in the United States.[1] Young women are disproportionately affected and disease burden is highest in blacks and lowest in whites in studies that report data by race.[1] Up to 75% of SLE patients will develop kidney disease, which is often asymptomatic and detected only by urinalysis. Pathologic classification of lupus nephritis (LN) is based on the location and degree of glomerular involvement coupled with the activity and chronicity of histologic changes. Specific classes of LN carry different prognoses. As such, immunosuppression is reserved for those classes associated with worse kidney survival. The goal of therapy is to quell inflammation, stabilize or improve kidney function, and induce a sustained remission. From the 1970s to the 1990s, rates of ESRD from lupus decreased because of improved immunosuppressive therapies. However, these rates have plateaued during the mid-1990s to 2000s.[2] Risk factors for ESRD include young age, female sex, and African-American (AA) race.[3] Despite early trends suggesting improved kidney survival, the recent plateau in outcomes is disappointing and highlights the pressing need for improved management, particularly in groups who have a higher risk of ESRD.

AREAS FOR IMPROVEMENT

The current biopsy classification is more than 15 years old and is undergoing revision to include new clinicopathologic outcomes data. Clinical biomarkers such as proteinuria, hematuria, Antinuclear Antibody (ANA)/double stranded DNA Antibody (dsDNA) titers, and complement levels have been in clinical use for decades but are not always well-correlated with lupus activity. Our standard-of-care (SOC) therapies are 50%-60% effective for inducing complete or partial remission.[4-6] The impact of therapy on hard outcomes such as ESRD and death has not been well-studied. Furthermore, our current therapies come with risks that are particularly problematic in a young female population, specifically with regard to fertility, pregnancy, bone health, and cardiovascular disease. Moving forward, we hope for a personalized approach to care where genetics, biomarkers, and histologic findings related to an individual's specific inflammatory milieu will lead to specific, well-tolerated, and highly effective therapies. To this end, this past year has been notable for some encouraging new developments, including a proposal for a new biopsy classification, an updated Cochrane review on treatment regimens including comments on biologics, and evaluation of new drugs, such as voclosporin and anifrolumab.

PATHOLOGY CLASSIFICATION

The first lupus classification was established in 1974, and it has since undergone several modifications. The 2003 classification was intended to reduce inter-observer and intra-observer variability and add prognostic value based on available clinicopathologic data.[7] However, inter-observer agreement on histologic lesions in class III and IV disease remains poor.[8] A proposal to modify the current classification has been put forth by the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) and includes more precise definitions, several additions (ie, an adapted activity and chronicity scoring index) and deletions of other categories where inter-observer variability is greatest.[9] Phase 2 recommendations will address areas with limited supporting evidence such as scoring of tubular and vascular lesions. Akin to the Oxford classification for immunoglobulin A (IgA) nephropathy, where pathologic findings have been validated across multiple patient cohorts, the investigation of the relationship between histologic features and clinical outcomes in LN must be undertaken, realized, and validated. Importantly, there seems to be a move to creating consistency across distinct classification systems for glomerulonephritides. We anticipate that the changes we have seen with the IgA and lupus pathologic classification will be extended to other glomerular diseases.

KIDNEY BIOPSY PRACTICES

As kidney biopsy classification becomes more meaningful with regard to patient outcomes, a movement toward

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performing more frequent kidney biopsies during the course of disease becomes arguably more relevant, particularly when the information gleaned from the procedure alters clinical management. As multiple studies have indicated, proteinuria may not reliably reflect remission of LN. Although biopsies are usually performed at disease onset, they may also provide valuable information at other timepoints, such as completion of induction regimen, preconception, and new flares. Surveillance biopsies may be essential to appreciating the evolving nature of LN, especially changes in class and assessment of activity and chronicity. Whether treating specific lesions and ongoing histologic activity found on surveillance biopsies associates with improved future outcomes remains unclear. Accordingly, the utility of repeat biopsies remains controversial.

BIOMARKERS

A less invasive measure of disease activity that heralds flares before changes in urine studies, differentiates between active and chronic disease, varies with treatment response, and indicates overall prognosis is greatly needed. Much effort has been put into this endeavor, and there are promising candidates: colony stimulating factor 1, urinary neutrophil gelatinase-associated lipocalin and monocyte chemoattractant protein-1, a proliferation-inducing ligand, B lymphocyte stimulator/B-cell activating factor, interferon-alpha, tumor necrosis factor-related weak inducer of apoptosis, and several cytokines including interleukins IL-6 and IL-10. Currently, none are available for routine clinical use.

Genetics

Genome-wide association studies (GWAS) have shed some light on the genetic susceptibility to SLE and the high degree of shared risk loci across different ethnic and racial groups.[10] Results from GWAS meta-analyses have supported epidemiologic data showing a higher prevalence of SLE in non-Europeans compared to Europeans. GWAS have also supported the possible roles of key inflammatory disease mediators such as type I interferon and nuclear factor kappa-light-chain-enhancer of activated B cells. Since most GWAS have been conducted in European and Asian populations, we anxiously await data from other populations that may reveal additional susceptibility loci. Correlating these data with those emerging from registries in less studied populations, such as the African Lupus Genetic Network,[11] may provide enhanced insights into genotype-phenotype associations. Ultimately, characterizing risk alleles has implications for understanding the pathogenesis of disease and the future development of specific, targeted therapies.

Treatment

Currently, SOC LN induction therapies are high-dose glucocorticoids in conjunction with either MMF or CYC, with several studies demonstrating similar efficacy and unsatisfyingly low *complete* remission rates of approximately 30%. Studies support the use of lower dose CYC-based induction therapy (ie, Euro-lupus dosing), due to reduced drug toxicity and similar efficacy. Importantly, a recent Cochrane review does not confirm the pervasive belief that MMF reduces infertility.[12] Recent trials in the United States have demonstrated that low dose CYC may be applicable to a multi-ethnic population.[13] Multi-target therapy consisting of glucocorticoids, calcineurin inhibitors (CNIs), and MMF has shown significant promise, and may allow for more choices of induction and maintenance therapy. Multi-target therapy has had much success in Asian populations and is attractive because lower doses of each medication class may lead to fewer class-specific side effects.[14] A novel CNI, voclosporin, similar to and more potent than cyclosporine, has been studied in a multi-ethnic cohort of patients with LN.[15] Addition of voclosporin to SOC therapy with MMF and steroids increased remission rates. Adverse events including death were greater in the voclosporin group. In parallel with findings of other studies, the complete remission rates immediately after induction therapy remained regrettably low across all groups (maximum 33%). Notably, this particular trial used pulse glucocorticoids followed by a low-dose steroid regimen (maximum dose 25 mg/d) tapered to 2.5 mg/d by week 16.

Given the low remission rates with older therapies, there was hope that biologics would yield better results. Yet, despite the successful use of some biologics in smaller studies, many larger randomized trials have failed to meet primary end points, thereby arguing for careful (re)assessment of potential flaws in study design prior to conclusion of ineffectiveness. Belimumab (Benlysta; previously, LymphoStat-B) is a human monoclonal antibody that inhibits B-cell activating factor/B lymphocyte stimulator. This antibody is the Food and Drug Administration-approved biologic therapy for SLE, which has an unclear role in the management of LN. The results of an ongoing clinical trial that evaluate the addition of belimumab to the SOC for LN are forthcoming. Anifrolumab, a human monoclonal antibody directed against the type 1 interferon receptor, is an attractive treatment given biomarker studies and GWAS data regarding interferon's role in lupus nephritis. Nonetheless, anifrolumab for moderate-to-severe LN did not meet the primary end point of reduced lupus activity. The Treatment of Uncontrolled Lupus via the Interferon Pathway phase II study is currently active and addresses the efficacy of anifrolumab in moderate-to-severe LN. The outcomes with biologic therapies have been underwhelming, yet the potential efficacy of biologics should not be completely dismissed because these agents serve a role in treatment-resistant disease and steroid-sparing therapy.[16,17]

For patients who achieve complete remission, it is unknown when it is safe to discontinue immunosuppression. Characteristics that are favorable for therapy withdrawal include longer length of therapy (3-5 years), longer duration of complete remission (>3 years), and ongoing hydroxychloroquine treatment.[18,19] Successful withdrawal of therapy is possible and may be done with very close supervision, while balancing the risks and benefits of long-term immunosuppression. Until a formal prospective study evaluates this issue, the withdrawal of maintenance therapy will remain an area of controversy.

Transplantation in LN

There are racial disparities in outcomes, and African Americans are have higher rates of ESRD compared to other ethnic groups.[20,21] Fortunately, LN patients who undergo kidney transplantation have similar patient and allograft survival rates as patients without SLE (superior to diabetes but inferior to autosomal-dominant polycystic kidney disease).[22,23] Recurrent LN post-transplant varies widely, occurring in 2%-43% of allografts. Histologic recurrence is more common than previously thought. However, clinically significant LN post-transplant remains rare. Differences in biopsy rates, definitions of recurrence (clinical vs histologic), and processing of biopsy tissue to detect features of LN account for much of the variability. Unfortunately, the same risk factors for LN-ESRD are true for allograft failure, namely AA race, younger age, and female sex suggesting a more severe course in this population.[24]

Healthcare Maintenance in SLE

Treatment-related comorbidities associated with long-term immunosuppression require a multi-disciplinary approach. Healthcare maintenance and monitoring for adverse events is of great importance but is often overlooked due to disease complexity and subspecialty focus. Lupus is associated with greater cardiovascular morbidity; therefore, lupus patients should be counseled on controlling cardiovascular risk factors such as dyslipidemia, obesity, and hypertension.[25] Long-term immunosuppressive medications increase the risk of infections and malignancies. Accordingly, practitioners should provide CDC-recommended vaccinations and age-appropriate cancer screening, including full body dermatological examinations as recommended for the kidney transplant population. For patients treated with chronic steroid therapy, bone densitometry scans may be considered for osteoporosis screening. Contraceptive counseling is required due to the risks associated with infertility, poor fetal outcomes, and maternal pregnancy complications such as hypertension, pre-eclampsia, and lupus flares.

CONCLUSION

In summary, LN is a common and serious complication of SLE. The pathologic classification of lupus is undergoing revision to provide an even more valuable tool for guiding clinical decision-making. We await the entry of novel serum and urine biomarkers into mainstream clinical practice. LN therapy has not changed during the past decade, and, at best, provides a 50%-60% probability of complete or partial remission. Although several new agents, have been evaluated in clinical trials, none have dramatically improved remission rates compared to SOC therapy. Furthermore, even with older therapies, the impact on reducing hard outcomes such as ESRD and overall mortality has remained unstudied. Consequently, it is an understatement to say that "there is much work left to do." Addressing these challenges is paramount. Breaking the lull of therapeutic efficacy will require invigorated action across multiple disciplines to improve LN outcomes.

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