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In Translation

Lupus Nephritis: The Evolving Role of Novel Therapeutics

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Immune complex accumulation in the kidney is the hallmark of lupus nephritis and triggers a series of events that result in kidney inflammation and injury. Cytotoxic agents and corticosteroids are standard of care for lupus nephritis treatment, but are associated with considerable morbidity and suboptimal outcomes. Recently, there has been interest in using novel biologic agents and small molecules to treat lupus nephritis. These therapies can be broadly categorized as anti-inflammatory (laquinamod, anti–tumor necrosis factor–like weak inducer of apotosis, anti-C5, and retinoids), antiautoimmunity (anti-CD20, anti–interferon α, and costimulatory blockers), or both (anti–interleukin 6 and proteasome inhibitors). Recent lupus nephritis clinical trials applied biologics or small molecules of any category to induction treatment, seeking short-term end points of complete renal response. These trials in general have not succeeded. When lupus nephritis comes to clinical attention during the inflammatory stage of the disease, the autoimmune stage leading to kidney inflammation will have been active for some time. The optimal approach for using novel therapies may be to initially target kidney inflammation to preserve renal parenchyma, followed by suppression of autoimmunity. In this review, we discuss novel lupus nephritis therapies and how they fit into a combinatorial treatment strategy based on the pathogenic stage.

INDEX WORDS: Lupus nephritis; systemic lupus erythematosus (SLE); novel therapies; biologics; small molecules.

BACKGROUND

Corticosteroids plus cytotoxic agents have been the de facto standard of care for treatment of proliferative lupus nephritis for decades. Cyclophosphamide use became prevalent after a landmark National Institutes of Health trial demonstrated superiority over corticosteroids alone in preventing renal flares and kidney failure during long-term follow-up.[1] By contrast, for the first 3-5 years after treatment initiation, the study showed that corticosteroids and cyclophosphamide were equally effective. Due to concerns related to cyclophosphamide toxicity, especially premature ovarian failure and predisposition to future malignancies, alternative lupus nephritis treatment regimens were designed using low-dose cyclophosphamide,[2] substituting mycophenolate mofetil (MMF) for cyclophosphamide,[3] or combining a calcineurin inhibitor with MMF and corticosteroids.[4] Trials of these regimens compared short-term complete and partial remission rates to standard-dose cyclophosphamide. They did not evaluate long-term kidney survival, the outcome for which cyclophosphamide had been shown to be beneficial. Low-dose cyclophosphamide and MMF were found to be equivalent to standard cyclophosphamide, whereas multitarget therapy with cyclosporine, MMF, and corticosteroids appeared to be superior to cyclophosphamide for short-term remission induction. However, before they can be generally recommended, multitarget therapy and low-dose cyclophosphamide will have to be verified in multiracial/ethnic populations because the original trials included Asian and mainly white participants, respectively.

Long-term follow-up studies demonstrated good preservation of kidney function with low-dose cyclophosphamide.[5] A 3-year follow-up of the original MMF trial, comparing MMF and azathioprine as maintenance therapies, showed a nonsignificant tendency for patients who underwent induction with cyclophosphamide to have had fewer long-term adverse kidney end points than those who underwent induction with MMF, regardless of the choice of maintenance immunosuppression.[6] Of considerable concern is the fact that all of these regimens continue to have a disappointing complete remission rate.[7]

Recently, there has been excitement surrounding the development and implementation of biologics and small molecules for the treatment of lupus nephritis. The expectation has been that these therapies would target specific disease pathways, increasing treatment efficacy while decreasing undesirable side effects. To date, these expectations have not been realized in lupus nephritis trials. For example, the addition of rituximab or abatacept to MMF and corticosteroids did not

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improve the complete renal response rates of 25%-30% at 1 year compared to MMF and steroids alone.[8,9]

A number of factors may have confounded the clinical trials of new lupus nephritis therapies. For example, there is no standard definition of complete renal response. Although all trials assess similar clinical variables, such as proteinuria and kidney function, variations in how these variables are used in renal response criteria can profoundly affect the interpretation of trial results.[9]

Another concern regarding trials of novel therapeutics is whether trial outcomes were anticipated correctly. Lupus nephritis reaches clinical attention only after a threshold of glomerular and tubulointerstitial damage from intrarenal inflammatory processes has been reached. These inflammatory processes are due to autoimmune mechanisms that are set into motion well before the clinical diagnosis of lupus nephritis is established. We suggest that short-term kidney responses will be improved with anti-inflammatory therapies (Fig 1). In contrast, therapeutics that target the autoimmune mechanisms leading to kidney inflammation would be expected to prevent future lupus nephritis flares and preserve kidney function (Fig 1). To exemplify, a therapy designed to eliminate autoreactive B cells and decrease autoantibody production would not be anticipated to directly affect established kidney inflammation during a current flare and so should not improve the complete renal response rate at 6 or 12 months. In contrast, removing autoreactive B cells, and thus the source of autoantibodies, from the kidney interstitium or circulation would be expected to decrease the likelihood of future lupus nephritis activity. If these issues are taken into account during trial design, the response rate to novel therapeutics should improve. This review examines where novel biologic and small-molecule therapies fit into such a paradigm.

CASE VIGNETTE

An 18-year-old African American woman was given a diagnosis of systemic lupus erythematosus (SLE) at age 16 years after developing a malar rash, polyarthritis, and leukopenia. She was

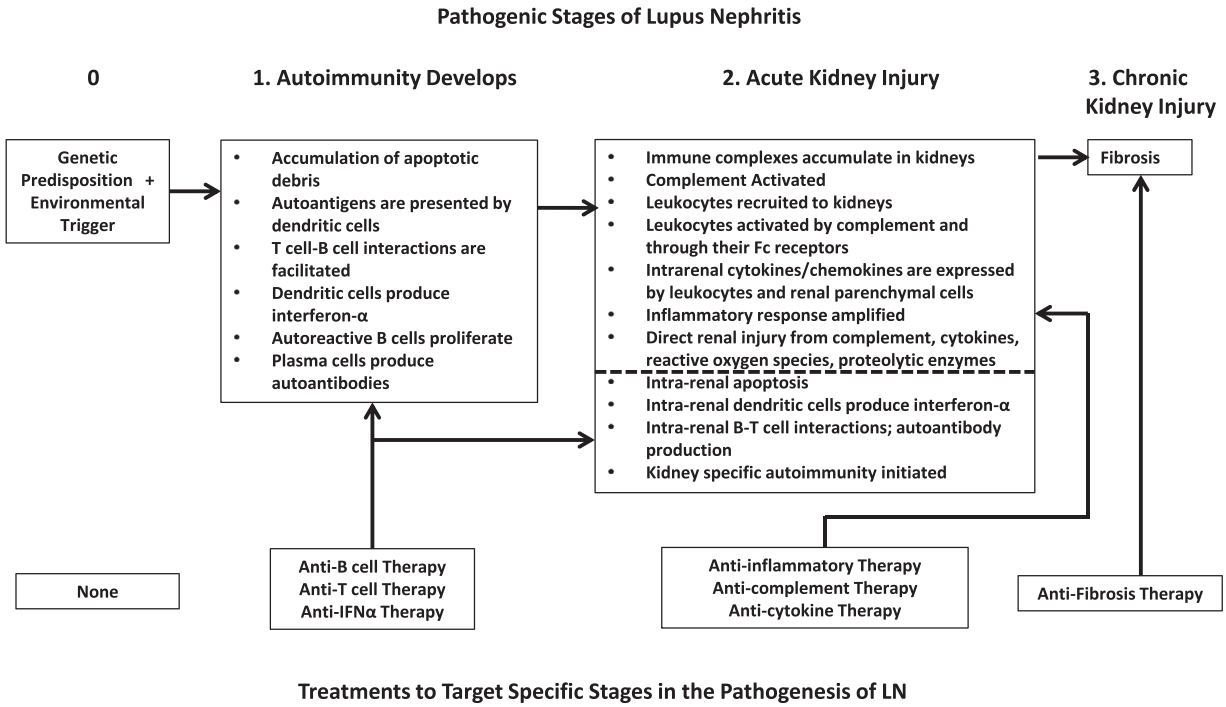

Figure 1. The pathogenic stages of lupus nephritis (LN) as a guide to therapy. Systemic lupus erythematosus and LN (upper boxes) occur in patients with a genetic predisposition to autoimmunity and presumably an environmental trigger to initiate disease (stage 0). Because these patients cannot be identified with accuracy in the general population, there currently are no therapies (lower boxes) that can be applied at this stage. After initiation, autoimmunity develops as the pathogenic processes listed under stage 1 occur. This would be an ideal point to intervene with drugs that target these pathways, such as B- and T-cell–directed therapies, but patients usually do not have clinical manifestations during stage 1 and the disease is relatively silent. Kidney involvement reaches clinical attention during stage 2, and clinical manifestations are due primarily to inflammatory processes initiated within the kidney (shown in the stage 2 box, above the dotted line). The induction therapy of LN therefore must control inflammation. In addition to intrarenal inflammation, the autoimmune processes of stage 1 likely are still active and kidney-specific autoimmunity may be developing (stage 2 box, below the dotted line). Thus, in addition to anti-inflammatory therapy, the antiautoimmune therapies that were applied to stage 1 also can be used in stage 2. These therapies would contribute less to controlling inflammation, but ideally would prevent further LN flares. Active inflammation also can lead to scarring of the kidneys. Addition of an antifibrotic agent, especially if interstitial fibrosis or glomerulosclerosis were confirmed by biopsy or novel biomarker, could stabilize kidney function and decrease the rate of chronic kidney disease progression. Abbreviation: IFNα, interferon α.