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Lupus Nephritis: The Evolving Role of Novel Therapeutics

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Abstract

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 apoptosis, 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.

Keywords

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

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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, multi-target 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 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 found to have elevated antinuclear antibody and anti-double-stranded DNA (anti-dsDNA) titers and was treated with hydroxychloroquine and prednisone. Her serum creatinine level increased from 0.8 mg/dL (estimated glomerular filtration rate [eGFR], 125 mL/min/1.73 m² using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation) to 1.5 mg/dL (eGFR, 59 mL/min/1.73 m²), and she developed new proteinuria with protein excretion of 3.5 g/d. Urinalysis showed acanthocytes and a few red blood cell casts. Kidney biopsy was interpreted as class IV-G (A) lupus nephritis with diffuse endocapillary proliferation, 30% cellular crescents, and severe tubulointerstitial inflammation, but no chronic lesions. She was treated with intravenous methylprednisolone, 1 g/d, for 3 days and then started on treatment with 1 mg/kg/d of prednisone and 1.5 mg/kg/d of oral cyclophosphamide. After 3 months, prednisone dosage was tapered to 10 mg/d, cyclophosphamide therapy was discontinued, and 2,000 mg/d of MMF was started. At month 6, serum creatinine level improved to 1.2 mg/dL (eGFR, 77 mL/min/1.73 m²), proteinuria decreased to protein excretion of 1.5 g/d, anti-dsDNA antibody levels decreased, and complement levels normalized. The patient remained on treatment with MMF and prednisone, and at month 12, serum creatinine level was 0.9 mg/dL (eGFR, 109 mL/min/1.73 m²), and protein excretion was 200 mg/d. Although still on maintenance MMF treatment at month 18, the patient reported fatigue, lower-extremity swelling, and foamy urine. Her proteinuria had increased to protein excretion of 3.0 g/d and serum creatinine level was 1.6 mg/dL (eGFR, 54 mL/min/1.73 m²). Kidney biopsy again showed diffuse proliferative lupus nephritis with active lesions, but new glomerulosclerosis and tubulointerstitial fibrosis was present, and the biopsy was now classified as IV-G (A/C) lupus nephritis.

This case illustrates that despite the use of the best available current lupus nephritis therapies and achieving an excellent clinical response, the kidney often sustains long-term damage (Fig 1; stage 2 of lupus nephritis) and maintenance of remission remains difficult.

PATHOGENESIS

The earliest step in the development of lupus nephritis is immune complex accumulation in the kidneys of patients with SLE, especially within glomeruli. These immune complexes initiate a series of events that result in kidney inflammation and kidney injury. Several mechanisms have been proposed to account for glomerular immune complex accumulation, including deposition of preformed circulating immune complexes, autoantibodies directed against intrinsic glomerular basement membrane proteins, and in situ formation of immune complexes between circulating antichromatin antibodies and extracellular glomerular

chromatin derived from apoptotic kidney cells. Recent evidence to support the latter mechanism has been found in both murine^{10,11} and human lupus nephritis.¹²⁻¹⁵

In addition to circulating autoantibodies, autoantibodies may be produced within the kidneys in lupus nephritis. T and B cells form aggregates and, in some cases, germinal centers in the tubulointerstitial compartment. Interstitial plasma cells within these aggregates appear to produce antibodies in a clonally restricted fashion.^{16,17} This may be a mechanism of generating kidney-specific autoimmunity.

Kidney-specific autoimmunity may be facilitated by intrarenal interferon α (IFN- α) expression.¹⁸ IFN- α drives the maturation of conventional dendritic cells into potent antigen-presenting cells,¹⁹ induces B-cell differentiation to plasma cells,²⁰ and contributes to the development of CD4 helper T (T_H) cells²¹ and CD8 central memory T cells.²² IFN- α -inducible genes are upregulated in peripheral-blood leukocytes of many patients with SLE, referred to as the IFN- α signature.^{23,24} The major source of IFN- α is the plasmacytoid dendritic cell (pDC). IFN- α is induced after engagement of pDC endosomal Toll-like receptors 7 and 9 (TLR7 and TLR9) by nucleic acids.^{25,26} In lupus nephritis, pDCs leave the circulation and accumulate in the kidneys, where they conceivably can interact with renal immune complexes and increase IFN- α levels within the kidneys.^{27,28}

Intrarenal immune complexes, especially those containing immunoglobulin G1 (IgG1) and IgG3 autoantibodies, are inflammatory because they activate complement and initiate renal recruitment of leukocytes through the chemotactic complement fragments C3a and C5a. The complement system also can injure the kidney directly through the formation of the membrane attack complex C5b-9.²⁹ Complement-mediated kidney damage, especially through the alternative pathway, has been demonstrated in murine and human lupus nephritis.³⁰⁻⁴⁰

Neutrophil and macrophage recruitment to the kidney can cause direct injury through secretion of oxygen radicals and proteolytic enzymes. Dying neutrophils may contribute further to lupus nephritis by releasing neutrophil extracellular traps, which are chromatin structures that can bind autoantigens.⁴¹⁻⁴³ Neutrophil extracellular traps also stimulate IFN- α secretion from dendritic cells,⁴¹ thereby amplifying intrarenal autoimmunity.

Leukocytes and intrinsic kidney cells produce proinflammatory cytokines and chemokines in response to immune complexes and complement fragments.⁴⁴⁻⁴⁶ Box 1 lists several of the cytokines and chemokines known to be upregulated in lupus nephritis kidneys.⁴⁷⁻⁵⁶

In lupus nephritis kidneys, T_H type 1 (T_H1) T-cell cytokines, including interleukin 12 (IL-12), IL-18, and IFN- γ , tend to be overexpressed compared to T_H2 cytokines, although some T_H2 cytokines, such as IL-10, also are increased.^{49,52,53,57} T_H1 cytokines are associated with activated macrophages and with the production of immunoglobulins that can initiate complement and Fc γ R pathways, further amplifying kidney inflammation. T_H17 and CD4⁺CD8⁺ T cells express the proinflammatory cytokine IL-17⁵⁸⁻⁶⁰ in the lupus nephritis kidney.⁵⁴ In addition to mediating inflammation, IL-17 may shift intrarenal T cells away from a regulatory phenotype (Treg) that is capable of attenuating immune responses, particularly autoantibody production.⁶¹⁻⁶⁵ Although the role of Tregs in human lupus

nephritis is not clear, several studies of humans have described lower circulating levels of Tregs in SLE (reviewed in^{63,66}), suggesting that restoring Treg levels may be beneficial.

Chemokines can amplify kidney inflammation by recruiting more leukocytes to the kidney in a positive-feedback loop. Cytokines can damage kidney parenchyma directly. For example, in murine lupus nephritis, exogenous IL-6 accelerated the progression of kidney injury, whereas treatment with an anti-IL-6 monoclonal antibody mitigated disease.⁵⁶ Cytokines also can mediate deleterious processes such as mesangial and glomerular epithelial cell proliferation, glomerulo-sclerosis, tubular atrophy, and interstitial fibrosis. As an example, tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK), a member of the TNF superfamily, promotes glomerular epithelial cell proliferation, inflammation, and apoptosis.^{4,67} Additionally, transforming growth factor β (TGF β) promotes scarring in injured glomeruli and tubulointerstitium through accelerated matrix deposition.⁶⁸ The role of specific cytokines and chemokines in lupus nephritis has been assessed by observing the effects of neutralization or genetic deletion on disease activity and histologic and clinical markers of kidney injury in murine lupus nephritis models.^{4,56,67-73} These experiments provide the rationale for therapeutically targeting cytokines and chemokines in human lupus nephritis.

In summary (see also Fig 1), active lupus nephritis can be characterized as an inflammatory response to immune complexes in the kidneys. Mediators of inflammation, including complement, infiltrating leukocytes, and cytokines derived from leukocytes and intrinsic kidney cells, injure renal parenchyma and network to amplify inflammation through a series of positive-feedback loops. Inflammatory kidney injury results in the local release of kidney antigens through apoptosis and necrosis. These antigens, in the presence of antigen-presenting dendritic cells, T cells, and B cells that have infiltrated the kidney and been conditioned by IFN- α and other cytokines, may result in intrarenal production of kidney-specific autoantibodies. This organ-specific autoimmunity may perpetuate kidney inflammation and facilitate future lupus nephritis flares. Therefore, treatment should focus on attenuating inflammation for current relief of lupus nephritis and addressing organ-specific autoimmunity for preventing reactivation of lupus nephritis.

RECENT ADVANCES

Patients who come to clinical attention and require treatment for lupus nephritis are most commonly in stage 2 of the kidney injury pathway (Fig 1). Some patients also may be on the way to stage 3, and that will be evident by the extent of glomerulosclerosis and interstitial fibrosis on kidney biopsy. We therefore suggest that for most patients, the ideal initial therapy of lupus nephritis would quickly and completely abrogate kidney inflammation. The history of lupus nephritis treatment suggests that this approach works. As discussed previously, anti-inflammatory doses of corticosteroids alone were as effective as corticosteroids plus cyclophosphamide in the early phase of lupus nephritis treatment.^{1,74} However, over time, corticosteroids alone proved to be inferior because patients had progressive kidney failure and more frequent lupus nephritis flares.^{1,74} In retrospect, this outcome is not surprising because focusing on inflammation alone probably does not adequately address the processes of systemic or kidney-specific autoimmunity (stage 1; Fig

1) that may be ongoing or poised to recur. The addition of cyclophosphamide to corticosteroid therapy likely attenuates some of these autoimmune processes. However, complete renal response rates to cyclophosphamide and other immunosuppressive agents remain fairly low.⁷ Recent data suggesting that cyclophosphamide promotes autoimmune mechanisms may at least partially explain this. In oncology patients, a single 3- to 4-g dose of intravenous cyclophosphamide had the expected cytotoxic effects, but also induced a type 1 interferon gene signature in peripheral-blood mononuclear cells, similar to that seen in SLE, and increased levels of the B-cell survival factor (B-cell activating factor [BAFF]).⁷⁵ Similarly, after cyclophosphamide-induced lymphocyte depletion in mice, reconstituting B cells were exposed to high levels of BAFF, and this was associated with anti-DNA autoreactivity and the appearance of circulating anti-DNA autoantibodies.⁷⁶ Thus cyclophosphamide may contribute to autoimmunity, although in patients with lupus nephritis, concomitant corticosteroid treatment may mitigate the proinflammatory effects of cyclophosphamide. We therefore suggest that concurrent with or shortly after anti-inflammatory therapy for lupus nephritis is initiated, novel therapies that target mechanisms of autoimmunity should be administered. It is expected that this approach will prevent lupus nephritis flares over the long term and thus limit progressive kidney failure.⁷⁷ This treatment paradigm also implies that trials to examine the efficacy of novel therapies need to collect data for long-term outcomes and not only short-term renal response rates, as most have done recently.

Novel therapeutics are summarized in Table 1 and discussed in detail next.

Anti-inflammatory Therapies

Because lupus nephritis is a severe manifestation of SLE and the implications of therapeutic failure include end-stage kidney disease and renal replacement therapy, new therapies almost always will be trialed initially as add-ons to corticosteroids plus an immunosuppressive. In this context, several novel biologics or small molecules may be useful in controlling inflammation more rapidly and/or more completely than current induction therapies. However, the possibility that some of these therapies could replace corticosteroids on the basis of efficacy and/or safety should not be overlooked. This would require a shift from add-on clinical trial design to substitution clinical trial design.

Laquinimod—Laquinimod is a small-molecule derivative of quinolone-3-carboxamide. It has been studied extensively as therapy for multiple sclerosis and just completed a phase 2 trial in lupus nephritis (clinical trial NCT01085097 at www.clinicaltrials.gov), with results expected in early 2014. In experimental autoimmune encephalitis, a model of multiple sclerosis, laquinimod behaves as an anti-inflammatory agent, decreasing infiltration of the central nervous system by monocytes and reducing proinflammatory cytokine and transcription factor expression, such as MCP-1 (monocyte protein 1) and NF-κB (nuclear factor-κB), respectively.^{78,79} Laquinimod also appears to modulate the inflammatory environment by polarizing T cells toward Tregs and away from T_H1 and T_H17 phenotypes.^{79,80} Human leukocytes or dendritic cells treated with laquinimod or taken from patients with multiple sclerosis treated with laquinimod show suppression of inflammatory cytokine and chemokine genes and decreased expression of NF-κB.^{80,81} Laquinimod also

may have a role in modulating autoimmunity (stage 1; Fig 1) because it can decrease the expression of genes involved in antigen presentation and reduces pDCs.^{80,81}

Synthetic Retinoids—Small-molecule synthetic retinoids that are ligands only for α/β retinoic acid receptors have been used to treat experimental autoimmune uveoretinitis and experimental autoimmune encephalitis.^{82,83} A trial of one such agent, tamibarotene, in SLE is planned (clinical trial NCT01226147, www.clinicaltrials.gov). In experimental inflammatory diseases, the retinoid AM80 decreased central nervous system and retinal infiltration by leukocytes, prevented retinal granuloma formation, and increased gene expression of an NF- κ B repression factor.^{82,83} AM80 also may increase Tregs and decrease TH17 cells. Some potential concerns with AM80 include its downregulation of the anti-inflammatory cytokine IL-10 and an inability to prevent chronic inflammation in experimental autoimmune encephalitis.⁸³

Eculizumab—Eculizumab is a recombinant fully humanized IgG2/IgG4 monoclonal antibody directed at human complement component C5. Eculizumab inhibits the conversion of C5 to C5a and C5b, thus preventing formation of the membrane attack complex (C5b-9) and the chemotactic fragment C5a. Eculizumab interacts with the complement system distal to classical pathway components and should not interfere with beneficial immune complex clearance activities of the classical pathway.³⁵ It is conceivable that in lupus nephritis, eculizumab could prevent direct complement-mediated injury to intrinsic glomerular cells and attenuate kidney inflammation by reducing renal leukocyte recruitment. Although eculizumab currently is approved only for treatment of atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria,⁸⁴ it was shown to be safe and well-tolerated in a phase 1 trial in SLE.⁸⁵

Anti-TWEAK—TWEAK and its receptor fibroblast growth factor inducible 14 (FN14) are expressed at low levels in healthy adult kidneys.⁸⁶ Under stress, including the immunologic injury of lupus nephritis,^{4,87-89} renal TWEAK and FN14 are upregulated, and binding of TWEAK to FN14 activates NF- κ B in renal tubular cells. Through NF- κ B, TWEAK induces renal tubular cell expression of several cytokines and chemokines, including MCP-1, IL-6, IP-10 (IFN- γ -induced protein 10), MIP-1 α (macrophage inflammatory protein 1), ICAM-1 (intercellular adhesion molecule 1), VCAM-1 (vascular cell adhesion molecule 1), and RANTES (regulated on activation normal T cell expressed).^{67,90} Sustained NF- κ B activation by TWEAK promotes renal tubular epithelial cell proliferation, inflammation, and apoptosis.⁸⁷ Neutralization of TWEAK in lupus nephritis thus would be expected to decrease kidney inflammation and injury, an outcome that has been demonstrated in several animal models of kidney disease.⁹¹⁻⁹³ Anti-TWEAK currently is being evaluated in a phase 3 lupus nephritis trial (clinical trial NCT01499355, www.clinicaltrials.gov).

Anti-IL-6—IL-6 is a multifunctional cytokine produced by leukocytes and intrinsic kidney cells that affects inflammation, increases mesangial cell proliferation, and also contributes to autoimmunity by stimulating terminal B-cell differentiation, autoantibody secretion, and T-cell differentiation.^{94,95} IL-6 works in synergy with IL-1 and TNF- α to promote inflammation, but also can be anti-inflammatory by termination of IL-1- and TNF- α -

mediated inflammatory cascades.⁹⁶ In murine and human SLE, IL-6 levels are increased in serum, urine, and glomeruli and correlate with disease activity.^{97,98} Neutralizing IL-6 or blocking the IL-6 receptor mitigates disease in murine models of lupus nephritis.^{72,95,99}

Tocilizumab is a humanized monoclonal antibody that blocks IL-6 from binding to its receptor. A phase 1 clinical trial of tocilizumab in SLE demonstrated safety and tolerability (clinical trial NCT00046774, www.clinicaltrials.gov). In this trial, 5 of 12 patients with lupus nephritis did not have a change in level of proteinuria during the 12-week treatment period, but urine sediment activity improved and anti-dsDNA titers were reduced.¹⁰⁰ Sirukumab is a humanized monoclonal antibody against IL-6 and presently is undergoing a phase 2 clinical trial to assess its safety and efficacy in lupus nephritis (clinical trial NCT01273389, www.clinicaltrials.gov).

Because IL-6 affects inflammation, cell proliferation, and autoimmunity, it is difficult to know its proper place as a therapeutic target within the paradigm presented in Fig 1. Although discussed under anti-inflammatory therapies, results of the current lupus nephritis trial will help in understanding how and when to best use IL-6 inhibition.

Antiautoimmunity Therapies

A number of recently introduced biologics that have been or will be tested in lupus nephritis are directed at the autoimmune mechanisms that predispose the kidney to inflammatory injury. Most of these studies examined short-term (6- to 12-month) renal response rates when added to conventional therapy. However, because these therapies attenuate autoimmune mechanisms, their role in lupus nephritis treatment may be to prevent recurrent disease activity (flares) and thereby the accumulation of organ damage (chronic or end-stage kidney disease). It is conceivable that antiautoimmunity therapeutics may decrease or eliminate the need for maintenance immunosuppressive therapy in lupus nephritis.

Rontalizumab and Sifalimumab—Rontalizumab and sifalimumab are humanized antibodies to IFN- α . Given the critical role of IFN- α in autoimmunity, neutralizing its activity would appear to be a good strategy in preventing further disease flares after kidney inflammation has been controlled. Some indirect clinical data support this approach. In 49 patients with SLE, 22% were found to have naturally occurring anti-IFN- α antibodies and a lower IFN- α gene signature than patients without such antibodies.¹⁰¹ These antibody-positive patients also tended to have a lower SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score, fewer positive lupus serologic test results, and higher complement levels than patients with the high IFN- α signature. However, ~35% of this cohort were low IFN- α signature but did not have anti-IFN- α autoantibodies, suggesting that not all patients will benefit from exogenous anti-IFN- α therapy. On the positive side, IFN- α gene signature may be a good biomarker for deciding which patients will benefit most from anti-IFN- α therapy.

Rontalizumab and sifalimumab already have been tested for safety in 3 small phase 1 studies, although most patients had only mild to moderate disease, were receiving no more than 20 mg of prednisone per day and no immunosuppressive agents, and did not have active lupus nephritis.¹⁰²⁻¹⁰⁵ In these studies, 50%-75% of patients demonstrated an IFN- α

gene signature, and in general, rontalizumab and sifalimumab inhibited the gene signature in a dose-dependent fashion, although inhibition was short lived and did not completely reverse the expression of IFN- α -activated genes. For example, sifalimumab caused an average IFN- α signature inhibition of 39%.¹⁰⁵ Despite decreasing the gene signature, rontalizumab did not decrease protein levels of IFN- α -activated genes or the patients' autoantibody levels.¹⁰³ Unexpectedly, a preliminary report of a phase 2 study of rontalizumab in SLE showed more benefit in patients who were low IFN- α signature, suggesting that higher antibody doses may be required to attenuate IFN- α activity in patients with a high gene signature.¹⁰²

Another approach to attenuating the effects of IFN in lupus nephritis is by blocking the IFN- α receptor. This may be more effective than directly blocking IFN- α because there are several type 1 IFN isotypes that all work through the same receptor. Medi-546 is a humanized anti-IFN- α receptor monoclonal antibody that currently is under investigation (clinical trials NCT01559090, NCT00930683, and NCT01753193; www.clinicaltrials.gov).

Rituximab and Other B-Cell-Directed Therapies—Rituximab is a humanized/mouse chimeric monoclonal antibody to CD20, which is present on most B cells but not plasma cells. The rationale for testing rituximab in SLE and lupus nephritis was to deplete autoreactive B cells and thereby attenuate the production of the autoantibodies necessary for disease manifestations. Although there now are a large number of reports on the apparent utility of rituximab in renal and nonrenal lupus, most of these are anecdotal case reports, small uncontrolled case series, or registries.^{106,107} LUNAR (Lupus Nephritis Assessment with Rituximab) and EXPLORER (Exploratory Phase II/III SLE Evaluation of Rituximab), the 2 large, prospective, placebo-controlled trials, failed to find a benefit of rituximab in renal or nonrenal lupus when added to standard-of-care treatment.^{8,108} In LUNAR, rituximab plus corticosteroids and MMF did not increase complete renal responses at 1 year compared to placebo plus corticosteroids and MMF.

The reasons for the failure of LUNAR continue to be debated. However, in hindsight and in the context of the paradigm presented in Fig 1, rituximab would be expected to provide long-term kidney protection and not be expected to improve short-term complete response rates. An interesting follow-up to the LUNAR investigation would be to see if complete responders who had received rituximab have had fewer lupus nephritis flares than complete responders who received placebo.

There are several caveats to anti-B-cell therapy with rituximab that should be considered. Because rituximab does not affect plasma cells, it does not cause an immediate decrease in pathogenic autoantibody levels, but instead a decline that depends on how quickly natural or therapeutic elimination of the existing generation of autoreactive plasma cells occurs. Rituximab also may promote autoreactive B cells. As B cells become depleted in response to rituximab, levels of the B-lymphocyte-stimulating factor BAFF increase.^{109,110} The presence of a high BAFF level as B cells reconstitute may increase the generation of new autoreactive B cells. Finally, human B regulatory cells (Bregs), which appear to attenuate inflammation through an IL-10-dependent mechanism, have been found in patients with SLE.¹¹¹ It is not known whether rituximab eliminates Bregs in patients, but anti-CD20

antibodies deplete Bregs in mice.¹¹² This could interfere with endogenous anti-inflammatory mechanisms.

In light of these findings, a combinatorial B-cell-directed approach may be useful in the treatment of lupus nephritis. A testable B-cell-focused trial design based on combinations of B-cell therapies is illustrated in Fig 2. The first goal of a combinatorial approach would be to eliminate plasma cells that are producing pathogenic autoantibodies. This would be done during lupus nephritis induction, followed by rituximab to deplete B cells and prevent the generation of new autoantibody-producing plasma cells. Eliminating plasma cells may give rituximab a clean-slate environment (with no autoantibodies) in which to work. In a mouse model of autoimmune diabetes, anti-CD20 antibodies were most effective in preventing diabetes if given before insulin autoantibodies appeared,¹¹³ suggesting that a clean antibody slate may be important. Also, not adding rituximab during acute kidney inflammation may prevent the depletion of Bregs at a time when they may be most effective. To prevent the reconstitution of B cells in a BAFF-enriched environment, BAFF inhibition would be initiated with rituximab.

Combinatorial B-cell-directed therapy is feasible with existing biologics and small molecules. The boronic acid derivatives bortezomib, carfilzomib, and delanzomib are proteasome inhibitors used for the treatment of multiple myeloma. These small molecules induce apoptosis in plasma cells because plasma cells are sensitive to intracellular stress.¹¹⁴ Proteasome inhibitors have been found to be effective in 2 murine models of SLE and lupus nephritis and can both prevent lupus nephritis and ameliorate established lupus nephritis.¹¹⁴⁻¹¹⁶ Importantly, these models provide evidence that the proteasome inhibitors target plasma cells. Lupus mice treated with proteasome inhibitors had significantly lower concentrations of circulating autoantibodies and reduced frequency of splenic autoantibody-secreting cells compared with controls.^{114,116} Finally, because the transcription factor NF- κ B needs a functional proteasome for activation, these drugs block the induction of several NF- κ B-dependent proinflammatory cytokines and also appear to increase Tregs in models of lupus.^{114,115} Thus proteasome inhibitors may have a dual effect in the induction phase of lupus nephritis treatment, acting both as an anti-inflammatory agent and to clear out autoantibodies for rituximab. A study of bortezomib in an experimental model of antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis showed that bortezomib worked well only if started early in the disease course.¹¹⁷ This suggests that proteasome inhibitors may not be sufficient stand-alone anti-inflammatory agents for lupus nephritis that has reached clinical attention and probably will need to be combined with an additional anti-inflammatory agent to fully attenuate intrarenal inflammation (Fig 2). These data also support the idea that B-cell therapies must be applied to lupus nephritis at specific stages of the disease course for efficacy. Finally, some caution with these drugs is necessary because at least bortezomib is known to have important neurotoxicity.¹¹⁸

To counteract the potentially detrimental increase in BAFF levels that occurs as rituximab depletes B cells, belimumab, a monoclonal antibody that neutralizes BAFF, is the last component of combinatorial B-cell-directed therapy.¹¹⁹ A key clinical question will be when to start belimumab treatment. It would not be unreasonable to use circulating BAFF as a biomarker and initiate belimumab therapy when BAFF levels start to increase over

baseline. Belimumab therapy would be continued until peripheral B cells have been reconstituted, and then possibly withdrawn. A recent post hoc analysis of phase 3 belimumab trials in nonrenal SLE examined renal outcomes¹²⁰ and showed that belimumab-treated patients tended to have fewer renal flares, providing some support for the use of B-cell-directed therapies in the maintenance phase of lupus nephritis.

Rituximab recently has been compared to cyclophosphamide in ANCA-associated vasculitis. Although short-term remissions were similar with both therapies, patients in the rituximab arms were not given maintenance immunosuppression and did as well as the cyclophosphamide group, which received maintenance azathioprine.¹²¹⁻¹²³ This finding supports the idea that attenuation of autoimmune mechanisms by B-cell depletion may be very effective at preventing reactivation of kidney diseases that typically relapse.

Abatacept—CTLA4 binds B7 molecules that are on the surface of dendritic cells or B cells and can block the costimulatory interaction between B7.1/B7.2 and CD28 on T cells.¹²⁴ Abatacept, a fusion protein between CTLA4 and IgG heavy chain components, was developed as a therapeutic agent to target costimulation. Abatacept recently has been tested in 2 large randomized controlled trials in lupus nephritis as an add-on to either low-dose cyclophosphamide (ACCESS [Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis] Trial, clinical trial NCT00774852, www.clinicaltrials.gov) or MMF (clinical trial NCT01714817, www.clinicaltrials.gov). The primary end points were 6- to 12-month complete renal response rates or time to complete renal response. The complete renal response end point was chosen for these trials based on murine studies that showed that abatacept in combination with low-dose cyclophosphamide was able to induce complete lupus nephritis remission in mice with established nephritis.^{124,125} Unfortunately, abatacept did not improve complete renal response rates in either clinical trial.^{9,126}

Differences in the effects of abatacept in mice and humans may have contributed to the differences between the murine experiments and clinical trial results. For example, kidney inflammation decreased significantly in mice after abatacept treatment.¹²⁵ However, in patients with rheumatoid arthritis, CTLA4-Ig reduced serum IFN- γ , but not IL-6, VEGF (vascular endothelial growth factor) or TNF- α and had no effect on circulating dendritic cells, indicating perhaps a limited anti-inflammatory effect in humans.¹²⁷

In the context of the paradigm presented in Fig 1, an ideal use for abatacept in lupus nephritis may be to interrupt interactions between T and B cells in the lymphocyte aggregates found in about half of lupus nephritis biopsy specimens.¹⁷ Such an intervention would be expected to decrease kidney-specific autoimmunity and prevent future nephritis activity. Consistent with this idea, abatacept-treated complete responders in the ACCESS trial were not started on maintenance immunosuppression after 6 months of induction therapy. During the following 6 months, 50% of these patients maintained their complete responses with no further immunosuppression.¹²⁶

Antifibrotic Therapies

As kidney inflammation heals, scars develop in the kidney parenchyma, manifested as glomerular sclerosis and interstitial fibrosis. As in other types of glomerular diseases,

patients with lupus nephritis who sustain sufficient chronic tubulointerstitial injury tend to have progressive kidney failure.¹²⁸ Arresting progressive fibrosis in lupus nephritis kidneys may now be feasible.

Fresolimumab—Fresolimumab is a humanized IgG4 monoclonal antibody that neutralizes all 3 isoforms of TGF β . It currently is undergoing a trial in primary focal segmental glomerulosclerosis (clinical trial NCT01665391, www.clinicaltrials.gov). A previous safety and pharmacokinetic study of single-dose fresolimumab was done in patients with focal segmental glomerulosclerosis (n = 16) and demonstrated that it was well tolerated and associated with a small decline in proteinuria.¹²⁹ The relevance of the proteinuria observation is not clear because the real potential of fresolimumab is in long-term preservation of kidney function in patients who have had progressive scarring. It is unlikely that fresolimumab will reverse scarring and therefore significant improvements in proteinuria would not be expected unless the inhibition of TGF β positively influences remaining podocyte number and function, an effect seen with early but not late TGF β inhibition in animal models.^{130,131} We envision fresolimumab being used in patients with lupus nephritis who have ongoing proteinuria and declining kidney function in the absence of (biopsy-proven) continued kidney inflammation (stage 3; Fig 1). An argument could be made that patients who have >25% interstitial inflammation, and thereby a poor prognosis,¹²⁸ should be treated with an antifibrotic at diagnosis. However, the consequences of blocking TGF β during active inflammation are difficult to predict and may be detrimental in lupus nephritis because TGF β has important anti-inflammatory and immune tolerance effects.¹³² Thus the timing of when to add fresolimumab in lupus nephritis will need to be critically evaluated.

SUMMARY

The goal of treatment in lupus nephritis is to induce remission, prevent disease recurrence, and preserve kidney function while minimizing side effects from therapy. Current standard of care is suboptimal and new agents have been developed that are intended to more specifically target mechanisms involved in the pathogenesis of lupus nephritis. Results of clinical trials of these novel therapies to date have been disappointing. Trial failures can be attributed to multiple variables, including the lack of standardized end points and the limitations associated with studies involving only specific populations. In this review, we have emphasized discordance between clinical expectations of new therapies and expectations based on their mechanisms of action as another factor contributing to trial failures. The clinical goal of improving short-term complete response rates, although important, has resulted in almost all trials of novel therapeutics being designed as add-on to standard-of-care trials.

Moving forward, it will be necessary to standardize clinical trial end points for lupus nephritis therapies. To determine whether a new therapy is equally effective in all races and ethnicities, it would be ideal to foster an international consortium of lupus nephritis investigators to facilitate trials in diverse populations. This is beginning to develop through working groups such as the Lupus Nephritis Trials Network (www.lupusnephritis.org). Finally, clinical trials will need to be designed with end points that better align with a drug's

mechanism of action. Combinatorial therapies targeting both kidney inflammation and intra- and extrarenal autoimmunity offer the potential of abrogating inflammation to improve short-term response rates and abrogating autoimmunity to prevent disease recurrence, chronic injury, and progressive kidney failure.

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Box 1. Mediators of Kidney Injury in Lupus Nephritis**Cytokines**

IFN- α , IFN- γ , TNF- α , TWEAK-Fn14, IL-6, IL-1 β , IL-18, IL-10, IL-17

Chemokines

IL-8, MCP-1, RANTES, IP-10, MIP-1

Growth factors

TGF β , BAFF

Adhesion molecules

ICAM-1, VCAM-1

Signal transduction/transcription/costimulation

P38 MAPK, NF- κ B, CD40/CD40L

Abbreviations: BAFF, B-cell activating factor; Fn14, fibroblast-growth factor inducible 14; ICAM-1, intercellular adhesion molecule 1; IFN- α , interferon α ; IL, interleukin; IP-10, interferon γ -induced protein; MCP-1, monocyte chemoattractant protein 1; MIP-1, macrophage inflammatory protein 1; NF- κ B, nuclear factor- κ B; P38 MAPK, P38 mitogen-activated protein kinases; RANTES, regulated on activation normal T cell expressed; TGF β , transforming growth factor β ; TNF- α , tumor necrosis factor α ; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; VCAM-1, vascular cell adhesion molecule 1.

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: IFN α , interferon α .

Figure 2.

A model of combinatorial B-cell-directed therapy for lupus nephritis. This algorithm represents a hypothetical approach to using B-cell-directed therapies in a lupus nephritis trial. The algorithm matches therapies to the pathogenic stage of the clinical disease and uses novel biomarkers of B-cell activity to guide initiation and termination of specific drugs. The timeline provided is a (non-evidence-based) guide to the desired or ideal clinical milestones after initiation of treatment. At flare, patients would receive a proteasome inhibitor to reduce/eliminate plasma cells producing autoantibodies and an anti-inflammatory drug to synergize with the anti-NF- κ B (nuclear factor κ light-chain enhancer of activated B cells) effects of the proteasome inhibitor and attenuate renal inflammation. Baseline data on B-cell numbers, B-cell activating factor (BAFF) levels, and antichromatin antibodies would be obtained. After 2-3 months, clinical parameters should be improving. If antichromatin antibodies become undetectable, the proteasome inhibitor would be discontinued and rituximab would be initiated to eliminate B cells and prevent repopulation of autoreactive plasma cells that had been killed by the proteasome inhibitor. Because BAFF levels increase as rituximab depletes B cells confounding the antiautoimmune effects of rituximab, belimumab would be started as BAFF levels increase over the time 0 baseline values. B-Cell and BAFF levels would be followed up prospectively, and after reconstitution of B cells in a BAFF-free environment, belimumab could be stopped. At 6 months, clinical parameters should be consistent with a complete renal response. At this time, the anti-inflammatory agents can be tapered off over time. Ideally, because inflammation will have been attenuated and autoreactive B cells eliminated, the patient will remain flare-free on no

immunosuppression. Abbreviation: TWEAK, tumor necrosis factor–like weak inducer of apoptosis.

Table 1

Novel Therapies for Lupus Nephritis

Drug	Type	Target	Clinical Trial Status	ClinicalTrials.gov Study ID
Rituximab	Monoclonal antibody	CD20 (B cells)	Phase 3 completed with results	NCT00282347
Belimumab	Monoclonal antibody	BLyS (B cells)	Phase 3 underway, FDA approved for nonrenal SLE	NCT01639339
Epratuzumab	Monoclonal antibody	CD22 (B cells)	Phase 3 underway for nonrenal SLE	NCT01262365
Abatacept	CTLA4-Ig	CTLA4-B7 interaction	Phase 3: 1 completed, 1 underway	NCT00430677 NCT00774852
Anti-CD40 ligand	Monoclonal antibody	CD40 ligand	Phase 2 in lupus nephritis stopped early; thromboembolic events	NCT00001789
Fresolimumab	Monoclonal antibody	TGFβ1	Phase 2 in FSGS underway, no studies in lupus nephritis	NCT01665391
Anti-TWEAK	Monoclonal antibody	TWEAK	Phase 2 underway	NCT01499355
Laquinamod	Small molecule	Inflammation	Phase 2 in SLE completed	NCT01085097
Tocilizumab	Monoclonal antibody	IL-6 receptor	Phase 1 completed	Illei et al ¹⁰⁰
Sirukumab	Monoclonal antibody	IL-6	Phase 2 underway	NCT01273389
Tamibarotene	Small molecule	Retinoic acid receptor α/β	Phase 2 underway	NCT01226147
Bortezomib	Proteasome inhibitor	Plasma cells	Phase 4 stopped	NCT01169857
Sifalimumab	Monoclonal antibody	INF-α	Phase 2 in SLE completed	NCT01283139
Medi-546	Monoclonal antibody	INF-α receptor	Phase 2 in SLE underway	NCT01559090
Rontalizumab	Monoclonal antibody	INF-α	Phase 2 underway	NCT00962832
Eculizumab	Monoclonal antibody	Complement component C5	Phase 1 completed	Barilla-Labarca et al ⁸⁵

Abbreviations: FDA, Food and Drug Administration; FSGS, focal and segmental glomerulosclerosis; Ig, immunoglobulin; IL, interleukin; INF-α, interferon α; SLE, systemic lupus erythematosus; TGFβ1, transforming growth factor β1; TWEAK, tumor necrosis factor–like weak inducer of apoptosis.