Therapy for Proliferative Lupus Nephritis

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KEYWORDS

• Lupus nephritis • Proliferative • Treatment • SLE • Immunosuppressive

KEY POINTS

- Overall remission rates for proliferative LN remain suboptimal, with up to 30% of LN patients progressing to ESRD. Proliferative LN requires prompt treatment with immunosuppressive agents.
- Recent studies have shown that mycophenolate mofetil (MMF) is as effective as cyclophosphamide (CYC) as an induction agent.
- There are fewer studies evaluating maintenance therapies, but existing literature favors the use of MMF with azathioprine as an acceptable alternative.
- Newly developed drugs target key molecules/pathways implicated in the pathogenesis of LN, including B-cell/T-cell costimulation, INF-α, the immunoproteasome, TWEAK, and IL-6.
- Ongoing clinical trials will further evaluate the efficacy of established and novel anti-B-cell and anti-T-cell therapies when added to standard of care induction and maintenance treatment regimens.

INTRODUCTION

Lupus nephritis (LN) is an immune complex–mediated glomerulonephritis that affects nearly 50% of patients with systemic lupus erythematosus (SLE).[1,2] Prompt diagnosis and treatment initiation are essential because renal involvement in lupus imparts high morbidity and mortality.[3–5] Recent literature has shed light on racial and ethnic differences in the incidence of LN, with people of African, Asian, and Hispanic descent having a significantly higher risk of LN compared with white persons.[1,6] Along these same lines, African-American and Hispanic patients with LN had a significantly higher rate of progression to end-stage renal disease (ESRD) compared with their white counterparts according to US Renal Data System data recorded between 1996 and 2004.[7]

The immune-complex LN classification system using the 2003 International Society of Nephrology/Renal Pathology Society nomenclature divides lupus-associated

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glomerulonephritis into six different classes based on kidney pathology. Proliferative LN, characterized by endocapillary and/or extracapillary glomerulonephritis, encompasses classes III and IV of the International Society of Nephrology/Renal Pathology Society LN classification scheme.[8] Class III refers to focal disease, affecting less than 50% of the glomeruli, and Class IV is defined by diffuse glomerular involvement affecting greater than 50% of the glomeruli. Both class III and IV are further characterized by the presence of active lesions (A), chronic lesions (C), or both active and chronic lesions simultaneously in the same biopsy sample (A/C). Class IV is further divided in to segmental (S) or global (G) glomerular involvement.

Because proliferative LN is an aggressive disease that may lead to ESRD, treatment relies on the use of intensive immunosuppressive medications. Before 1970, the 5-year survival rate was reported to be a dismal 20% for patients with diffuse LN.[9,10] Although current treatment regimens have improved renal outcomes and survival rates beyond those reported historically, recent studies of either intravenous (IV) cyclophosphamide (CYC) or mycophenolate mofetil (MMF) for LN induction therapy still demonstrate overall remission rates of 50% to 55%.[11–13] This highlights a pressing need for development of targeted therapies with greater efficacy than those currently in use while maintaining acceptable safety profiles.

In this review, we explore the key findings of clinical studies centered on induction and maintenance treatment regimens for proliferative LN, and review novel therapeutic agents and regimens that are currently under investigation.

EVIDENCE BEHIND INDUCTION THERAPIES

Induction therapy refers to the use of immunosuppressive agents to treat the renal-immune-complex-mediated injury responsible for producing the primary manifestations of LN flares (reduced renal function, hematuria, and proteinuria). Induction treatment is standard of care in active proliferative LN (class III and IV LN) and also in membranous LN (class V LN) with persistent nephrotic range proteinuria. The first major study to demonstrate the superiority of cytotoxic therapy compared with corticosteroids alone involved 111 patients, mainly with class IV or membranoproliferative LN, who were randomized to one of five groups: (1) high-dose prednisone only; (2) oral CYC; (3) oral azathioprine (AZA); (4) oral CYC and AZA; and (5) IV CYC, dosed 0.5 to 1 g/m^2 every 3 months.[14] The CYC and AZA groups all additionally received low-dose prednisone. Therapy was continued for a minimum of 18 months after achievement of complete remission or until completion of 4 years of protocol therapy. After a 5-year period of observation, patients who received high-dose oral prednisone were less likely than the other groups to have preserved renal function. After a median 7-year follow-up period, IV CYC therapy achieved significantly better renal outcomes compared with oral prednisone overall, especially among a subgroup of high-risk patients characterized by either fibrosis or glomerulosclerosis on renal biopsy. There were notable differences in rates of adverse events: all CYC-containing regimens were associated with increased rates of herpes zoster infection and premature ovarian failure, whereas the risk of hemorrhagic cystitis was increased only in those patients receiving oral CYC.

The superiority of CYC to glucocorticoids as induction therapy for proliferative LN was later solidified by another National Institutes of Health (NIH)-sponsored trial that evaluated renal outcomes in patients receiving extended courses of IV methylprednisolone and IV CYC.[15] This study randomized 82 participants, most of whom were white persons, with hematuria, at least 1 g of proteinuria, and an average serum creatinine of 1.6 to 2 mg/dL, to one of three treatment groups (all given in conjunction with oral prednisone): (1) 12 monthly infusions of IV methylprednisolone, (2) 6 monthly infusions