Human Clinical Trials in Lupus Nephritis

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Summary: Improved patient survival after treatment of lupus nephritis with corticosteroids, immunosuppressants, and renal replacement therapy allows greater emphasis on long-term management issues. In particular, the recent focus has been on therapies to treat nephritis with fewer adverse effects compared with cyclophosphamide and immunosuppressive regimens. Issues complicating clinical trial design in lupus nephritis have severely limited comparisons across trials. These issues, including recognition and stratification of high-risk populations, comparable remission and response criteria, and appropriate use and interpretation of activity and damage indices have been the subject of much discussion and emerging consensus. Mycophenolate mofetil (MMF) has been used in the field of transplantation for more than 10 years. After initial anecdotal reports describing the benefits of MMF in the treatment of lupus nephritis, randomized controlled trials have established a role for MMF in the treatment of lupus nephritis. A host of newer agents including rituximab, abatacept, and monoclonal antibodies blocking costimulatory targets are in current clinical trials for lupus nephritis. As long-term outcomes in lupus nephritis improve, the toxicity of therapy and risk of relapse become increasingly important determinants of the choice of therapeutic agents. Semin Nephrol 27:115-127 © 2007 Elsevier Inc. All rights reserved.

Keywords: *Glomerulonephritis, lupus nephritis, mycophenolate mofetil, immunosuppressive therapy, autoimmunity*

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by the production of autoantibodies, a striking female predominance, and the frequent development of immune complex–mediated glomerulonephritis. The diagnosis of SLE is a clinical diagnosis based on combined clinical, pathologic, and laboratory findings enumerated in the criteria established by the American College of Rheumatology in 1982 (Table 1).[1] The 1987 modification recognized antiphospholipid antibodies in place of the LE cell prep criterion because most institutions no longer perform this test.[2] These criteria are useful in establishing a diagnosis of SLE, although the requirement that a patient show at least 4 of 11 signs or symptoms applies only to clinical research. In fact, many parameters in frequent clinical use, such as hypocomplementemia and renal biopsy results, are not included.[3] These criteria currently are undergoing reassessment by an international rheumatology group.

Renal disease caused by SLE significantly affects 25% to 40% of patients and is mediated largely by the renal deposition of immune complexes. The diagnosis of lupus nephritis (LN) usually is made after a renal biopsy in the presence of proteinuria and/or hematuria, positive serologies, and extrarenal manifestations of SLE. The presence of renal disease remains the most important predictor of morbidity and mortality in patients with SLE.[4,5] SLE affects predominantly young females of childbearing age with a peak incidence between ages 15 and 40. The incidence and prevalence of SLE and LN differ among different ethnic groups. African Americans have a 3-fold increased incidence of SLE, develop disease at younger ages, more frequently express anti-Smith and ribonuclear protein (RNP) antibodies, and have increased mortality when compared with Caucasians.[6,7]

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Supported in part by National Institutes of Health (RR00046).

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0270-9295/07/$ - see front matter

 doi:10.1016/j.semnephrol.2006.09.011

Table 1. The 1982 Revised Criteria for the Classification of SLE

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to skip over the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—convincing history of pleuritic pain, rubbing heard by a clinician, or evidence of pleural effusion Or pericarditis—documented by EKG or rub, or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >.5 g/d or >3+ if quantitation is not performed Or cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures—in the absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, or electrolyte imbalance) Or psychosis—in the absence of offending drugs or known metabolic derangements (eg, uremia, ketoacidosis, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia with reticulocytosis Or leukopenia—<4,000/mm^3 total on 2 or more occasions Or lymphopenia—<1,500/mm^3 on 2 or more occasions Or thrombocytopenia—<100,000/mm^3 in the absence of offending drugs
Immunologic disorder	Positive lupus erythematosus cell preparation Or anti-DNA—antibody to native DNA in abnormal titer Or anti-Sm—presence of antibody to Sm nuclear antigen Or false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced SLE

Data from Tan et al.[1]

African Americans also develop nephritis earlier in their course of SLE. In an inception cohort of lupus patients in the southeastern Untied States, the difference in renal disease in African Americans versus Caucasians within a median of 13 months from diagnosis was significant (31% of African American patients versus 13% of Caucasian patients).[8] Hispanics also have greater frequency and severity of nephritis compared with Caucasians.[9] The proportion of patients receiving dialysis for end-stage renal disease for LN is increasing in the United States.[10,11]

Several demographic, serologic, and genetic risk factors are associated with an increased risk of developing kidney disease. Patients with LN are more likely than SLE patients without renal involvement to have a family history of SLE, anemia, high anti–double-stranded DNA (dsDNA) antibody titers, and hypocomplementemia.[12] Age at disease onset and sex also are important: patients with onset of SLE at younger than age 16 develop LN more frequently than adults (~85% versus 40%), as do males compared with females.[8] However, onset of SLE in older patients is not milder because race confounded initial reports that elderly patients were less likely to develop LN, and greater morbidity and