Lupus nephritis is one of the more serious manifestations of the systemic autoimmune disease, systemic lupus erythematosus, and is associated with considerable morbidity and even mortality. Treatment remains problematic, particularly in terms of controlling the underlying disease process while at the same time preventing unacceptable side effects of therapy. In recent years, clinical trials have started to define optimum regimens of the immunosuppressive agents presently in use. The etiology and pathogenesis of systemic lupus erythematosus and lupus nephritis still are understood incompletely. Nevertheless, insights gained from basic science research in both animals and human beings now are being translated into newer therapies that have the potential to be safer and more specific than those currently available.

Semin Nephrol 26:95-104 © 2006 Elsevier Inc. All rights reserved.

**KEYWORDS** lupus, nephritis, autoimmunity

Systemic lupus erythematosus (SLE) is defined and diagnosed by its clinical features in conjunction with the presence of 1 or more autoantibodies directed against nuclear antigens or phospholipids. The most commonly used diagnostic criteria are those developed by the American College of Rheumatology. The clinical presentations of SLE are remarkably diverse, and, as Cameron has proposed, it is helpful conceptually to regard SLE as a syndrome in which a number of different immunologic events may lead to similar final common pathways and thus similar, but varied, clinical pictures. This concept is consistent with a large amount of experimental animal data, some of which are discussed briefly later.

Approximately 25% to 60% of unselected patients with SLE have renal involvement as assessed by urinalysis or impairment of renal function, but often the disease is mild. As with SLE in general, the spectrum of lupus nephritis is wide, encompassing the acute nephritic syndrome, nephrotic syndrome, acute or chronic renal failure, and isolated abnormalities of the urinary sediment. However, proteinuria is the most constant feature, being present in almost every patient with clinical lupus nephritis. Although microscopic hematuria is common, it rarely occurs in isolation. The large majority of patients with lupus nephritis will have SLE by the American College of Rheumatology criteria mentioned earlier at the time of diagnosis of the renal disease. A notable exception to this is membranous lupus nephropathy, which may predate the development of extrarenal and serologic features of SLE. Important, but largely unanswered, questions are why some patients with lupus develop nephritis whereas others do not, and what accounts for the marked heterogeneity of disease expression among those who do develop nephritis.

**Etiology**

The etiology and pathogenesis of SLE is complex. Genetic predisposition, sex, environment, and stochastic factors all contribute, and the marked heterogeneity of disease expression likely reflects varying combinations of these contributory factors in different subgroups of patients.

The concordance rate for SLE in monozygotic twins is between 24% and 57%, indicating a substantial impact of genetic predisposition to disease development. This genetic susceptibility is not caused by a single gene defect except in the rare cases of homozygous complement deficiencies, but rather is caused by the combined impact of multiple contributing susceptibility genes. The individual genes linked to SLE in human beings have been reviewed recently. Those linked particularly with lupus nephritis include those encoding the Fcγ receptors type IIA and IIIA, programmed cell death 1, and angiotensin-converting enzyme. The linkage with Fcγ receptor type IIA, however, was not found in a subsequent meta-analysis study.
Receptors type IIA and IIA polymorphisms associated with lupus result in the decreased ability of these receptors to bind immune complexes, consistent with a role for impaired immune complex clearance in SLE pathogenesis. Genetic analysis of murine lupus models continues to yield important information relevant to the pathogenesis of lupus and lupus nephritis, but is not discussed in this review because of space constraints.

The overall prevalence of SLE in the United States varies between 15 to 51 per 100,000 individuals, and is highest in the black female population at approximately 200 per 100,000. In countries with a largely white population, prevalence varies from 12 to 39 per 100,000. Lupus nephritis also is more severe in the black population, although the relative contributions of genetic and socioeconomic factors to this increased risk are unclear. Sex is a major risk factor for the development of SLE, which predominantly affects women in their reproductive years with an 8 to 12:1 female: male ratio. Although it is conceivable that some sex-linked genes may contribute to the genetic predisposition for the disease, other likely candidates for this bias in sex are the sex hormones estrogen and prolactin.

The precise sequence of events leading from the initiation of the autoimmune response in SLE to clinical disease is far from clear. Nevertheless, work by many investigators over the years has enabled the identification of certain features of the disease that are found in most patients with SLE and have important implications for understanding the pathogenesis. A detailed discussion of these studies is beyond the scope of this review and the reader is referred to other reviews for further information. Here, a brief overview is given, with certain more recent areas of research discussed in greater detail.

### Pathogenesis of SLE

SLE pathogenesis initially involves a loss of tolerance to self-antigen, followed by expansion and amplification of the autoimmune response, leading to sustained disease and end-organ damage. In human beings, the initial loss of tolerance, as evidenced by the presence of autoantibodies, may preceede the diagnosis of clinical disease by many years, with an apparent ordered and sequential appearance of particular autoantibody specificities. Of note, those specificities most closely associated with clinical disease are among the last to appear.

Studies in mice have shown clearly that loss of self-tolerance resulting ultimately in lupus-like disease can be induced by a wide range of perturbations of immune system function. Broadly speaking, many of these perturbations can be classified either into those directly or indirectly increasing the activation state or survival of T or B lymphocytes or those impairing the clearance of apoptotic cells or chromatin fragments. Increased circulating levels of DNA and nucleosomes also have been shown in patients with SLE consistent with the model of impaired self-antigen clearance as a critical factor in the pathogenesis of human SLE.

Overall, there is abundant evidence in both mice and human beings that autoantibody production and the autoimmune response in SLE is driven by self-antigen and requires the participation of autoreactive B and T cells. More recently, a central role for plasmacytoid dendritic cells also has been proposed, as is discussed later. These various components of the immune system interact, leading to the activation of a number of additional downstream effector cells and soluble proinflammatory mediators, including cytokines and chemokines, to cause end-organ disease.

### Pathogenesis of Lupus Nephritis

The autoantibody repertoire in lupus is diverse, but is focused predominantly on components of chromatin or ribonucleoprotein. As such, the commonly measured autoantibodies in SLE include those directed against double-stranded DNA (dsDNA), single-stranded DNA, nucleosome, histones, Smith antigen, ribonucleoprotein, Ro, and La. Of these, antibodies against dsDNA are associated most strongly with nephritis, although the association is not sufficiently robust to be useful clinically as a biomarker to guide therapy in lupus nephritis. In addition, particularly in certain groups of young black women, antibodies against Smith antigen and Ro may be associated with nephritis even in the absence of anti-dsDNA antibodies.

Despite the association of nephritis with anti-dsDNA antibodies, it has been more difficult to show the degree to which these autoantibodies contribute directly to the pathogenesis of nephritis. Possible pathogenic mechanisms, in addition to their role in DNA–anti-DNA immune complex formation, include cross-reactivity with structural renal antigens such as α-actin and direct penetration of glomerular cells with nuclear binding and consequent induction of cellular dysfunction. The identification and analysis of subsets of anti-dsDNA autoantibodies with high nephritogenic potential remains an active area of research.

Immune complexes containing immunoglobulin and complement nearly always are seen in diseased glomeruli. They also frequently are seen in the tubulointerstitium and in the walls of small renal arteries. Although difficult to prove conclusively in human beings, it is likely that these complexes initiate inflammatory pathways, which contribute substantially to the pathology of lupus nephritis. This may be mediated, at least in part, through the engagement of stimulatory Fcγ receptors as has been shown in one, but not another, mouse lupus model. Anti-C1q autoantibodies, if present, may aggravate the nephritis by amplifying pathogenic complement activation within the kidney.

The precise composition of the immune complexes and their mechanisms of formation still are under investigation. They potentially could derive from the deposition of preformed circulating immune complexes, and/or from in situ binding of autoantibody to autoantigens already bound in the glomerulus. For example, nucleosome, a major autoantigen in SLE, binds very effectively to the glomerular basement membrane. Although DNA-containing complexes can be found in the kidneys of patients with SLE, these may represent only a minority of immune complexes, with autoanti-
bodies of unknown antigenic specificities possibly accounting for the majority of immunoglobulin present.65

In addition to the immune complex–induced inflammatory responses, direct T-cell cytotoxicity may contribute importantly to renal injury, in particular to tubulointerstitial nephritis.52,53 Vasculitis and arteriolar thrombi also may coexist and aggravate disease. Antiphospholipid antibodies in patients with lupus nephritis have been reported to increase the long-term risk for developing chronic renal failure.54

There are accumulating data from human studies and mouse lupus models consistent with an important role for dysregulated interferon (IFN)-alpha production in lupus pathogenesis.55-57 One note of caution is that although IFN-alpha induces disease in certain mouse lupus models,58,59 it is protective in others.60 Whether there are subsets of patients with differing responsiveness to IFN-alpha remains to be established.

Separate and apart from the potential role of IFN-alpha in disease pathogenesis overall, there are data indicative of an effect of IFN-alpha within the kidneys of patients with lupus nephritis. Tubuloreticular inclusions are structures composed of ribonucleoprotein and membrane that are seen frequently within glomerular endothelial cells in lupus nephritis.61-63 They can be induced experimentally in B-cell lines by IFN-alpha, and therefore are believed to constitute an IFN footprint.64 By using microarray analysis of gene expression patterns in laser-captured glomeruli, a recent study identified a subset of patients with class III/IV lupus nephritis having enhanced expression of IFN-alpha–inducible gene transcripts.65 Interestingly, this subgroup of patients appeared to have less severe nephritis as judged by activity/chronicity indices than did certain other subgroups identified on the basis of differing gene-expression profiles. In studies that use the expression of IFN-alpha–inducible genes in peripheral blood mononuclear cells as an indicator of an effect of IFN-alpha (the interferon signature), this IFN signature has been found to correlate with nephritis and with other aspects of disease activity.66,67 It would be interesting to know how the IFN signature in peripheral blood mononuclear cells compares with the IFN signature in the kidney in individual patients.

What then are the likely sources of IFN-alpha production in lupus? Viral infections, which have been linked to lupus flares, are one possibility, although there is no solid evidence of infection in the majority of patients with SLE.20 An alternative possibility results from the work of Ronnblom, Alm and colleagues.68,69 They showed that DNA–anti-DNA immune complexes in the sera of patients with SLE could induce IFN-alpha production by plasmacytoid dendritic cells, the major cell type in the body specifically dedicated to IFN-alpha production. The interferogenic activity was dependent completely on the DNA within the complex. This shows an important concept that has emerged in recent years, namely that mammalian nucleic acids have important immunostimulatory capacities once endocytosed,70,71 and are not simply passive targets of an autoimmune response. The DNA-reactive receptors involved in mediating this activation are the subject of ongoing investigation. However, Toll-like receptor 9 (TLR9) appears to be one of the receptors involved because it contributes substantially to the activation of autoreactive B cells and dendritic cells by mammalian DNA in vitro.72-75 TLR9 is the critical receptor involved in the recognition of bacterial DNA, although its ability to recognize mammalian DNA only recently has been appreciated.66 Thus, the correlation between anti-dsDNA antibodies and lupus nephritis may involve not only direct effects on the kidney itself as discussed earlier, but also may reflect effects of DNA or DNA-containing immune complexes on immune system activation. Furthermore, a similar immunostimulatory potential may pertain to RNA autoantigens, with TLR7 likely playing an important role.77,78 In addition to their role in the recognition of self-antigen as discussed earlier, TLRs might increase the severity of lupus nephritis in some cases by inducing an inflammatory response after their engagement by microbial antigens.79

Biomarkers

At present, assessment of response to therapy and diagnosis of lupus nephritis flares are based imprecisely on overall clinical assessment including changes in the levels of serum creatinine, autoantibodies, and complement, the degree of proteinuria, and the presence or absence of dysmorphic red cells and red cell casts in the urinary sediment. Thus, there is great interest in the identification and validation of new biomarkers in lupus that are associated closely with specific disease activity and therefore could be used to make treatment decisions.80 Current biomarkers such as anti-dsDNA antibodies for lupus nephritis are not precise enough to use in this way and therefore have limited clinical use. Promising newer biomarkers include IFN-alpha or IFN-alpha–induced gene expression, markers of lymphocyte activation especially soluble interleukin-2 receptor, markers of endothelial activation such as soluble vascular cell adhesion molecule-1 (VCAM-1) and serum thrombomodulin, and CD27high plasma cells.81 Of these, serum levels of the soluble interleukin-2 receptor and thrombomodulin have been linked specifically to disease activity in lupus nephritis. Thrombomodulin is expressed on the luminal surface of the vascular endothelium, and the soluble form is released into the serum after endothelial cell injury.

Renal Histopathology and Clinical Pathologic Correlation

Renal biopsy examination is valuable in patients with SLE, and is indicated in nearly all cases involving abnormalities of the urine sediment or impaired renal function. There are 2 main reasons for this. First, it is not possible in an individual patient to predict the renal histology with any accuracy from the clinical manifestations of renal disease although, in general, more severe histology tends to correlate with more severe clinical disease. Second, in untreated patients, the renal histology as classified by the World Health Organization...
(WHO) is a powerful predictor of eventual outcome, and thus helps guide initial therapeutic decisions.

The widely adopted 1982 WHO criteria for the classification of lupus nephritis were modified in 1995. In addition, a further modification of these criteria has been proposed recently by a working group under the auspices of the International Society of Nephrology and the Renal Pathology Society. The important differences between the various classification schemes have been reviewed. Most of the clinical trials discussed in this review were performed using the WHO classification, which is discussed briefly here. In addition to the standard WHO classification, it is usual for each biopsy specimen to be assigned a semiquantitative score of activity and chronicity (scarring) based on certain defined histologic criteria. The value of these scores in helping to predict renal outcome, however, has been questioned by some investigators. It is not unusual for transformation from 1 class to another to occur over time, either spontaneously or after treatment. Thus, a renal biopsy examination performed during an initial evaluation might not reflect the actual histologic lesion at a later time, and repeat biopsy examinations may be required to guide therapy if the clinical presentation changes.

There are 6 histologic classes in the WHO classification. A class I biopsy specimen is normal by light microscopy, but sometimes can be associated with minimal mesangial deposits on immunofluorescence microscopy. Renal function and urinalysis are normal except for mild proteinuria in some cases. Class II is seen in 10% to 20% of cases. This describes mesangial lupus nephritis in which immune complexes containing immunoglobulin (Ig)G, IgM, and C3 are seen only in the mesangium on immunofluorescence and electron microscopy. In class IIIB mesangial proliferation is seen by light microscopy, whereas little or no proliferation is seen in class II A. Class III is seen in 30% to 40% of cases. This describes a focal (involving <50% of all glomeruli) and segmental (involving <50% of the glomerular tuft) proliferative lesion on light microscopy, often with areas of necrosis. There are diffuse mesangial and focal subendothelial immune deposits on immunofluorescence and electron microscopy. IgG usually is predominant, but IgA and IgM also may be seen and C3, C4, and C1q usually are present. Proteinuria is common and nephritic syndrome occurs in about 30% of patients. Class IV is seen in 40% to 60% of cases. It describes diffuse (involving >50% of all glomeruli) proliferative lupus nephritis, the most aggressive lupus renal lesion. The nephritic syndrome and impaired renal function are common. The histologic findings are similar to those of class III, except that nearly all of the glomeruli are involved and the lesions themselves are more severe. Crescents also may be present, but inflammation and necrosis of the glomerular tuft is predominant. Class V, seen in 10% to 15% of cases, describes membranous lupus nephropathy, so named because of its close similarity both clinically and histologically to idiopathic membranous nephropathy. Glomerular pathologic processes appear identical to those of idiopathic membranous nephropathy, except that the presence of abundant mesangial immune deposits, multiple immunoglobulin isotypes (IgG, IgA, IgM), or tubuloreticular structures in glomerular endothelial cells favors a diagnosis of lupus nephritis. In some cases, class III or IV lupus nephritis can coexist with class V. Class VI describes a biopsy specimen with diffuse glomerulosclerosis.

The presence of tubulointerstitial nephritis and/or lesions of the intrarenal vasculature are not taken into account in the assignment of disease class, although it usually is recommended that they be described in the text of the biopsy examination report. Both are seen frequently, particularly in class III and IV lupus nephritis, and their presence is associated with a poorer renal prognosis. The interstitial infiltrate comprises mainly T cells and monocytes, and direct infiltration of the tubules, referred to as tubulitis, can be seen in active disease. Rarely, tubulointerstitial nephritis can present in the absence of glomerular disease as acute renal failure with a relatively bland sediment. There are a number of types of renal vascular involvement in SLE. Uncomplicated vascular immune deposits are seen commonly but do not appear to influence disease outcome. A noninflammatory necrotizing vasculopathy is not uncommon and is associated with a worse prognosis. A true inflammatory vasculitis is rare, but does occur. Thrombotic angiopathies, including renal vein thrombosis, thrombotic thrombocytopenic purpura (either isolated or part of the antiphospholipid syndrome), and isolated glomerular microthromboses all can occur and may require anticoagulant therapy.

**Prognosis and Treatment**

As previously noted, lupus nephritis is remarkable for the heterogeneity of disease expression. This is reflected in different natural histories of the lupus nephritis subtypes, and the therapeutic approach chosen for an individual patient takes these natural histories into account. A delay between the onset of renal disease and initiation of treatment has been linked to the subsequent development of renal insufficiency. Additional factors including increased serum creatinine levels, anemia, black race, and hypertension have been associated with a poor prognosis in some studies, but not in others. However, at the present time, renal histology in untreated patients is the best predictor of eventual outcome, and treatment decisions are based largely on the renal biopsy examination result.

Patients with class II lupus nephritis generally have an excellent renal prognosis, although occasionally the disease may transform into class III or IV. Some physicians will treat class II with a course of corticosteroid monotherapy, although there is no good evidence that this prevents the subsequent evolution of severe disease in those occasional cases that transform. The management of pure class V (membranous) lupus is discussed briefly later, but in those patients in whom class III or IV proliferative nephritis coexists with class V, treatment is directed toward the class III or IV disease. Gradations of disease severity exist within class III ranging from mild to severe, which complicates prognosis in this class. Patients with milder disease have a better prognosis and may need limited immunosuppression, although there are
insufficient data to draw certain conclusions in this regard.93 Most patients with class IV and severe class III will develop progressive renal failure, and in these groups of patients immunosuppressive treatment clearly is indicated.2,92,94 This treatment is discussed in the following sections.

The goals of immunosuppressive treatment include the following: (1) induction of renal remission, (2) avoiding renal flares, (3) preventing chronic kidney disease, and (4) accomplishing these goals with minimal toxicity to the patient.93 However, with current treatment protocols only about 80% of patients achieve renal remission with initial therapy, approximately 30% experience renal flares, 5% to 20% of patients progress to end-stage kidney disease, and treatment-related toxicity is appreciable.93 Thus, there is a need for alternative therapeutic options.

Although definitions of clinical renal remission vary, attaining remission appears to be a good predictor of good long-term renal outcome.96,97 Renal flares predict a poor renal outcome.98,99 In general, induction therapy involves relatively short-term administration of high levels of immunosuppressive agents, for which gaining control of an aggressive disease process is the primary aim. In contrast, maintenance therapy (avoiding renal flares, preventing chronic kidney disease) involves the long-term administration of just enough immunosuppression to prevent the relapse of a relatively indolent disease process, while minimizing toxicity. This strategy is hampered to some extent by insensitive measures of response to therapy and of disease progression. For example, delayed resolution of subnephrotic proteinuria may not signify lack of response to therapy, and the serum creatinine level is an imprecise marker of progression of renal dysfunction in SLE.100-103

Corticosteroids

Early studies indicated that high-dose oral steroids were effective in the treatment of lupus nephritis.104,105 Subsequently, intravenous (IV) methylprednisolone pulse therapy also was shown to be effective.106 IV pulse methylprednisolone back up by varying oral doses of prednisone from the start of treatment now probably is the most commonly used steroid regimen. This is not because it is more efficacious than high-dose oral steroids (this has not been shown definitively), but because it may have fewer side effects, particularly in terms of the development of cushingoid features.2,107 Steroids are used in nearly all immunosuppressive regimens, both in the induction and maintenance phases. However, steroids alone in many cases fail to control disease, and always are associated with side effects ranging from troublesome to life-threatening.107 This led to the search for additional therapies, both to improve efficacy and also to allow steroids to be used at doses at which their side effects would be manageable.

Cytotoxic Drugs

The preponderance of data suggest that patients treated with cyclophosphamide and steroids have a better renal prognosis than those treated with steroids alone.2,87,107-109 Azathioprine and steroids may be less effective. An important point to emerge from the original National Institutes of Health IV cyclophosphamide trial was that differences in renal function between the cyclophosphamide/steroid groups and the steroid-alone group only started to become evident more than 5 years after initiation of therapy.110,111 This has implications for the interpretation of other studies in which the follow-up period is of shorter duration. However, in another study from the National Institutes of Health, the superiority of the cyclophosphamide/steroid group compared with the steroids-alone group was seen earlier, after about 24 to 36 months, possibly because patients in this study had more severe disease initially.108 The optimal route (IV pulse or oral), dose, and duration of cyclophosphamide therapy continue to be debated.2,87,99,107 In a European population, low-dose IV cyclophosphamide was as effective as high-dose IV cyclophosphamide in inducing remission.97,112 Some studies with IV cyclophosphamide have involved administration of the drug well beyond the point of induction of renal remission, sometimes as long as 4 years. Longer-term administration of cyclophosphamide into the maintenance phase is associated with fewer renal relapses than is seen with short-term administration, and therefore likely improved long-term renal outcome.108 However, the risk for malignancy and infertility with cyclophosphamide treatment is related to the total cumulative dose.107 Thus, there has been a move recently to use agents other than cyclophosphamide for maintenance therapy in an attempt to limit these potential toxic effects (see maintenance therapy section later). Although not related to cumulative dose, infection is another side effect of concern.

Mycophenolate mofetil has been compared recently with cyclophosphamide as induction therapy.100,113,114 The use of mycophenolate is logical because it is a potent inhibitor of B and T lymphocytes, both of which are implicated strongly in lupus pathogenesis.115 These studies showed that mycophenolate was at least as effective as cyclophosphamide for induction therapy, and caused fewer side effects. These studies can be criticized either for short follow-up duration and/or for restriction of patients to a particular ethnic population (Hong Kong Chinese). Nevertheless, at a minimum, mycophenolate together with steroids can be considered for induction therapy when there is particular concern about the potential toxicities of cyclophosphamide.

Maintenance Treatment

Maintenance treatment is given once remission has been achieved to maintain remission, avoid renal flares, and prevent chronic kidney disease. As noted earlier, maintenance treatment with cyclophosphamide and steroids leads to better renal outcomes than steroids alone, however, toxicity is a concern. Other medications that have been used for maintenance treatment include azathioprine and mycophenolate. A recent study directly compared cyclophosphamide, azathioprine, and mycophenolate for maintenance therapy after the induction of remission with cyclophosphamide.101 The use of azathioprine or mycophenolate resulted in a lower rate of
death or chronic renal failure than did the use of cyclophosphamide. Furthermore, side effects, in particular amenorrhea and infections, were lower in the azathioprine and mycophenolate groups. Based on these data, it is hard to justify the use of cyclophosphamide for maintenance therapy. Steroids also are used during the maintenance phase, but generally only at the minimum levels needed to control extrarenal manifestations of SLE.

**Failure to Achieve Renal Remission**

The diagnosis of true resistance to induction therapy is problematic, and hence estimates of its frequency vary. Repeat renal biopsy examination may be helpful in making this diagnosis in some instances. Once diagnosed, treatment includes administration of an induction regimen not used previously. For example, if mycophenolate was used in the first instance, a course of cyclophosphamide then might be tried. Other therapeutic modalities in certain selected cases include autologous stem cell transplantation, immunoblaive doses of cyclophosphamide, and plasma exchange, as has been reviewed recently. Given the effectiveness of drugs such as cyclosporin A, tacrolimus, and sirolimus in inhibiting both T- and B-lymphocyte responses, it is surprising that there are not more data available on the use of these agents in lupus nephritis. They also potentially could be used in combination with mycophenolate, similar to the immunosuppressive protocols used successfully in renal transplantation. Newer agents, as discussed briefly later, are just starting to enter the clinical arena and have been used in some patients with refractory disease.

**Newer Therapies**

Based on an increased understanding of the pathogenesis of SLE, a number of newer biologic agents currently are, or soon will be, under development and eventually may provide more specific and less-toxic therapy for SLE and for lupus nephritis. These have been reviewed recently. BAFF (or BlyS), a member of the tumor necrosis factor family, is a fundamental survival factor for B cells. BAFF overexpression in mice leads to lupus-like disease, and BAFF serum levels are increased in some patients with SLE. Belimumab, a human monoclonal antibody that specifically inhibits BAFF, is currently in a phase 2 clinical trial for the treatment of SLE. LJP 394 is a synthetic molecule composed of 4 dsDNA epitopes that can be recognized by, and thereby induce tolerance in, dsDNA-reactive B cells. LJP 394 is currently in a phase III trial to determine whether it is more effective than placebo in delaying the time to renal flare in SLE patients with a history of renal disease. CTLA4Ig, an inhibitor of T-cell costimulation, is an effective treatment for rheumatoid arthritis. Given the importance of T cells in lupus pathogenesis, CTLA4Ig may be an attractive candidate therapy for SLE as well, although studies to determine this have not yet been performed. Inhibitors of IL-10 and IFN-α are also of potential future interest.

However, of the newer therapies, the most promising results thus far have come from studies of B-cell depletion with Rituximab. Rituximab is a humanized chimeric monoclonal antibody specific for human CD20, with the variable regions of a murine antihuman CD20 B-cell hybridoma fused to human IgG and κ constant regions. CD20 is expressed on B cells, but not on plasma cells, and treatment with this antibody leads to effective B-cell depletion. Although data still are preliminary, effectiveness has been shown both in lupus and in lupus nephritis, including a small number of patients who had failed cyclophosphamide induction therapy. The precise mechanisms by which the B-cell depletion leads to therapeutic benefit are not defined fully. However, it seems to extend beyond effects on autoantibody production per se, and may be related to the role of B cells in antigen presentation.

**Treatment of Membranous Lupus Nephritis**

As mentioned previously, patients who have class III or IV lupus nephritis together with membranous lupus nephritis usually are treated for the class III or IV disease. The optimal treatment of pure membranous lupus nephritis is not well defined. This is in large part because, as with idiopathic membranous nephropathy, the natural history of the disease is unclear. Although most patients have a slow or nonprogressive course with persistent proteinuria, some patients do progress to end-stage renal failure. In patients with protracted nephrotic syndrome or worsening renal function, consideration should be given to immunosuppressive therapies including corticosteroids, cyclosporine, mycophenolate, or cyclophosphamide, although there are limited data to recommend specific therapeutic regimens. In all patients, antiproteinuric therapy should be given with an angiotensin-converting enzyme inhibitor and/or angiotensin II–receptor blocker, and hypertension should be controlled with additional agents if necessary. In addition, other cardiovascular risk factors, including hyperlipidemia, should be treated aggressively. Attention to these nonimmunologic therapies is important in all other forms of lupus nephritis as well, not only in membranous lupus.

**Complications of Lupus**

Complications of lupus are seen frequently and include sepsis, thromboses, avascular necrosis of bone, neoplasia, and accelerated atherosclerosis. These may be seen without immunosuppressive treatment, although such treatment may aggravate these complications further. The accelerated atherosclerosis accounts for the substantially increased cardiovascular mortality seen in lupus patients, and is caused by both traditional and nontraditional cardiovascular risk factors, although the latter remain poorly defined.
Future Directions

More recent clinical trials have built on the earlier landmark studies in lupus nephritis treatment, and have led to the introduction of additional agents such as mycophenolate to the therapeutic armamentarium. In addition, they have allowed the development of updated protocols using the more established immunosuppressive therapies, based on a better understanding of their risk-benefit profile. Clinical trials, of adequate power and duration to allow definitive conclusions to be reached, will continue to be a critical component of future research, particularly as newer targeted therapies become available for potential use in lupus nephritis.

The identification and validation of accurate biomarkers of disease activity will be important for a number of reasons. First, it will allow physicians to define and diagnose renal remission and renal flares with more certainty. This will enable therapy to be tailored to response in individual patients. Second, if it turns out that certain biomarkers are found to be strongly predictive of long-term outcome (surrogate markers), these might enable the length of clinical trials to be shortened, thereby greatly facilitating the clinical testing of new therapeutics.  

Histopathologic criteria currently are used to define subgroups of patients with lupus nephritis and to guide the choice of therapy. However, recent studies discussed earlier have suggested that it will be possible to classify patients further using alternative criteria such as gene expression analysis of peripheral blood mononuclear cells or kidney tissue. A proteomics approach, looking at protein-expression analysis in lupus nephritis, also might prove informative. It remains to be seen whether these approaches identify subsets of patients who might benefit from particular forms of therapy, but this is an exciting possibility. At a minimum, it is likely that these studies will yield important insights into disease pathogenesis.

Ultimately, the development of new therapies and biomarkers is most likely to come from ongoing efforts to understand the underlying pathogenesis of lupus and lupus nephritis. This is likely to come both from basic science and from translational studies. Although progress has been made, much still remains to be learned. For example, we still know relatively little about the nature of the autoreactive T-cell response, or the mechanisms whereby autoantigen itself activates the immune system. What factors lead to the increased levels of apoptotic material in lupus patients, and might tissue-specific expression of autoantigen play a role in determining organ involvement in the disease? We also need to know more about the complications of lupus, such as the nontraditional risk factors responsible for the accelerated atherosclerosis and increased cardiovascular mortality seen in patients with SLE.

Acknowledgment

The authors thank Dr. David Salant for his careful reading of the manuscript and helpful comments.

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