Lupus nephritis: current issues
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The best approach to treatment of renal disease in systemic lupus erythematosus remains unresolved

THE MULTIPLE FACES OF SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE), the prototype of systemic autoimmune disorders, has been considered for many years a classic model of immune complex mediated disease. However, earlier data demonstrate that multilevel dysfunction of cellular and humoral immunity underlie the pathophysiology of the disorder. The expression and clinical course of SLE vary enormously from very mild, with arthralgias and skin rashes, to life threatening, when the renal and central nervous system function are severely compromised; from complete quiescence to full blown expression of the disease. Coexistence or even evolution into other types of autoimmune disorders, such as Sjögren’s syndrome and mixed connective tissue disease can also occur. Finally, subsets of SLE were early recognised: distinct clinical entities such as antiphospholipid syndrome (APS) or subacute lupus erythematosus are considered to be part of the “SLE” clinical spectrum.

RENAI DISEASE IN SLE

Among the various organs affected in SLE, the kidney appears to be one of the most common, and at the same time, more serious complication. In unselected lupus patients, abnormalities in urine or renal function occur in about 25–50% early in the course of the disease. In the study of Vlachoyiannopoulos et al renal disease manifested as proteinuria, microscopic haematuria, decreased clearance of creatinine, increased creatinine levels, or the presence of casts was found in about 50% of cases. In other published series, using similar definitions, the prevalence of renal disease ranged from 29 to 75%.

Proteinuria is considered the sine qua non of renal disease in lupus. In a comprehensive review on lupus nephritis, proteinuria was reported in 100% of patients, with nephrotic syndrome in 80% of patients, with nephrotic syndrome in 100% of patients.

Renal disease in APS is characterised by interstitial tubular or glomerular injury due to obstruction of large, medium sized, or small vessels. Renal manifestations are increasingly recognised in association with antiphospholipid antibodies, including thrombotic microangiopathy, renal vein thrombosis, renal infarction, renal artery stenosis and/or malignant hypertension, increased allograft vascular thrombosis, and reduced survival of renal allografts. In a recent study of Vlachoyiannopoulos et al, renal disease was studied in a cohort of 248 patients with APS and SLE with a positive titre of antiphospholipid antibodies, among which 40% had evidence of renal disease.

The implication of ethnic origin differences is also supported by earlier data, which suggested that renal survival was significantly worse in black subjects than in white patients with lupus nephritis. Differences in renal outcome were independent of age, duration of lupus, history of hypertension, hypertension control during treatment, and activity or chronicity indices on renal biopsy. An explanation for the increased incidence and severity noted in this racial group of patients may be provided by the implication of certain genetic factors, which affect the clearance of immune complexes. These subjects are less likely to express the immunoglobulin receptor allele FcγRIa-H131, a receptor normally expressed on macrophages which recognised IgG2. Therefore, inappropriate deposition in the kidney of circulating immune complexes composed of IgG2 antibodies occurs owing to inadequate clearance by hepatic and splenic macrophages.
glomerulonephritis, and most commonly presented with nephritic syndrome. Death and end stage renal failure were quite uncommon in primary APS during the follow up period compared with secondary APS or SLE alone.18

“Hypertension is often the first indicator of renal disease in APS”

A more recent retrospective study evaluated the findings on renal biopsy in 114 patients with SLE and kidney dysfunction showing that APS nephropathy occurs in about one third of patients with SLE, confirmed by renal biopsy, in addition to, and independently of, lupus nephritis histopathological findings. Lesions on renal biopsy suggestive of APS nephropathy included thrombotic microangiopathy, fibrosus intima hyperplasia, organised thrombi with recanalisation, and subcapsular ischaemic cortical atrophy. APS nephropathy was found to be statistically correlated with arterial thromboses, fetal loss, and the presence of lupus anticoagulant. In contrast, no association was reported with the presence of anticardiolipin antibodies and venous thromboses of APS. It is also considered to be an independent risk factor, which contributes to an increased prevalence of hypertension, raised serum creatinine, and increased ischaemic cortical atrophy. APS nephropathy is reported to be the initial manifestation of renal disease in APS also in the study of Karim and coworkers.20

Therefore, renal biopsy findings are very important for the further approach to treatment of these patients: when the renal biopsy findings are consistent with treatment of these patients: when the renal biopsy findings are consistent with the importance of lupus nephritis. However, limitations of the long term use of cyclophosphamide are an increasingly recognised problem. Bone marrow suppression, haemorrhagic cystitis, gonadal toxicity and, eventually, the development of neoplastic disorders are adverse effects of which clinicians are well aware in their every day practice.21 On the other hand, data are scarce on remission rates, predictors of relapse, and the ability to achieve a second remission with currently recommended intravenous cyclophosphamide (IVC) regimens.

To investigate these issues further, 85 patients with proliferative lupus glomerulonephritis treated with IVC were studied.22 The median time to remission was 10 months, whereas 22% of patients had not remitted after two years. Predictors of remission included a delayed initiation of treatment from the time nephritis was clinically diagnosed and a higher level of proteinuria. The median time to relapse among 63 patients who had achieved remission was 79 months. Predictors of earlier relapse for patients entering remission included a longer time to remission, a history of central nervous system disease, and WHO histology IV. Among the 23 patients who relapsed during follow up, the median time to re-remission was 32 months. Except for three patients, all the others took longer to remit the second time compared with their first remission. The time to re-remission was longer in patients who had taken longer to remit the first time, in patients who had relapsed earlier after the first remission, and in those with evidence of chronicity in the original kidney biopsy. On the basis of the above findings the authors conclude that prolonged courses of IVC with a cumulative risk of toxicity seem to be necessary in order to achieve remission in many first-treated patients and in most patients treated for a second time.

“ Toxicity is a risk in the prolonged courses of intravenous cyclophosphamide needed to induce remission in proliferative lupus glomerulonephritis”

Another major concern about the long term use of cyclophosphamide, is the development of ovarian failure. Patient age and cumulative drug dose are the two major factors that determine the risk of ovarian failure, with older patients being more susceptible, according to the earlier data of Boumpas and coworkers.23

In another more recent study of Ioannidis et al predictors of IVC induced sustained amenorrhoea, especially in young premenopausal women with SLE, were identified in a cohort of 67 premenopausal women with SLE who received a pulsed IVC regimen (monthly doses of 0.75–1.00 g/m²) for nephritis (n=59) or other indications (n=8).24 Twenty one of 67 women developed sustained amenorrhoea of >12 months’ duration, with age being the strongest adverse predictive factor. For women >31 years old, D50 (cumulative dose resulting in sustained amenorrhoea in 50% of patients) was 8 g/m² and D90 (cumulative dose resulting in sustained amenorrhoea in 90% of patients) was 12 g/m². Conversely, only 5/44 women aged <31 years old at onset of IVC developed sustained amenorrhoea. In this group of younger women the risk was increased by the prior SLE disease duration and the presence of anti-U1RNP and anti-Ro antibodies. Therefore, in women aged ≥32 years there is a substantial risk of sustained amenorrhoea even with very short IVC courses, while in younger women the risk of sustained amenorrhoea is much smaller, especially in the absence of anti-Ro/SSA, anti-U1RNP antibodies, and shorter disease duration (≥5 years).24

Furthermore, in another retrospective study investigating cyclophosphamide induced bone marrow toxicity, white blood cell counts and platelet counts were determined in 92 patients with SLE (96 courses), who received 1623 doses of cyclophosphamide, in view of the higher risks of cumulative toxicity. It was found that IVC and SLE disease activity have independent effects in lowering white blood cell counts, with serious myelotoxicity of IVC quite uncommon.25

LUPUS NEPHRITIS: NEW THERAPEUTIC OPTIONS

In view of the above data, long term use of IVC necessary for remission together with the risks from cumulative dose of IVC make the need to develop alternative treatments even more imperative. In a recent European multicentre study it was shown that in patients with SLE with proliferative lupus nephritis, a remission-inducing regimen of low dose IVC followed by azathioprine had effects comparable with those of a high dose regimen.26 These data raise questions about the standard practice for the extended use of intravenous pulses of cyclophosphamide, in view of the higher risks of cumulative toxicity.

Evidence based guidelines for treatment of membranous lupus nephritis are lacking. Corticosteroids either intravenously or orally, azathioprine, chlorambucil, cyclophosphamide, cyclosporin, plasmapheresis have all been used in non-randomised, placebo controlled trials. Therefore, the current approach to treatment of membranous disease is mainly empirical.

In recent studies intravenous immunoglobulin and mycophenolate mofetil

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seem to be promising, effective, and relatively safe alternative therapeutic agents for proliferative forms of the disease with cyclophosphamide is toxic or ineffective. However, long term data are lacking. 

Recent data suggested a possible role of biological agents in the treatment of lupus nephritis. The monoclonal anti-CD40 ligand antibody, initially promising in its management was complicated by unexpected thrombotic events, leading to premature termination of the study. 

The use of high dose cyclophosphamide without stem cell rescue led to long lasting remission in 35% of patients, despite a history of resistance to multiple immunosuppressive regimens in the past. 

Finally, the use of autologous haematopoetic stem cell transplantation seemed to be a safe approach in the management of lupus nephritis, leading to a remarkable improvement of renal function and normalisation of anti-DNA and complement levels in most patients. 

In the forthcoming years, biological agents such as blockers of their cyclo- regulatory pathways (for example, CTLA4-Ig), monoclonal antibody against CD20, anticomplement (anti-C5b) and anticytolytic pathways (for example, CTLA4-agents such as blockers of other costimulatory molecules) 

**REFERENCES**


**CONCLUSIONS**

Despite the progress, the approach to treatment of renal disease in SLE remains an unresolved issue. Two decades after the initial reports, cyclophosphamide, although revolutionary in the management of lupus nephritis, can no longer be considered a “panacea”. The identification of adverse predictors for IVC toxicity and recurrence of the disease is important in order to delineate those groups in whom alternative treatments would be beneficial. In the meantime, prospective randomised long term controlled trials are eagerly awaited.


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