The dialysis scenario in patients with systemic lupus erythematosus

David Cucchiari, Giorgio Graziani and Claudio Ponticelli

Nephrology and Dialysis Unit, Humanitas Clinical and Research Center, Rozzano, MI, Italy

Correspondence and offprint requests to: David Cucchiari; E-mail: david.cucchiari@gmail.com

ABSTRACT

Although prognosis of lupus nephritis has improved over time, a substantial amount of lupus patients still reach end-stage renal disease and require dialysis. Treatment of these patients can be challenging, since the disease poses a number of problems that can portend a poor prognosis, such as infections, lupus reactivations, vascular access thrombosis and cardiovascular complications. Consensus is lacking among investigators about the real incidence of these complications and related diagnosis and treatment. Moreover, the choice of the type of dialysis treatment and the overall prognosis are still a matter of debate. In this paper, we have reviewed the currently available literature in an attempt to answer the most controversial issues about the topic. Keywords: dialysis, ESRD, lupus, SLE

INTRODUCTION

The prognosis of lupus nephritis has considerably improved over time. In 1964 the seminal study of Pollak et al. [1] reported that only 20% of patients treated with high-dose
steroids were still alive without renal failure but more recent studies report a 10-year renal survival ranging between 84% [2] and 97% [3]. This improvement is partly attributable to an earlier recognition of disease and referral in comparison with the past. However, a major advance is represented by better refinement of therapy and by the introduction of new drugs such as mycophenolate salts and rituximab. Today, the treatment of lupus nephritis is generally subdivided into induction and maintenance therapies.

Induction therapy is usually based on the administration of high-dose steroids (usually three i.v. pulses of methylprednisolone followed by oral prednisone 1 mg/kg slowly tapered after 6–8 weeks) associated with either cyclophosphamide (intravenously or orally) or mycophenolate. More recently, rituximab has also been used for induction therapy. A randomized controlled trial was unable to show its superiority compared with standard treatment in lupus nephritis [4]. However, observational studies reported complete or partial renal response in 67–77% of patients, when rituximab was added to the standard treatments [5]. The drug seems to be well tolerated, but when given to patients who received aggressive treatment with high-dose steroids and/or immunosuppressive agents, its use is associated with an increased risk of developing severe infections and, rarely, posterior leukoencephalopathy. In summary, rituximab may allow to improve the prognosis in severe cases of lupus nephritis, but when used, the doses of steroids or immunosuppressive drugs should be reduced. A main limitation to its use is represented by the high cost of the therapy.

Maintenance therapy is aimed to prevent flares of activity while minimizing the iatrogenic adverse events. It usually consists of the lowest and best tolerated dose of corticosteroids plus azathioprine or mycophenolate. However, while single-centre studies reported a continuous improvement in long-term patient- and renal-survival, less optimistic are the data reported by large surveys, although one should take into account the different distribution of factors that influence prognosis (Table 1). A review of the US Renal Data System reported that the risk of end-stage renal disease (ESRD) due to lupus nephritis did not change between 1996 and 2004 [6]. Recently, Costenbader et al. showed an absolute increase of the incidence of ESRD among African Americans and in individuals younger than 40 years in the same period of time. This could be explained by a decrease in early mortality due to systemic lupus erythematosus (SLE) in this cohort of patients [7] that carry a high risk to develop ESRD. The treatment of the disease has certainly improved over the years but it is likely that even in the future a still high proportion of patients would reach ESRD, because of the increasing incidence of SLE in the developed countries [8] and the lower mortality rate due to the improved management. For the nature of their disease, these patients pose a series of issues that are not routinely met in dialysis care (Table 2). The aim of this review is to address the most common problems met by the nephrologists in the care of these patients in dialysis.

### DIALYSIS OR TRANSPLANTATION?

There is a general agreement that renal transplantation can not only offer better life expectancy [9] and quality of life [10] in comparison with regular dialysis, but can also result in minor cost in the long term [11]. While in the past the results of kidney transplantation were worse in lupus patients than in subjects with other renal diseases, more recent papers reported that patient and graft survival probabilities were similar in patients with SLE and in non-SLE controls, not only in the short term but also in the long term [12–15]. Nephritis recurred in <10% of transplant recipients with SLE and did not influence graft survival when lupus patients were compared with matched controls [16]. Other studies showed that renal transplant recipients with SLE had better survival and lower complication rates than lupus patients treated with hemodialysis or peritoneal dialysis [17]. However, patients with anti-phospholipid syndrome (aPS) (diagnostic criteria are listed in Table 3) have an increased risk of early graft failure due to renal artery thrombosis [19] and seems that even the presence of

| Table 1. Main prognostic factors for ESRD in patients with lupus nephritis |
|----------------|-----------------------------|
| **Traditional risk factors** | **Other risk factors** |
| Male gender | Anaemia |
| Younger age | Antiphospholipid antibodies |
| Elevated serum creatinine | Delayed treatment |
| Nephrotic proteinuria | No remission |
| Activity index | Renal flares |
| Chronicity index | Poor socioeconomic status |
| Histological classes | Poor adherence to prescriptions |

| Table 2. Main clinical problems of lupus patients with ESRD |
|----------------|-----------------------------|
| Transplantation versus dialysis | Patient and graft survival in SLE patients are similar to those observed in non-SLE recipients. Transplant offers better quality of life in comparison with dialysis. Transplant should be done only in patients with inactive lupus |
| Survival on dialysis | It is similar in SLE patients and in patients with other diseases |
| PD or HD | The patient survival is similar between patients treated with HD and PD. Patients on PD are susceptible to peritonitis that can trigger lupus flares and sclerotic peritonitis. On the other hand, patients on HD may develop more frequently anti-phospholipid antibodies for the extracorporeal treatment |
| Lupus activity on dialysis | Some patients have a progressive reduction of lupus activity, particularly after the first year of dialysis, but in other patients there is still a hectic activity of lupus |
| Infections | Infections are more frequent in patients with aggressive SLE requiring high doses of steroids and/or other immunosuppressive drugs. The differential diagnosis between infection and flare-up can be difficult. Some patients may have both complications at the same time |
| Antiphospholipid antibodies | In HD patients, antiphospholipid antibodies may be more frequent due to the extracorporeal treatment. The presence of these antibodies has been associated with an increased prevalence of vascular thrombosis and stenosis of the vascular access |

PD, peritoneal dialysis; HD, haemodialysis.
antiphospholipid antibodies, without the overt clinical syndrome, may increase the risk of graft failure especially in those patients who have no history of haemodialysis [20]. Moreover, after transplantation infections are more frequent in SLE patients who received long-term and vigorous immunosuppression before transplantation and represent the leading cause of death in young recipients. Bartosh et al. [21] found in a retrospective analysis a trend towards an increased mortality due to infection in SLE patients compared with age-matched transplanted patients, although the cohort was too small to give a solid answer. Because of the increased cardiovascular risk in these patients, the pre-transplant work-up should include a stress echocardiography or scintigraphy and, in case, a coronary angiography. Moreover, bone mineral density should be assessed as well, especially in those patients who have been treated extensively with corticosteroids, in order to guide future osteoporosis prophylaxis [22]. In summary, the available data indicate that in SLE patients renal transplantation may offer at least the same expectancy of life as dialysis. However, there is now a bulk of evidence to suggest that successful transplants are associated with a significantly better quality of life in comparison with dialysis [23], so that kidney transplantation remains the best option for SLE patients with ESRD.

### DOES THE OUTCOME ON DIALYSIS VARY AMONG PATIENTS WITH LUPUS AND DIFFERENT DISEASES?

A survey of the US Renal Data System reported that the patient survival in dialysis was lower in patients with SLE than in those with other causes of ESRD [24] and this excessive mortality was attributable to the burden of cardiovascular disease. However, another recent report of the Taiwan National Health Insurance Research Database showed no difference in 8-year survival between dialysis patients with SLE and patients without SLE [25]. It is not clear whether racial differences justify this difference in outcome. It has been speculated that people of Asian ancestry have a better survival in dialysis than Caucasians [26], although they have worse disease expression and outcomes [27]. However, this issue has never been assessed in a multiracial cohort of SLE patients submitted to regular replacement therapy. It is more likely that the difference between the two registries is due to the fact that the Taiwanese data were adjusted for age, sex, dialysis modality and comorbidities. The general impression, however, is that the prognosis of lupus patients treated with dialysis largely depends on predialysis comorbidity [28]. The causes of death are different if the event occurs early after starting dialysis or later. In the first 3 months of dialysis the most frequent cause of death is sepsis, mainly related to the heavy immunosuppression used in patients with strong activity of lupus [29]. In the following months, cardiovascular and cerebrovascular complications are the leading causes of death. However, whether the risk of cardiovascular events is more frequent in SLE patients than in patients with other renal diseases is still a matter of debate. By a retrospective analysis of the US Renal Data System, Ward found that the risk of myocardial infarction, after adjusting for confounding factors, was similar in SLE patients and in non-SLE patients (excluding diabetics), 16.4/1000 patient/years and 18.5/1000 patient/years, respectively. Also the risk of cerebrovascular diseases was similar, 18.5/1000 patient/years versus 19.2/1000 [30]. In other studies, however, cardiovascular events were more frequently observed in SLE patients. This high cardiovascular burden cannot be completely explained by the presence of traditional risk factors [24, 31]. Actually, corticosteroids [32], antiphospholipid antibodies [33], endothelial cell activation [34], anaemia [35] and metabolic syndrome [36] can further promote the development of cardiovascular disease. It is now widely accepted that a chronic inflammatory condition can accelerate the progression of atherosclerosis [37]. Moreover, haemodialysis itself is associated with a continuous inflammatory load, due to infections, the procedure itself and the presence of comorbidities [38]. Therefore, it does not seem unrealistic to think that the increased risk of cardiovascular disease in lupus patients is caused by the concurrence of two conditions with a heavy inflammatory and atherosclerotic burden, such as the disease itself and haemodialysis. For these reasons, a rigorous monitoring and treatment of traditional and non-traditional cardiovascular risk factors is strongly recommended in SLE patients on regular dialysis. Apart from cardiovascular risk, SLE patients may be more susceptible to haematological malignancies [39] favoured by both immunosuppression and disease activity itself [40]. In summary, the life expectancy of patients on dialysis is similar for patients with SLE and those with other renal diseases. However, a subset of lupus patients may run a higher risk of life-threatening cardiovascular or malignant complications, mainly related to the severity of SLE and aggressive steroid and immunosuppressive treatment, with the possible contribution of haemodialysis.

---

**Table 3. Diagnostic criteria of aPS**

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular thrombosis</td>
<td>One or more clinical episodes of arterial, venous or small vessel thrombosis in any tissue or organ</td>
<td>Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart.</td>
</tr>
<tr>
<td>Pregnancy morbidity</td>
<td>(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation</td>
<td>Anti-cardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titre (i.e. &gt;40 GPL or MPL, or &gt;the 99th percentile), on two or more occasions, at least 12 weeks apart</td>
</tr>
<tr>
<td></td>
<td>(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because either eclampsia or severe preeclampsia or recognized features of placental insufficiency</td>
<td>Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titre &gt;the 99th percentile), present on two or more occasions, at least 12 weeks apart</td>
</tr>
<tr>
<td></td>
<td>(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded</td>
<td></td>
</tr>
</tbody>
</table>

aPS is present if at least one of the clinical criteria and one of the laboratory criteria above are met [18].

---

**Do not hallucinate.**

-FULL REVIEW-
HAEMODIALYSIS OR PERITONEAL DIALYSIS?

Only a few studies have compared clinical outcomes between haemodialysis and peritoneal dialysis in SLE patients so far and the conclusions drawn are conflicting (Table 4). While one group reported a better survival on haemodialysis [41], other groups could not find any difference in patient survival between peritoneal dialysis and haemodialysis [17, 42, 43]. By reviewing the National database in Taiwan, Chang et al. [44] found that male SLE patients on peritoneal dialysis had a significantly better outcome than males on haemodialysis, while there was no survival difference among female SLE patients with different dialysis modalities. These discrepancies may be partly accounted for by the different clinical conditions of the patients and by the modalities of dialysis. Patients who receive high-dose steroid at the beginning of peritoneal dialysis are more susceptible to infection and have a poorer survival technique than age- and gender-matched non-SLE patients [45]. Other drawbacks of peritoneal dialysis are the possibility that lupus-associated serositis may predispose to sclerosing encapsulated peritonitis [46] and that peritonitis can trigger SLE reactivations [47]. On the other hand, in haemodialysis patients, the frequent contact of blood with non-compatible membranes may promote the creation of an inflammatory milieu that may eventually contribute to the development of cardiovascular disease. Haemodialysis may also favour the production of anti-phospholipid antibodies, with an increased risk of vascular thrombosis, particularly when cuprophane membranes are used [48, 49]. Thus, in patients with inactive SLE, haemodialysis and peritoneal dialysis may have equivalent advantages and drawbacks. However, since the risk of infection with peritoneal dialysis is higher in patients with hectic SLE activity, this technique should be limited to patients with quenching SLE.

CAN LUPUS REMAIN ACTIVE DURING DIALYSIS TREATMENT?

Both clinical and serological parameters of SLE activity tend to quench or even normalize over time in patients on dialysis [50–52]. Flares are more frequent after beginning of dialysis and tend to decrease in the following years [53]. This reduced activity of SLE has been attributed to an immunodeficiency status induced by uraemia [54], removal of immune-complexes by the phagocytic system in the lung during haemodialysis [55] and/or removal of plasma factors that can induce lupus reactivation [56]. On the other hand, a number of papers reported a high rate of flares in dialysis patients [57–62]. Clinically, these flares are characterized by fever, rash, myalgia, serositis, anaemia and even by cerebritis. Flares usually occur in patients with an active SLE at the start of dialysis and can be severe and refractory to treatment with corticosteroids. There is agreement that patients with recent activity of SLE should continue corticosteroid administration and hydroxychloroquine, while many investigators tend to minimize or even completely eliminate corticosteroids and...
immunosuppressive agents in patients with inactive SLE to avoid the possible side effects of these drugs. However, a recent report challenged this policy. Out of 80 SLE patients undergoing renal replacement therapy in an urban tertiary care centre, 22 (28%) were followed in rheumatology clinics frequently (two or more visits per year) and 58 patients (72%) were followed infrequently (fewer than 2 visits per year). Patients with SLE followed frequently after starting dialysis had significantly higher 4-year survival. The hazard ratio (HR) for death was halved in patients who continued to receive prednisone (HR 6.1) when compared with that of patients who did not receive any specific medication for SLE (HR 13.0). According to the authors, these data suggest that active disease in patients with SLE undergoing renal replacement therapy may be underrecognized and undertreated, leading to increased mortality [63]. At any rate, it is recommended to monitor the activity of the disease in SLE patients, independently of the type of dialysis. Patients should be visited by a nephrologist at least once every month and should be instructed to report early any sign or symptom (fever, arthralgias, skin rash etc.) that may evoke SLE activity. Anti-dsDNA antibodies, serum C3 and C4 and anti-C1q antibodies (when available) should be checked every 3 months. Clinical manifestations should be promptly treated, as far as diagnosis is established, while we are not in favour of treatment on the basis of biological parameters alone. The choice of treatment depends on the clinical conditions of the patient and previous immunosuppression. No evidence exists about optimal immunosuppression in dialysis. The main problems are the different drug metabolism in ESRD and the already depressed immune status of these patients [64], so treatment choices rely on physician’s clinical experience. We prefer to use mini-pulses of i.v. methylprednisolone (80–120 mg each) during the morning in peritoneal dialysis patients or at the end of haemodialysis. Small doses of mycophenolate mofetil (0.5–1 g per day) and/or hydroxychloroquine may be added to maintain remission. In patients with steroid toxicity or steroid resistance, a monotherapy with rituximab can be advised on the basis of scanty, anecdotal reports [65]. Of note, rituximab is not detectable in the dialysate fluid and therefore the dosage should not be modified in haemodialysis patients [66]. Instead, the use of cytotoxic drugs should be limited to those few patients who do not respond to previous treatments. In fact, these agents can aggravate anaemia, platelet dysfunction and leucocytosis.

**HOW TO DISTINGUISH BETWEEN SLE FLARES AND INFECTIONS?**

It may be difficult in lupus patients to distinguish a flare-up from an infection. The two complications require opposite treatments and therefore a misdiagnosis can lead to disastrous consequences. SLE patients are more vulnerable to infection because the disease itself and its treatment weaken the immune system. The uraemic milieu can further contribute to an immunodeficient status and so increasing the risk of infection. The differential diagnosis with lupus flare can be difficult in case of sepsis, which has many signs and symptoms in common. Serological parameters such as lower C3 and C4 levels and/or higher titres of anti-DNA antibodies may help in the characterization of lupus flare [67], while positive blood cultures obviously speak for infection. Unfortunately, however, lupus flare and sepsis can occur simultaneously and diagnosis in these cases is extremely challenging. Other useful biomarkers have been proposed to assess the presence of an infection. C-reactive protein (CRP) is not increased in SLE flares [68]. However, CRP levels can rise during serositis and polyarthritis. Therefore, the physician should consider this issue in the interpretation of a high CRP level [69]. Another biomarker of sepsis is procalcitonin (PCT), which is considered to be a highly specific indicator for bacterial infections [70]. However, PCT levels are increased in ESRD and are influenced by the filters used in haemodialysis [71]. Moreover, its value in discriminating between infections and SLE flares is controversial [72, 73] and so its role in SLE is currently equivocal. Among biomarkers under investigation, the most promising seems to be CD64, which is the FCy Receptor I for IgG, whose expression increases on the neutrophil surface. This parameter is both sensitive and specific, is not influenced by the use of immunosuppressive drugs and rises early after infection, providing a timely clinical evaluation [83]. At present, however, the differential diagnosis between a flare-up of SLE and an infectious complication is mainly based on clinical signs and symptoms as well as on the good sense and expertise of the physician.

**SLE AND ANTIPHOSPHOLIPID SYNDROME IN DIALYSIS PATIENTS**

The possible presence of antiphospholipid antibodies should be accurately searched for in SLE patients undergoing renal replacement therapy. Antiphospholipid syndrome (aPS) is present in 15% of SLE patients [74]. Moreover, antiphospholipid antibodies are present in a high proportion of patients on haemodialysis, irrespective of SLE, with a prevalence ranging from 10 to 30% [75, 76]. Putative causes are poor biocompatibility, exposure to endotoxins and renal failure itself [77]. Therefore, it is likely that SLE patients submitted to haemodialysis may have an increased prevalence of antiphospholipid antibodies because of the nature of their disease and the extracorporeal treatment itself. This issue is relevant since the presence of these antibodies has been associated with thrombosis and stenosis of the vascular access [18, 78–80]. This assumption has been confirmed in SLE patients by a retrospective series [48]. The presence of antiphospholipid antibodies may indicate a thrombophilic state and is usually considered as an indication to prophylaxis with subcutaneous heparin [81]. However, only few studies have investigated this approach and the relative benefits of longer vascular access life were balanced by an increased risk of bleeding [82].

**CONCLUSIONS**

Although prognosis of lupus nephritis has improved over time, a number of patients affected by this disease still require regular replacement therapy. In these patients, as well as in...
most other patients with ESRD, renal transplantation remains the treatment of choice. However, in those patients who arrive to ESRD devastated by a too vigorous immunosuppression, a period of dialysis may be recommended, because of the risk of exposing too early these frail patients to the heavy immunosuppressive regimen of renal transplantation. Recent reports show no difference in survival between patients with or without SLE, although those lupus subjects who received aggressive immunosuppressive treatment before dialysis are more susceptible to life-threatening complications. Both haemodialysis and peritoneal dialysis may obtain good results in lupus patients, although the risk of infection is more elevated in the few patients with hectic lupus activity treated with peritoneal dialysis. The general impression is that the activity of SLE tends to burn out under dialysis. However, these patients should be frequently monitored in order to promptly treat extra-renal flares of lupus. In this regard, it is crucial to distinguish between flares of SLE activity and infections. Although some biological parameters may help in the differential diagnosis, a diagnostic and therapeutic decision should be generally taken on the basis of clinical signs and symptoms.

In summary, there are still differing views among investigators about the real clinical behaviour of SLE patients in dialysis. This is mainly related to the nature of the available retrospective studies. At any rate, although it is difficult to draw firm conclusions from the current literature, the general impression is that most lupus patients may have a fair outcome with regular dialysis. Severe reactivation of the disease is rare and usually occurs in the period shortly after starting dialysis. However, patients with recurrent flares, aPS and those who received aggressive treatment before starting dialysis may have a poor prognosis because of the increased risk of cardiovascular events, infections and vascular thrombosis.

CONFLICT OF INTEREST STATEMENT

C.P. has been consultant of Novartis Italy until December 2011. In the last two years he received honoraria for invited lectures from Novartis, University of Calgary (Canada), North Shore Hospital of New York (USA), University of Zurich (CH).

REFERENCES
