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

| 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. |

Table 2. Main clinical problems of lupus patients with ESRD

<table>
<thead>
<tr>
<th>Traditional risk factors</th>
<th>Other risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Younger age</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>Delayed treatment</td>
</tr>
<tr>
<td>Nephrotic proteinuria</td>
<td>No remission</td>
</tr>
<tr>
<td>Activity index</td>
<td>Renal flares</td>
</tr>
<tr>
<td>Chronicity index</td>
<td>Poor socioeconomic status</td>
</tr>
<tr>
<td>Histological classes</td>
<td>Poor adherence to prescriptions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 1. Main prognostic factors for ESRD in patients with lupus nephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional risk factors</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Younger age</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
</tr>
<tr>
<td>Nephrotic proteinuria</td>
</tr>
<tr>
<td>Activity index</td>
</tr>
<tr>
<td>Chronicity index</td>
</tr>
<tr>
<td>Histological classes</td>
</tr>
</tbody>
</table>

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.

### Table 3. Diagnostic criteria of aPS

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular morbidity</td>
<td>Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart.</td>
</tr>
<tr>
<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>(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because either eclampsia or severe preclampsia or recognized features of placental insufficiency</td>
<td>Anti-β2 glycoprotein-1 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>(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].

**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.
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 antimalarials. For patients with quenched SLE, the treatment with corticosteroids can be reduced or even stopped, but should be reapplied whenever a flare is suspected or documented. Infections are usually highlighted in patients starting haemodialysis, and in particular on the dialysis catheters, and inflamed peritoneal dialysis catheters should be removed in case of infection and replaced with a new catheter. Infections in peritoneal dialysis patients are usually due to peritonitis, which can cause peritoneal sclerosis and may lead to end-stage renal disease. However, in haemodialysis patients, infections can shorten survival, especially if the infection involves the bloodstream. Therefore, the role of dialysis in treating these infections should be considered in the context of the patient's SLE activity and the infection severity. Unfortunately, patients with SLE frequently present with autoimmune diseases, and the management of these patients can be challenging. The optimal management of these patients is still under debate and needs to be tailored to individual patient's needs.
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 filter 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

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 Fcγ 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.

Dialysis in lupus patients
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 immuno-
suppression regimen of renal transplantation. Recent reports
show no difference in survival between patients with or
without SLE, although those lupus subjects who received ag-
gressive 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 ele-
vated 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 pa-
tients 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. Al-
though 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 investiga-
tors 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 conclu-
sions from the current literature, the general impression is that
most lupus patients may have a fair outcome with regular dial-
sis. 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

1. Pollak V, Pirani CL, Schwartz FD. The natural history of the renal mani-
festations of systemic lupus erythematosus. J Lab Clin Med 1964; 63:
537–550
3. Moroni G, Quaglini S, Gallelli B et al. The long-term outcome of 93 pa-
tients with proliferative lupus nephritis. Nephrol Dial Transplant 2007; 22:
2531–2539
4. Rovin BH, Furie R, Latini K et al. Efficacy and safety of rituximab in pa-
tients with active proliferative lupus nephritis: the Lupus Nephritis As-
5. Gunnarsson I, Jonsdottir T. Rituximab treatment in lupus nephritis—
6. Ward MM. Changes in the incidence of endstage renal disease due to
63–67
7. Costenborder KH, Desai A, Alarcón GS et al. Trends in the incidence,
demographics, and outcomes of end-stage renal disease due to lupus
nephritis in the US from 1995 to 2006. Arthritis Rheum 2011; 63:
1681–1688
8. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus
erythematous: a comparison of worldwide disease burden. Lupus 2006; 15:
308–318
9. Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all pa-
tients on dialysis, patients on dialysis awaiting transplantation, and recipi-
Transplantation 2001; 72(Suppl. 12): S67–S74
11. Klarenbach S, Barnich L, Gill J. Is living kidney donation the answer to
the economic problem of end-stage renal disease. Semin Nephrol 2009; 29:
533–538
12. Stone JH. End-stage renal disease in lupus: disease activity, dialysis
13. Ward MM. Outcomes of renal transplantation among patients with end-
14. Deegens JK, Arzt MA, Hoijtsma AJ et al. Outcome of renal transplant-
ation in patients with systemic lupus erythematosus. Transplant Int 2003;
16: 411–418
after renal transplantation in Malaga. Transplant Proc 2012; 44: 2067–2068
45: 903–911
different renal replacement therapy in patients with end-stage renal
18. Miyakis S, Lockshin MD, Atsumi T et al. International consensus treat-
ment on an update of the classification criteria for definite antiphospho-
tic intervention in end-stage renal disease patients with antiphospholipid
20. Wagenknecht DR, Becker DG, LeFor WM et al. Antiphospholipid anti-
odies are a risk factor for early renal allograft failure. Transplantation
1999; 68: 241–246
21. Bartosh SM, Fine RN, Sullivan EK. Outcome after transplantation of
young patients with systemic lupus erythematosus: a report of the North
American pediatric renal transplant cooperative study. Transplantation
2001; 72: 973–978
Nephrol Dial Transpl 2008; 23: 3056–3060
23. Tonelli M, Wiebe N, Knoll G et al. Systematic review: kidney transplanta-
tion compared with dialysis in clinically relevant outcomes. Am J Trans-
plant 2011; 11: 2093–2109
24. Sule S, Fivush B, Neu A et al. Increased risk of death in pediatric and adult
25. Chen HA, Wang JI, Chou CT et al. Predictors of longterm mortality in pa-
tients with and without systemic lupuserythematosus on maintenance dia-
26. Roderick P, Byrne C, Casula A et al. Survival of patients from South Asian
and Black populations starting renal replacement therapy in England and
Wales. Nephrol Dial Transplant 2009; 24: 3774–3782
27. Kumar K, Chambers S, Gordon C. Challenges of ethnicity in SLE. Best
28. Lian CC, Lin HH, Wang IK. Influence of predialysis comorbidity and
damage accrual on mortality in lupus patients treated with peritoneal dia-
lysis. Lupus 2010; 19: 1210–1218
29. Moroni G, Tantardini F, Ponticelli C. Renal replacement therapy in lupus
30. Ward MM. Cardiovascular and cerebrovascular morbidity and mortality
among women with end-stage renal disease attributable to lupus nephritis.
31. Esdaile JM, Abrahamowicz M, Grodzicky T et al. Traditional Framingham
risk factors fail to fully account for accelerated atherosclerosis in systemic