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Review article

Therapeutic approach to the lung-kidney syndrome associated with systemic lupus erythematosus, a medical emergency that is a challenge for the clinician

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ABSTRACT

The lung-kidney syndrome associated with Systemic Lupus Erythematosus is a rare condition, but with a high burden of morbidity and mortality. There is little evidence regarding the prevalence, distribution of the disease and, even less regarding the therapeutic options. It is worth highlighting the impact that the early and effective establishment of treatment represents in the natural evolution of this pathology. This is a field that has been very little explored and that therefore requires more clinical trials and from them evidence. This is the reason for conducting a semi-structured review of the literature about the therapeutic strategies available at this time, represented using cyclophosphamide and rituximab, plasmapheresis, and corticosteroids, as well as their impact on mortality and outcomes. These therapies can compromise vital organs that can lead to acute respiratory failure and in other cases, require renal replacement therapy.

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Abordaje terapéutico del síndrome pulmón-riñón asociado con lupus eritematoso sistémico, una urgencia médica que es un reto para el clínico

Palabras clave:
Nefritis lúpica
Ciclofosfamida
Rituximab
Plasmaféresis

RESUMEN

El síndrome pulmón-riñón asociado con el lupus eritematoso sistémico es una condición poco frecuente, pero con alta carga de morbimortalidad, de la que se tiene escasa evidencia en cuanto a su prevalencia y distribución, y menos aún sobre opciones terapéuticas. Es de resaltar el impacto que representa la instauración temprana y eficaz del tratamiento en la evolución natural de esta patología, un campo poco explorado que por lo mismo requiere mayores ensayos clínicos y con esto, su evidencia. Esta es la razón para llevar a cabo una revisión semiestructurada de la literatura acerca de las estrategias terapéuticas disponibles, representadas en el uso de ciclofosfamida y rituximab, plasmaféresis y corticoesteroides, así como de su impacto en la mortalidad y los desenlaces, que pueden comprometer órganos vitales, derivar en insuficiencia respiratoria aguda y en algunos casos requerir terapia de reemplazo renal.

Introduction

Lung-kidney syndrome (LKS) is defined as the simultaneous manifestation of diffuse alveolar hemorrhage (DAH) and rapidly progressive glomerulonephritis (RPGN). Vasculitides associated with anti-neutrophil cytoplasmic antibodies (ANCA) constitute the main cause in more than 65% of cases, followed by anti-glomerular basement membrane disease, to a lesser extent, in approximately 12–17.5% of cases. Even less frequent are some autoimmune diseases such as systemic lupus erythematosus (SLE), polymyositis, and scleroderma, which together account for less than 10% of cases, followed by ANCA (-) and drug-induced vasculitis.[1]

In the case of ANCA-associated vasculitides, LKS has an incidence that varies from 1 to 10 cases per 10 million inhabitants/year. Given their rare presentation in SLE, there are no epidemiological data available; however, when they are considered independent entities, lupus nephritis is present in between 40% and 90% of patients with SLE (associated or not with rapidly progressive kidney involvement), whereas DAH has a prevalence of less than 2%[1,2] but with an alarming impact on mortality that is around 50%, and even higher.

At present, there is still a discrepancy regarding the therapeutic schemes in this clinical condition, rare but catastrophic, which can put at risk the functionality of an organ and even lead to death.[3] Consequently, a semi-structured review of the literature is proposed, in order to establish the available evidence in relation to this condition, the therapeutic possibilities and the outcomes in mortality and compromised functionality of specific organs in patients with SLE who have associated LKS.

Methods

To address the aforementioned work, a search was conducted in the PubMed and Embase databases, using the Mesh and no Mesh terms for “Lung-kidney syndrome”, “Systemic lupus erythematosus”, “Diffuse alveolar hemorrhage”, “Lupus nephritis”, “Cyclophosphamide”, “Rituximab” and “Plasmapheresis”, filtering the publications made between 1980 and October 2020, in people over 18 years of age.

In addition, meta-analyses, experimental studies, systematic reviews, case reports and series reports in which patients had a diagnosis of SLE associated with DAH and/or RPGN were included. The exclusion criteria included age less than 18 years, pregnancy status, ANCA positivity, and other conditions known to cause pulmonary hemorrhage, such as concomitant antiphospholipid antibody syndrome, uremia, disseminated intravascular coagulation, or cytomegalovirus (CMV) pneumonia. Articles with no individual survival data available were excluded.

The initial search yielded a total of 242 results, of which 19 articles were filtered by review of each title, being included in the final analysis. Data on adverse effects, survival and organ-specific outcomes were analyzed (Fig. 1).

Lung-kidney syndrome

A term implemented in 1919 by Goodpasture that implies the simultaneous presentation of renal and ventilatory failure as manifestations of RPGN and DAH, respectively, in the context of autoimmunity. It entails a short-term mortality of up to 40% if timely intervention is not performed, in addition to a risk of relapse of around 15% at 18 months. However, fortunately, it is a clinical condition of low prevalence. Survival trend figures seem to show a significant change in recent decades: approximately 25% around 1980 vs. 67% in the current decade.

For treatment, it is ideally considered as a prerequisite that patients be admitted to an intensive care unit for monitoring, resuscitation and stabilization processes, as well as the start of targeted therapy (Fig. 2).

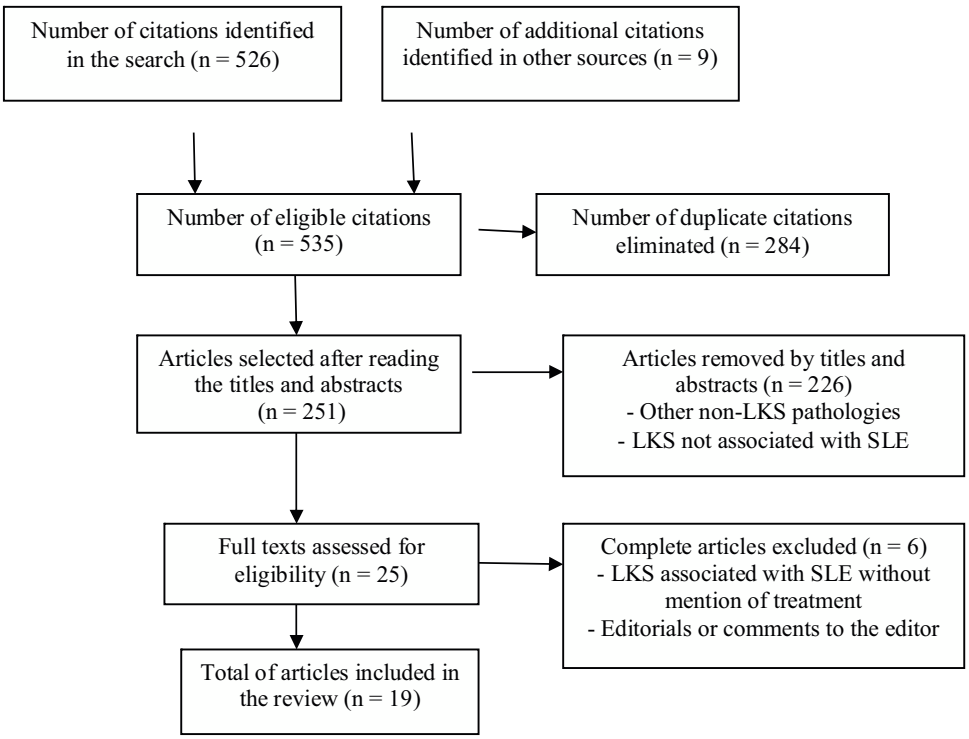

Figure 1 – Search diagram.

Cyclophosphamide

This alkylating agent has been widely used in patients with a diagnosis of SLE with life-threatening disease activity, as well as in those patients with lupus nephritis, and effective disease control has been achieved, even up to the point of achieving remission in 71% of cases, according to the results of The Euro-Lupus Nephritis Trial.[4]

Regarding patients who also have alveolar hemorrhage, the evidence points to the fact that, in combination with steroids, cyclophosphamide seems to improve survival up to 67%, according to the results of the systematic review published by Ednalino et al. in 2015.[5] However, the evidence initially indicated that by the year 1997, those patients with SLE and alveolar hemorrhage who received cyclophosphamide had increased mortality due to the requirement for invasive mechanical ventilation, and a greater tendency to infection, according to the results of Zamora et al.[6] It is probable that cyclophosphamide itself does not lead to an increase in mortality, on the contrary, the patients who received it had more factors associated with death. This is considered an error of interpretation, since over time it was demonstrated that they were clinically sicker patients, with a higher probability of fatal outcomes.

It is highlighted that the fact that the patient with SLE starts with RPGN associated with alveolar hemorrhage is considered a rare but lethal manifestation and is directly related to the disease activity, with higher mortality extrapolated from case series with DAH higher than 50%.[7]

To date, there is no evidence in relation with those cases of SLE that present with LKS, different from some case reports in which due to the absence of a clear management guide in the literature, the treatment approach continues to be individualized and depends on the clinical condition of the patient; however, evidence suggests to initiate early and aggressive treatment, since it is a condition with a high mortality rate in the short and long term.

Plasmapheresis

Therapeutic plasmapheresis is an extracorporeal procedure in which whole blood is removed, its components are subsequently separated and filtered through a high-permeability membrane, and the substance with a molecular weight higher than 3×10 exp 6 Da (e. g., immunoglobulins, immune complexes, complement factors) are separated to latter apply them to the patient. During the procedure, a determined volume of plasma is extracted, estimated by calculating the oncotic pressure, using a nomogram, by the Kaplan formula, which depends on the weight and the hematocrit of the patient[8]:

Estimated plasma volume = $(0.065 \times \text{weight (kg)}) \times (1 - \text{hematocrit})$

Once the plasma volume is extracted, is replaced by a solution with adequate colloidal activity ((plasma or albumin solution), the indication for each one being individualized. In the case of 5% albumin, it has the advantages of a lower risk of infection, a low incidence of side effects, and the fact of being iso-oncotic; however, it is more expensive and the patient may present hypotension, nausea, and depletion of plasma proteins. With respect to fresh frozen plasma, it is mainly indicated in patients with a history of deficiency of coagulation factors or immunodeficiencies, it has the advantage of not depleting plasma proteins and provides deficient coagulation factors; however, it has the disadvantage as for

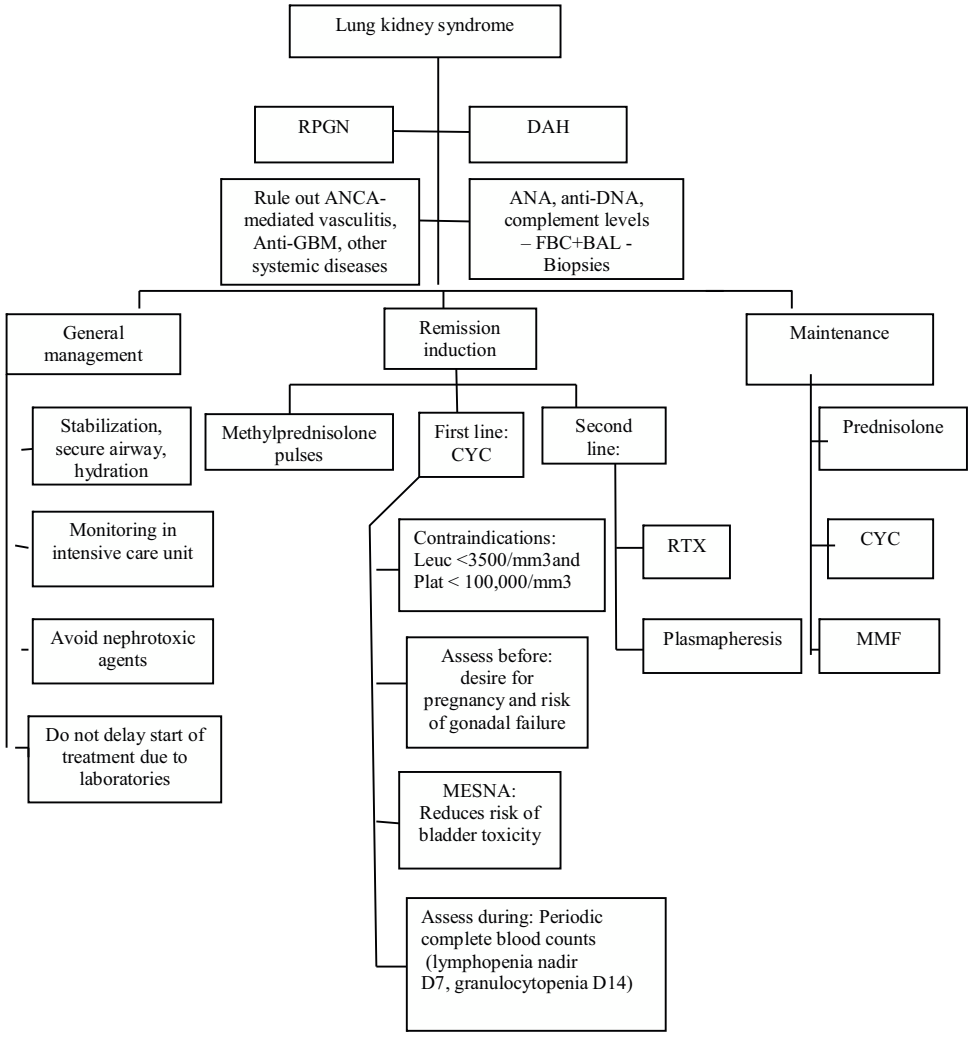

Figure 2 – Therapeutic algorithm.[1,2,4]
ANA: antinuclear antibodies; ANCA: Anti-neutrophil cytoplasmic antibodies; Anti-GBM: anti-glomerular basement membrane antibodies; CYC: cyclophosphamide; FBC + BAL: fiberoptic bronchoscopy + bronchoalveolar lavage; RPGN: rapidly progressive glomerulonephritis; DAH: diffuse alveolar hemorrhage; MESNA: sodium 2-mercaptoethanol sulfonate; MMF: mycophenolate mofetil; RTX: rituximab.

the risk of transmission of infections, allergic reactions and the compatibility of the ABO system, in addition to its high cost.[8]

An average of three to five plasmapheresis sessions are required, taking into account that between 45% and 75% of the total immunoglobulins are removed in each session, until reaching a removal of 90% at the end of the indicated sessions. Nevertheless, after the procedure there is a reaccumulation of molecules in the intravascular space due to: lymphatic drainage, simple diffusion through the capillary wall and endogenous synthesis by plasma cells.[9]

Due to the low frequency of presentation of SPR in the context of SLE, there are no studies evaluating plasmapheresis in this setting; however, there are publications in which its outcomes are assessed separately in DAH and lupus nephritis. In a systematic review conducted by Enaldino et al. in 2015,[5] with 140 patients who presented DAH/SLE, it was found that 80% had renal involvement, without clarifying the histological class; 43 patients received plasmapheresis, with a survival of 53% (23 patients), compared with those patients who received cyclophosphamide, a group in which survival was higher in comparison with those who did not receive such therapy (71% vs. 49%).[5]

In another multicenter randomized clinical study, published in 1992 by Lewis et al.[10], which involved 86 patients with lupus nephritis, mortality and renal outcomes were evaluated. Of this group, 46 patients received standard therapy (prednisone + cyclophosphamide) and 40 received standard therapy + plasmapheresis. In a 136-week follow-up, there were no statistically significant differences between the two groups in terms of mortality (13% in the control group and 20% in the intervention group) and renal failure (17% in the control group and 25% in the intervention group).

The Pexivas study,[11] in which the outcomes of plasmapheresis in patients with ANCA-associated vasculitis were evaluated, clarifying that patients with SLE were excluded,

was recently published and the researchers concluded again that there were no differences in mortality, but it was demonstrated that a regimen of low-dose corticosteroids is not inferior to the standard dose.

In conclusion, to date, it has not been demonstrated that plasmapheresis reduces mortality in patients presenting with lupus nephritis or DAH, and extrapolating previous data to the context of an LKS, today there is no evidence to support this intervention in this group of patients; however, it is worth noting its possible benefit in sparing corticosteroids, a pharmacological group associated with a high volume of adverse effects.

Glucocorticoids

In the standard therapy of LKS associated with SLE, in addition to the elimination of antibodies, is fundamental the role played by the use of glucocorticoids, which are administered as coadjutants in immunosuppressive therapy, in favor of a double therapeutic purpose: blocking the production of new antibodies and limiting the propagation of inflammatory lesions in the target organs. Thus, glucocorticoids (in combination with cyclophosphamide) end up being one of the pillars of the remission induction treatment, during which is recommended to administer methylprednisolone in pulses of 500–1000 mg/kg for three to five days (although it does not always seem necessary in the case of early initiation of plasmapheresis), followed by oral prednisolone at 1 mg/kg in decreasing doses for six to twelve months, up to a maintenance dose of 10 mg at six months.[12]

Rituximab

It is a chimeric monoclonal antibody, specific for the CD20 transmembrane protein molecule, present in B lymphocytes (in the majority of them) in pre-B stages and mature forms, causing transient and selective depletion of this subpopulation,[13] for approximately 24 weeks, through antibody-dependent and complement-mediated cytotoxicity.[14] As a consequence, the preservation of pro-B cells and plasma cells with terminal differentiation, which do not express CD20, is achieved.[15] Its role in B cell-mediated immune regulation has justified the interest in systemic autoimmune diseases in recent years.

As a treatment in LKS, it has a solid evidence in ANCA-associated vasculitis, with FDA (Food and Drug Administration) approval since 2011 for patients diagnosed with granulomatosis with polyangiitis and microscopic polyangiitis.[14] However, in LKS mediated by immune complexes, particularly in association with SLE, the information is scarce,[16] therefore, its use is based on extrapolation from other clinical conditions.

In SLE, as well as in other systemic autoimmune rheumatic diseases different from rheumatoid arthritis, in which B lymphocytes play a central role in the pathophysiology,[17] its usefulness in patients refractory to conventional therapies has been described, awaiting studies with solid evidence that will consolidate it as a first-line therapeutic option. Regimens in the context of SLE associated with nephritis (Lunar 2012,[18] classes III and IV) or SLE complicated by other conditions (Explorer 2010[19]), in which there is specific involvement of extrarenal organs: hemolytic anemia and thrombocytopenia, joint involvement, association with antiphospholipid syndrome and prevention of recurrence of thrombotic events have been evaluated.[14] All these, in their great majority, are uncontrolled studies in which the corticosteroid-sparing effect is highlighted, without much support for its superiority with respect to other therapies, but allowing it a space in the ACR and EULAR guidelines as a recommendation in refractory cases.[17]

In lupus nephritis, in 2005, Sfikakis et al.[20] showed, in a group of 10 patients with active proliferative LN, that eight of them reached goals of partial remission with a mean of two months, while five achieved complete remission in three months, which was sustained in a period of one year in four patients, associated with glucocorticoids. Less promising results, but in which inferiority is not described, have been observed in therapies combined with cyclophosphamide or mycophenolate mofetil; however, the optimal dosing regimen, the frequency of retreatment, and the combination with other immunosuppressants remain unknown.[15]

On the other hand, SLE-associated DAH is a rare manifestation of the disease which is characterized by high mortality rates, even despite multiple therapies that include pulses of corticosteroids, cyclophosphamide, and plasmapheresis, which also imply a risk of a large number of adverse events.[21] In this context, the use of rituximab has only been evaluated in publications of isolated case reports or small series, in which it takes place after a poor response to cyclophosphamide or if relapse occurs. However, starting it as first-line monotherapy is probably associated with favorable outcomes, based on reports in which the patient presents intolerance or potential toxicity, especially in pancytopenia and gonadal failure.[22]

There are no standardized recommendations on the use of rituximab in relation to the effect it generates on susceptibility to infections and modulation of the immune system (permanent or transient). For this reason, in 2020 the Education Program of the American Society of Hematology proposed: (i) to evaluate the immunization status and vaccinate against encapsulated microorganisms; (ii) assess for hepatitis B infection with surface antigen (HBsAg) and antibody against hepatitis B core antigen (anti-HBc); (iii) document immunoglobulin levels and B cell subsets, with regular follow-up (on average every six months).[23] The above mentioned recommendations arise in the context of the use of rituximab in non-malignant hematological disorders (Tables 1 and 2).

Discussion

According to the current review, there are no randomized clinical studies on the evaluation of renal outcomes and mortality in the context of LKS related to SLE, which is a low-prevalence pathology but with a high morbidity rate and fatal outcome. Despite this, the evidence extracted from studies on DAH and lupus nephritis as independent manifestations of SLE activity seems to favor cyclophosphamide as induction therapy, due to the evidenced impact on mortality and organ-specific outcomes, particularly in its association with corticosteroid pulses.

Table 1 – Drugs and induction doses.[5,10,12,17]

Drugs in induction	
Methylprednisolone	500–1000 mg/d for 3–5 days. Administer in 30 minutes
Cyclophosphamide	15 mg/kg/pulse (reduce in >60 years and kidney disease) - Intravenous 0.5–1 g/m^2 monthly for 6–9 doses - Oral 1–2 mg/kg/d MESNA: 20% of the dose of CYC in hours 0, 4 and 8 (total 60% of CYC)
Rituximab	- 375 mg/m^2/weekly for 4 weeks - 1000 mg IV, weeks 0 and 2
Plasmapheresis	60 ml/kg each session (total 3–5 sessions)

Table 2 – Drugs and maintenance doses.[5,10,12,17].

Drugs in maintenance	
Prednisolone	0.5–1 mg/kg/d for 4 weeks (then, bimonthly decrease)
Cyclophosphamide	Intravenous 0.5–1 g/m^2 quarterly
Rituximab	1000 mg IV, weeks 24 and 26

Other therapies, such as rituximab, lack clinical evidence and their use is based on series and case reports in which they could apparently lead to outcomes similar to those observed with cyclophosphamide, highlighting their better safety profile. The low prevalence of this condition limits the reproduction in randomized clinical studies and for this reason it is considered a second-line therapy in relation with refractoriness or relapse, as well as in case of contraindications for the use of cyclophosphamide. This highlights the need for further research that in a near future will allow to assess the effectiveness and the outcomes for this monoclonal antibody.

With respect to plasmapheresis, there is no evidence so far to justify its use in the SLE scenario, since the studies available to date for the management of lupus nephritis have not shown results that impact mortality or organ-specific outcomes, and although it seems that it may be useful as a steroid-sparing method, this evidence is only applicable in ANCA-associated vasculitis.

Conclusions

It is of vital importance to timely diagnose the clinical course of LKS in patients with SLE, considering that this pathology is a true emergency for the treating physician. Once the diagnostic suspicion has been identified, the start of treatment must be guaranteed without delay, choosing the least morbid therapeutic strategy with the greatest or equal impact on mortality that allows reducing the risk of progression to severe acute respiratory failure and/or renal failure, and even to death. Likewise, it is important to know the management of the complications that can be generated, due to the adverse effects that the patient faces and that must be informed in detail prior to its administration.

The remission rates of the disease are higher than 90% with the current protocols and there are effective second-line therapies for those cases that do not reach it. The universal treatment of LKS related to SLE includes the use of high-dose intravenous corticosteroids. Intravenous cyclophosphamide has been used in 55% and plasmapheresis in 31%. The fact that cyclophosphamide is considered the first-line treatment seems to be associated with increased survival, while plasmapheresis does not seem to influence its outcome; so far, it should be considered as the therapy of choice, awaiting evidence that more strongly supports the implementation of other promising therapies, apparently associated with a lower risk of adverse events.

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Conflict of interest

The authors declare that they have no conflict of interest for the preparation and submission of this article.

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