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Review Article - Meta-analysis

Interstitial lung involvement in systemic sclerosis☆

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ABSTRACT

Introduction: Systemic sclerosis can involve the lung parenchyma leading to serious complications and even death.
Objectives: To describe the most relevant aspects of interstitial lung disease related to systemic sclerosis emphasizing diagnosis and treatment.
Materials and methods: A literature review was performed searching in the databases Medline and EMBASE using the MESH terms «Scleroderma, Systemic", «Lung Diseases, Interstitial» and «Pulmonary Fibrosis»
Results and conclusions: Interstitial lung disease is a common clinical manifestation of systemic sclerosis and one of the main causes of death. Treatment options are limited and have a modest effect in most of the cases.
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Compromiso intersticial pulmonar en esclerosis sistémica

Palabras clave:
Esclerodermia sistémica
Enfermedades pulmonares intersticiales
Fibrosis pulmonar

RESUMEN

Introducción: La esclerosis sistémica puede potencialmente comprometer el parénquima pulmonar llevando a serias complicaciones e incluso a la muerte.
Objetivos: Describir los aspectos más relevantes en cuanto a las generalidades de la enfermedad pulmonar intersticial en esclerosis sistémica, su diagnóstico y tratamiento.
Materiales y métodos: Se realizó una búsqueda de literatura en las bases de datos Medline y EMBASE utilizando los términos Mesh «Scleroderma, Systemic", «Lung Diseases, Interstitial» y «Pulmonary Fibrosis».
Resultados y conclusiones: La enfermedad pulmonar intersticial es una manifestación frecuente de la esclerosis sistémica y una de las principales causas de muerte en los pacientes que la padecen. Las opciones terapéuticas son limitadas y su efecto es, en muchos casos, modesto.
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Introduction

Systemic sclerosis (SSc) is an autoimmune disease that can involve multiple organs in addition to the skin, with the lungs being one of the most frequently affected. The disease has a profound impact on life expectancy, with an increased risk of mortality of 250% in comparison with age- and sex-matched general population.[1] An analysis of the EUSTAR found a 3-year survival rate of 89.3% being the main causes of death interstitial lung disease (ILD) (16.8%), pulmonary arterial hypertension (PAH) (14.7%), cancer (13.1%), primary heart disease (12.0%) and infection (9.1%).[2] This review aims to describe the most relevant aspects of the diagnosis and treatment of interstitial lung disease in systemic sclerosis.

Methods

A literature search was conducted in the Medline and EMBASE databases with no restrictions regarding publication dates. The search was restricted to topic reviews, systematic reviews and original articles in English and Spanish languages, without date limits. The MESH terms used were the following: «Scleroderma, Systemic"[Mesh], «Lung Diseases, Interstitial»[Mesh] and «Pulmonary Fibrosis»[Mesh]. The Boolean operator AND was used for each of the terms.

Results

580 papers were obtained including meta-analyses, clinical trials, reviews and case reports. The most relevant articles were chosen by consensus of the authors considering that they provide information about the topics needed to write this article. Based on the information obtained, a narrative review of the literature was written reviewing general aspects, diagnosis and treatment of interstitial lung disease in systemic sclerosis.

Discussion

Relevance of interstitial lung disease in systemic sclerosis

SSc is a severely incapacitating and life-threatening disease which has a standardized mortality ratio of 3.53 (95% CI 3.03, 4.11; $P<0.0001$), with a mean age at the time of death of 71.4 ± 12.8 years and higher mortality in men.[1,2] Risk factors for decreased survival due to SSc include diffuse cutaneous involvement, SSc nephropathy, cardiac disease, anti-SCL70, anti-RNAP antibodies and pulmonary affection.[3] Interstitial lung disease (ILD) is a frequent manifestation of systemic sclerosis, with a prevalence that varies according to the method by which it is defined, being evident in high-resolution tomography in 85% of patients and less frequently, between 25 and 41%, when its presence is determined by restriction in pulmonary function tests.[4] The prevalence is variable depending on the subtype of systemic sclerosis: 53.4% in the diffuse cutaneous forms and 34.7% in the limited cutaneous forms. Beyond its frequency, the importance of ILD lies in its high mortality, since it accounts for 16% of deaths in individuals with systemic sclerosis displacing renal complications, which a few years ago occupied the first place within the causes of death.[5]

Taking into account the aforementioned, it is of vital importance to make emphasis on timely diagnosis, follow-up and treatment of this serious manifestation in order to impact its unfavorable outcomes.

Screening of interstitial lung disease in systemic sclerosis

High-resolution computed tomography (HRCT) of the chest

Prior to the development of computed axial tomography (CAT), the detection of interstitial lung disease was hindered by the low specificity of the exercise tolerance test, the wide range to define normality in lung function tests based on the age, size and gender[6] and the low sensitivity of the chest radiograph, as well as its lack of precision to determine the extent of parenchymal involvement.[7]

HRCT is a technical adaptation of the conventional CAT which obtains detailed images based on the generation of thin sections of one to two millimeters, and thus allows identifying small structures and detecting subtle anomalies in the lung parenchyma,[8] hence becoming the gold standard for the diagnosis of interstitial lung disease in systemic sclerosis.[9]

The most common tomographic pattern in systemic sclerosis (50–77.5% of cases) is non-specific interstitial pneumonia (NSIP), characterized by irregular infiltrates with ground-glass attenuation, which can be associated with bronchiectasis and bronchiolar ectasis and which, may spare subpleural areas.[10,11,12] The second most frequent pattern is usual interstitial pneumonia (UIP), which is characterized in HRCT by the presence of reticular opacities, traction bronchiectasis and honeycombing, the latter defined as the finding of aggregates of cystic spaces of similar size, between 3 and 10 mm and with well-defined walls. In UIP the infiltrates are typically basal, subpleural and peripheral and it is also possible to find ground-glass infiltrates, but these are less extensive than the reticulation. According to the presence of certain characteristics, the HRCT can be classified into three groups: UIP pattern, possible UIP pattern and inconsistent with UIP pattern.[13] Other less frequent tomographic forms in systemic sclerosis include organizing pneumonia, aspiration pneumonia, alveolar hemorrhage and pulmonary diseases related to certain medications.[11,14]

In addition to the classification by patterns, the HRCT allows to define the extent of parenchymal compromise, being defined as limited when it involves less than 20%, extensive when it affects 20% or more, or undetermined when the percentage is not clear.[15] The cut-off point of 20% was defined as a result of data that have revealed that starting from this point there is increased mortality in patients with systemic sclerosis with pulmonary involvement compared to individuals with systemic sclerosis without this complication.[16] The ten-year survival in the presence of extensive tomographic involvement is only 43%, while in cases with limited involvement, it reaches 67%; in addition, in those limited cases, the mortality does not have an exact correlation with the extent of imaging abnormalities.[16]

In indeterminate cases, in which the percentage affected is not quantifiable by HRCT or the parenchymal involvement is between 10–30 %, it has been proposed the use of the FVC,

which when is lower than 70% of the predicted value, suggests extensive compromise. When the FVC is used for this purpose, the time difference between performing the HRCT and the spirometry should not exceed 90 days.[15,16]

Other imaging techniques

Although the diagnostic performance of HRCT is high, the radiation dose of this diagnostic aid is 5–7 milliSievert (mSv), which is equivalent to between 250 and 350 chest radiographs.[17]

Taking into consideration that the effect of ionizing radiation is cumulative and leads to an increased risk of cancer,[18,19] other imaging methods that rationalize repetitive irradiation in patients with systemic sclerosis and interstitial lung disease, such as HRCT with limited number of sections, nuclear magnetic resonance imaging of the thorax and pulmonary ultrasound have been explored.

HRCT with limited number of sections (reduced HRCT)

It uses only nine sections, the first three at the level of the sternal manubrium, the carina and the lower lobe, with increments of 80 mm between each other, followed by six basal sections with increments of 15 mm, arranged according to the classical distribution with apicobasal gradient of interstitial lung disease in systemic sclerosis. In this way a reduction of 96.2% in the irradiation dose can be achieved, compared with the HRCT, with high accuracy and a sensitivity of 88.3% for the detection of interstitial lung disease.[20,21]

Magnetic resonance imaging of the thorax (MRI)

Even though HRCT is the test with the best diagnostic performance in interstitial lung disease, its usefulness to define areas of active inflammation is limited, since these can have the same appearance of ground glass as certain areas with fibrosis, and may go unnoticed in the middle of a pattern of UIP or fibrotic NSIP.[22] On the contrary, the contrasted T2 sequences in MRI have proven to be useful to detect parenchymal alterations and to differentiate between fibrosis and inflammation. Based on this premise, MRI has been postulated as a potentially useful imaging method in interstitial lung disease in systemic sclerosis, and studies have been conducted in this regard, finding good correlation between the findings in NMR and FVC, DLCO and HRCT, proposing even cut-off points of 0.8% and 5.7% to classify the parenchymal commitment in MRI as limited or diffuse, respectively, although these cut-off points have not yet been validated.

So far, pulmonary MRI is postulated as an alternative to determine the extent of lung parenchymal involvement and to differentiate between inflammation and fibrosis, however, this test has limitations such as the inability to properly define the radiological pattern and the high cost that it implies, and the evidence of its usefulness in interstitial lung disease is still insufficient.[23]

Pulmonary ultrasound

Despite the low penetrance of ultrasound through the air, the predominantly subpleural distribution of the parenchymal commitment in the interstitial lung disease in systemic sclerosis makes pulmonary ultrasound a potentially useful technique.[17]

The interpretation of pulmonary ultrasound is based on the detection of B-lines, defined as vertical hyperechoic artifacts that arise from the pleura and move synchronously with breathing.[24]

A concordance of 83% between ultrasound and HRCT has been demonstrated, and additionally a sensitivity between 83 and 100% and a specificity between 59 and 96% has been found for the detection of interstitial lung disease by ultrasound according to the number of B-lines,[17] being ten B-lines a cut-off point from which the likelihood of interstitial lung disease is high, being worthwhile then to proceed with an HRCT to detail the type of commitment.[25]

F-Fluorodeoxyglucose positron emission tomography scanning (18F-FDG PET/CT)

Increased 18F-FDG uptake has been demonstrated in SSc-ILD lungs compared with normal lung tissue, and the areas of increased uptake correlate with ground glass and reticulation on HRCT; nevertheless, data are limited by the small number of patients and the retrospective design of the studies and further research is required before this technique can be recommended routinely in SSC-ILD.[26]

Pulmonary function tests (PFTs)

ILD manifests itself with a restrictive pattern on pulmonary function tests, represented as follows:

- Spirometry: normal forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) ratio (FEV1/FVC greater than or equal to 70%) in the presence of decreased FVC.[27]
- Lung volumes: total lung capacity (TLC) below the lower limit of normal.[28]
- Diffusing capacity of the lungs for carbon monoxide (DLCO): lower than 70 to 80% in the absence of pulmonary vascular disease.[29,30]

These tests are useful not only for diagnosis, but also for follow-up, in which the clinically significant progression has been defined as:

- Decrease in FVC greater than or equal to 10%
- Decrease of 5–10% in FVC associated with a decline of 15% in DLCO.[31]

Benefits and limitations of PFTs

PFTs have the advantage of being noninvasive and safe but have also limitations: when the comprehensive definition of restriction is based on a TLC less than 80% of predicted, FVC less than 80% of predicted, or DLCO less than 70% of predicted and a normal FEV1/FVC value, the sensitivity is 72.0% but the specificity is just 43.0%.[29] The DLCO is the most sensitive of the PFT but can be adversely affected by factors as emphysema and pulmonary vascular disorders such as pulmonary hypertension.[28]

Six-minute walk test

It is an exercise tolerance test that has been commonly used as an outcome in various clinical studies of lung disease treatment, particularly in pulmonary fibrosis and idiopathic

pulmonary hypertension. In systemic sclerosis-related ILD, however, the interpretation of this test becomes difficult due to the presence of other factors such as pulmonary hypertension, arthralgias/arthritis, myalgias, weakness and peripheral vascular disease which may also contribute to the decreased exercise tolerance.[32] Despite these limitations, there is a demonstrated relationship between an abnormal distance covered (less than 400 m) and an altered delta of oxygen saturation (basal saturation - saturation at the end of the 6 min greater than or equal to four percent) with indexes of dyspnea, positivity for anti-Scl-70 and FVC lower than 80% of predicted.[33] On the contrary, there is no demonstrated relationship between the six-minute walk and the DLCO nor with the extent of parenchymal involvement in the high-resolution chest tomography,[34] and a recent study, which reported an association between this test and the presence of pulmonary hypertension, did not find such relationship with interstitial lung disease.[35]

Bronchoalveolar lavage (BAL)

In healthy individuals the cellularity in the BAL is mainly given by alveolar macrophages, with a small amount of neutrophils (less than three percent), eosinophils (less than two percent), lymphocytes (less than fifteen percent) and respiratory epithelial cells. It has been postulated that an abnormal cellularity in BAL, mainly with neutrophilia, may be an indicator of severity and extension in interstitial lung disease; however, this finding alone is nonspecific and, so far, the evidence is insufficient to recommend this study as a predictor of unfavorable outcomes in systemic sclerosis.[36,37] BAL may also be used to rule out infections, which may coexist with noninfectious ILD or trigger the onset of diffuse lung infiltrates.[38]

Lung biopsy

In surgical lung biopsy, the most frequent histological pattern in systemic sclerosis (77% of cases) corresponds to NSIP, with a predominance of fibrotic NSIP over cellular NSIP.[39] UIP may also be less frequently seen, which, unlike the cases of idiopathic pulmonary fibrosis, manifests itself with more inflammation, a greater amount of germinal centers and fewer fibroblast foci. Other types of histological patterns can be also evidenced but they are much less common than NSIP and UIP.[10]

Although the lung biopsy provides important information, HRCT is in most cases sufficient to determine the presence of NSIP or UIP; there is a high correlation with tissue findings and histopathological confirmation is only necessary in cases in which the images are not conclusive or when clinical manifestations suggest alternative causes of imaging disorders, such as infections or drug toxicity.[40]

Initial assessment and follow-up

Velcro crackles have been proposed as a sign for early diagnosis in IPF and have been proved to be associated with a radiological UIP pattern, making auscultation relevant as an early warning of the presence of a fibrosing ILD.[41]

The factors related to the development and progression of pulmonary fibrosis in systemic sclerosis include a FVC lower than 70% and extensive involvement on HRCT. An initial assessment with spirometry and HRCT allows to group the patients with systemic sclerosis into subtypes of high or low risk of interstitial lung disease. In the low risk group, the follow-up with HRCT is not justified unless there are changes in symptomatology or pulmonary function tests (PFT) during the clinical course. In high risk patients, conversely, it is necessary to carry out a stricter follow-up.[42] While pulmonary function tests are useful to identify advanced cases of interstitial lung disease, they are insufficient for screening, since they have a non-negligible number of false negatives in early stages and in asymptomatic patients.[29] There are different opinions regarding which should be the initial tests to detect interstitial lung disease and how often they should be repeated during follow-up. Taking into account the estimates of risk of progression of ILD according to the extension of the initial involvement, and knowing the insufficient sensitivity of the pulmonary function tests, it is proposed to perform an initial HRCT in all patients with systemic sclerosis. If the tomographic compromise is mild, PFT can be continued every 3–6 months. If the baseline HRCT is normal, clinical follow-up every 3–6 months is recommended to monitor for the onset of cardiopulmonary symptoms. If they appear, PFT should be performed along with HRCT if they are abnormal. On the contrary, in cases of clinical stability, it may be sufficient to perform PFT once a year.[30]

Treatment

The stage, activity and severity of the disease are important factors to decide if therapy should be started and how intense should the treatment be; a “wait and watch” approach is a common and valid option in mild disease cases.[43]

General measures

Supportive care measures such as supplemental oxygen, influenza and pneumococcal vaccinations and pulmonary rehabilitation therapy may be needed in addition to immunosuppressive therapies. Aggressive management of reflux symptoms is also a target given the association between gastroesophageal reflux disease (GERD) and ILD.[44]

Management of gastroesophageal reflux

Although the organic commitment in systemic sclerosis is mainly due to the activation of fibroblasts and the development of fibrosis induced by uncontrolled inflammatory reactions in response to vascular injury and endothelial activation, there is a demonstrated important role of esophageal dysmotility and dilation in the development and progression of interstitial lung disease in systemic sclerosis, and even in the rejection of the graft after lung transplantation. Thus the importance of an aggressive management of reflux in patients with systemic sclerosis and interstitial lung disease.[45–47]

Pharmacologic therapy

Cyclophosphamide: the strongest evidence for this drug comes from a randomized clinical trial (SLS)[48] in which oral cyclophosphamide at doses up to 2 mg/kg/day was compared with placebo for one year finding a difference of 2.53% in FVC and 4.09% in TLC as well as a clinically relevant difference in the traditional dyspnea index and in the HAQ disability

score in favor of CYC. One year after the study concluded, the difference in FVC between the two groups remained[49]; however, an analysis carried out 2 years after the end of the intervention period, showed that the change in FVC and TLC was not maintained, and at this time the only apparent difference was found on the dyspnea index.[50] Although the radiographic change was not included as an outcome in the SLS, the images of the patients of the SLS who had a baseline HRCT and another at the twelfth month were analyzed later, showing that at the end of that period the fibrosis scores were worse in the placebo group.[51] Intravenous CYC has also been studied in systemic sclerosis, with a regime consisting of six monthly infusions of IV CYC 600 mg/m^2, along with prednisolone 20 mg every other day and followed by maintenance with azathioprine (AZA) 2.5 mg/kg/day which, when compared with placebo at twelve months, showed a trend towards statistical significance in the change in FVC and in the infiltrates in HRCT in favor of the intervention, without improvement in the dyspnea scores.[52]

Mycophenolate mofetil (MMF): taken into account the potential toxicity of cyclophosphamide, MMF has been considered as a safer therapeutic alternative. The SLSII compared MMF 1500 mg every 12 h for 24 months with oral CYC 2 mg/kg/day for 12 months followed by 12 additional months of placebo without finding significant differences between the two treatment groups at the end of the two years of intervention.

Although, based on previous studies of extension of the SLS, it was expected that after month 18 there would be a decrease in the effect on FVC in the CYC group, this pattern of behavior was not repeated and, in fact, in the post-hoc analysis, both intervention groups showed an increase in FVC even in month 24.[53]

Based on the SLS II, it can be inferred that MMF is the medication of choice since it is as effective as CYC but it has a more favorable safety profile.

Rituximab (RTX): within the EUSTAR (European Scleroderma Trial and Research) cohort, an analysis was made of patients with FVC less than 70% or fibrosis on HRCT who received at least one cycle of RTX finding that at six months of follow-up the FVC remained stable and the DLCO improved with respect to the initial values, while the controls that did not receive the drug had a significant decrease in the FVC.[54] Daoussis and collaborators compared two cycles of RTX with the standard treatment finding that at one year the FVC and the DLCO increased in the RTX group, while in the control group there was stability and deterioration in these parameters, respectively. It is noteworthy that a significant percentage of patients in both groups were being treated with MMF, which was continued throughout the study.[55] The same author evaluated the effect of two or more semi-annual cycles of RTX, finding that at seven years there was an increase in FVC and stability in the DLCO with RTX while both parameters worsened with the standard therapy (methotrexate, azathioprine or MMF). In those who suspended RTX at some point in the study, a decrease in FVC was documented, which suggests that treatment should not be discontinued.[56] A recent subsequent analysis of the EUSTAR database was performed aiming to include more patients with lung involvement with longer follow-up. With a median follow up of 24.3 months the analysis showed that patients treated with RTX did not have significantly different rates of decrease in FVC > 10% nor in DLCO, which is consistent with the lack of effects of rituximab in patients with SSc and ILD. The observational design of the study was a limitation to provide a robust answer regarding the potential stabilization of ILD following rituximab therapy and this question must be addressed in the future by prospective randomized trials.[57]

Tocilizumab (TCZ): The faSScinate study was a 96-week trial which consisted of a 48-week double-blind period (in which patients were assigned (1:1) to receive weekly subcutaneous injections of tocilizumab 162 mg or placebo with the option of escape therapy with hydroxychloroquine, mycophenolate mofetil or methotrexate after 24 weeks if the SSc had worsened) followed by a 48-week open-label period (continuous-tocilizumab and placebo-tocilizumab groups, respectively). During the first 48 weeks there was a smaller decrease in FVC for tocilizumab than for placebo from baseline to 24 weeks (tocilizumab −34 mL vs. placebo −171 mL; p = 0·0368) but the difference was not significant from baseline to 48 weeks. More patients on placebo had worsening of percent predicted FVC and had more than 10% decrease in percent predicted FVC from baseline at 24 and 48 weeks. During the open-label period from weeks 48–96 no patients experienced >10% decline in %FVC and the proportion of patients with worsening in %FVC was similar for both treatment groups (42% of patients in the placebo-tocilizumab group and 46% of patients in the continuous-tocilizumab group). These results differ from the ones in the double-blind period from weeks 0–48, in which there was a worsening in %FVC in 83% of patients receiving placebo and in 54% of patients receiving tocilizumab.[58,59] Narváez et al. evaluated TCZ for at least 6 months in nine patients with progressive SSc-ILD despite receiving other immunosuppressants. All patients remained on MMF while receiving TCZ and 78% received concomitant treatment with prednisone (≤5 mg/day). At the end of the 12 months median follow-up period only four patients remained on treatment; in the remaining five patients, TCZ was discontinued, mainly due to inefficacy, which make it difficult to draw any firm conclusions regarding TCZ effectiveness.[60] Recently, Khanna et al. presented the results of a phase 3 trial of TCZ vs. placebo for 48 weeks, in which a decline ≥10% in FVC occurred in 5.4% of TCZ-treated and in 16.5% of patients in the placebo group.[61] Some of the aforementioned studies suggest that tocilizumab may have a disease-modifying effect in SSc-associated ILD by slowing the decline in lung function, although it is difficult to draw definitive conclusions since some points were not always met.

Antifibrotic agents: Recently, the results of the SENSCIS study, which compared the antifibrotic agent nintedanib 150 mg every 12 h vs. placebo, in patients with systemic sclerosis and interstitial lung involvement of 10% or more on HRCT were published, finding at week 52 of treatment less deterioration in the FVC in favor of nintedanib (−52.4 ml per year vs. 93.3 ml per year) with a p-value of 0.04 but a wide confidence interval. This study postulates nintedanib as a treatment with beneficial effect in terms of reducing the rate of decline in FVC.[62]

Hematopoietic stem cell transplantation (HSCT)

Three important clinical trials have compared this intervention with different schemes of intravenous CYC: ASSIST,[63] ASTIS[64] and SCOT,[65] the latter with a myeloablative protocol based on total body irradiation.

The ASSIST study showed an improvement with HSCT in different parameters at twelve months follow-up, including changes in FVC and HRCT, which were deteriorated in the CYC group.[63] The ASTIS trial showed an increase in FVC and TLC in the HSCT group and a decline of these parameters in the CYC group[64] and the SCOT trial evidenced a significant improvement at five years in favor of the HSCT in the primary outcome ǵlobal rank composite score" which includes, among others, respiratory failure-free survival and changes in FVC.[65]

Lung transplantation

Lung transplantation in end-stage scleroderma lung disease has been controversial mainly because of concerns that extrapulmonary manifestations would adversely affect survival and because of an increased risk of graft failure related to bronchiolitis obliterans syndrome (BOS) linked to gastroesophageal reflux disease.[66] A retrospective cohort study found an increase in the 1-year post-transplantation mortality rate in patients with SSc when compared to those with non–SSc-related ILD (hazard ratio 1.48 [95% confidence interval 1.01–2.17]) but no difference when compared to those with non–SSc-related PAH. Nevertheless, recent studies have found similar post-transplant survival rates after 1, 3, and 5 years in patients with scleroderma lung disease when compared to age- and gender-matched controls with ILD not due to connective tissue disease.

Conclusions

Interstitial lung disease is a frequent manifestation in systemic sclerosis which, although it may have a variable course, in many cases it has a progressive behavior associated with significant morbidity and mortality. There are different therapeutic strategies ranging from traditional immunosuppressive drugs to hematopoietic stem cell transplantation and antifibrotic agents with variable response and impact mainly on spirometric outcomes.

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