Long-term survival of lung transplantation for interstitial lung disease associated with connective tissue diseases: a study of 26 cases from a referral centre

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Abstract

Objective

Interstitial lung disease (ILD) is a leading cause of mortality in patients with connective tissue diseases (CTD). Lung transplantation has become a viable option for patients with end-stage CTD-ILD. However, patients with CTD are often considered suboptimal candidates for lung transplantation because of concerns of worse outcomes. We assessed post-transplant survival of patients with CTD-ILD compared to patients with idiopathic pulmonary fibrosis (IPF).

Methods

Medical records of patients who underwent lung transplantation for CTD-ILD at a single referral centre for lung transplantation in Northern Spain between 1998 and 2018 were reviewed. This cohort was compared with patients with IPF (group-matched for age ±3.3 years, transplant year and use of basiliximab induction previous to transplant). Cumulative survival rates after transplantation were estimated by the Kaplan-Meier method and compared between groups using the log-rank test.

Results

We studied 26 patients with CTD-ILD and 26 patients with IPF. The underlying diseases of CTD-ILD patients were rheumatoid arthritis (n=9), scleroderma (n=6), Sjögren's syndrome (n=4), ANCA-associated vasculitis (n=3), anti-synthetase syndrome (n=2), and dermatomyositis, systemic lupus erythematosus (1 each). Baseline characteristics were similar in both groups. CTD-ILD patients experienced acute graft rejection less commonly than those with IPF (32.0% vs. 62.5%; p=0.032). However, a non-statistically significant increased frequency of chronic graft rejection was observed in CTD-ILD patients (20.0% vs. 8.3%; p=0.417). In this regard, the 5-year cumulative survival rates after transplantation was reduced in CTD-ILD (42.4% vs. 65.8%) but the difference did not achieve statistical significance (p=0.075).

Conclusion

Long-term post-transplant survival in Northern Spanish patients with CTD-ILD is reduced compared with IPF.

Key words

lung transplantation, interstitial lung disease, connective tissue diseases, rheumatoid arthritis

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Received on May 12, 2019; accepted in revised form on July 22, 2019.

This study was presented in part as an oral presentation at the ACR/ARHP Annual Meeting of Rheumatology held in Chicago in October 2018.

Funding: this work was partially supported by RETICS Programs, RD08/0075 (RIER), RD12/0009/0013 and RD16/0012 from Instituto de Salud Carlos III' (ISCIII) Spain. Competing interests: M.A. Gonzalez-Gay received grants/research support from Abbvie, MSD, Roche, Sanofi, and consultation fees/participation in company sponsored speaker's bureau from Abbvie, MSD, Pfizer, Roche and Sanofi; R. Blanco received grants/research support from Abbvie, MSD and Roche, and consultation fees/participation in company sponsored speaker's bureau from Abbvie, Lilly, Pfizer, Roche, Bristol-Myers, Janssen and MSD; the other co-authors have declared no competing interests.

Introduction

Interstitial lung disease (ILD) represents a group of diffuse parenchymal lung disorders that frequently have no identifiable underlying cause. Its incidence is increasing over the last years (1). In some cases, ILD is associated with connective tissue diseases (CTD). Scleroderma, rheumatoid arthritis (RA) and myositis-antisynthetase syndrome (ASS) are the most common CTD associated with ILD, although all patients with CTD are potentially at risk for developing ILD (2). Noteworthy, ILD is one of the most serious complications associated with CTDs.

Nowadays, there are no global guidelines for the treatment of CTD-associated ILD (CTD-ILD) and many of the currently used treatments are largely ineffective. Conventional therapies for CTD-ILD include a combination of glucocorticoids and glucocorticoid-sparing agents. Immunosuppressive therapies can be beneficial in some patients with CTD-ILD. However, progression to irreversible interstitial lung fibrosis often occurs. With respect to this, there is only limited experience with newer biological and antifibrotic agents in these patients (3-6). Because of that, ILD remains to be a major cause of mortality in patients with rheumatic diseases and lung transplantation becomes the only option for patients in end-stage-ILD.

Although the presence of a rheumatic disease was considered for many years as an absolute contraindication for lung transplant, around 1% of all lung transplants worldwide between 1995 and 2016 were due to patients with CTD-ILD (7). In this regard, the International Society for Heart and Lung Transplantation (ISHLT) guidelines indicate that lung transplantation should be considered an option in patients with a CTD (8). Nonetheless, survival rates of patients with CTD-ILD after lung transplantation are not well known.

Taking all these considerations into account, the purpose of our study was to assess post-transplant survival at 5 years in patients with CTD-ILD and compare post-transplant survival in patients with CTD-ILD with the post-transplant survival in those with idiopathic pulmonary fibrosis (IPF).

Methods

Study design and clinical definitions

We retrospectively reviewed the medical records of all patients who underwent lung transplant between January 1998 and April 2018 at a single referral centre for lung transplant in Northern Spain. For the purpose of the present study we included all patients who underwent lung transplantation in the study period due to CTD-ILD (n= 26 patients). Thus, the CTD-ILD cohort included patients who had been diagnosed with CTD by a rheumatologist.

CTD encompasses a heterogenous group of systemic disorders characterised by autoimmune serologic findings and immune-mediated organ damage. We searched for patients with autoimmune diseases such as RA, systemic SSc, primary Sjögren syndrome (SjS), polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), ASS and ANCA-associated vasculitis (ANCA-v). All CTD diagnosis were made by an experienced rheumatologist and they were retrospectively confirmed according to the available classification criteria for each disorder. Lung involvement in the setting of CTD was assessed by both rheumatologists and pneumologists. A diagnosis of ILD was made based on clinical and radiological findings and pulmonary function test abnormalities. Histological features obtained by lung biopsy confirmed the presence of ILD prior to lung transplantation. In addition, all patients had been evaluated by our lung transplantation medical board and listed for that procedure using standardised protocols.

As a comparison cohort we selected patients with a diagnosis of IPF because of the hypothetical similar spectrum of lung disease and prognosis of both conditions (9-11).

We designed a retrospective study in which we matched our cohort of 26 patients with CTD-ILD to the comparison group of 26 patients with IPF based on age ±3.3 years at transplant, year of transplantation and use of basiliximab induction treatment previous to transplant. Basiliximab is an interleukin (IL)-2 receptor antagonist that has been shown to be safe and effective to reduce the rate of acute and chronic

rejection in lung transplant recipients (12). In our institution, basiliximab was only used in patients with renal failure or severe pulmonary hypertension. After that date, basiliximab has been used per protocol in all patients. To the best of our knowledge, this is the first study that considers this confounding factor to compare cumulative survival rates between CTD-ILD and IPF.

Data collection

Relevant clinical data and laboratory testing were reviewed and verified by our lung transplant team. All data were prospectively gathered and retrospectively analysed. We collected baseline characteristics and transplant features: age, sex, time on waiting list, smoking habit, type of transplantation (unilateral/bilateral), cytomegalovirus (CMV) mismatch and basiliximab induction therapy. We also assessed pulmonary function tests and right catheterisation measurements. Information on treatment with glucocorticoids and/or immunosuppressive drugs received by the patients before lung transplantation was also included in the analysis. Besides, we reviewed the histological pattern on lung pathology specimens of the explant of each patient.

Our primary outcome measure was survival at 5 years. Survival was measured as time from transplant to death or censor date (April 30, 2018). We also collected data on additional allograft outcomes, including development of acute and chronic allograft rejection.

The study was approved by the Local Institutional Review Board (IRB No. 2018-110).

Statistical analysis methods

All continuous variables were tested for normality, and results were expressed as mean ± SD or as median and interquartile range (IQR) as appropriate. Student's t-test or Mann-Whitney U-test were used to compare continuous variables, and chi-squared test for categorical variables. Patient survival was depicted using Kaplan-Meier methods. Differences across groups (CTD-ILD *vs*. IPF) were determined using log-rank test. A p-value <0.05 was considered as statistically significant in all the calculations. Data management and analysis were performed using SPSS Statistics for Windows, v. 18.0 (SPSS Inc, Chicago, IL, USA) (13).

Table I. Comparison of baseline characteristics, lung transplant features and allograft outcomes between the study groups.

Variables	IPF (n=26)	CTD-ILD (n=26)	*p-value*
General characteristics			
Age (years), median [IQR]	60.0 [57.0-65.0]	58.0 [50.0-63.0]	0.06
Sex (women), n (%)	6 (23.1)	18 (69.2)	**0.001**
Time on waiting list (days), mean ± SD	151.7 ± 159.6	127.0 ± 119.8	0.55
Smokers, n (%)	19 (73.1)	11 (42.3)	0.07
Type of transplantation (bilateral), n (%)	8 (30.8)	13 (50.0)	0.16
CMV positive donor and CMV negative recipient, n (%)	4 (15.3)	2 (7.7)	0.72
Basiliximab induction therapy, n (%)	9 (34.6)	9 (34.6)	0.99
Variables at transplant			
FEV 1 (%), mean ± SD	55.7 ± 19.1	50.1 ± 15.6	0.27
FVC (%), mean ± SD	52.7 ± 15.8	54.7 ± 15.9	0.66
FEV1/FVC, mean ± SD	80.4 ± 11.6	77.6 ± 16.8	0.50
DLCO, mean ± SD	31.0 ± 14.3	34.9 ± 17.8	0.48
KCO, mean ± SD	62.8 ± 20.5	65.1 ± 23.6	0.54
Serum creatinine (mg/dL), mean ± SD	0.79 ± 0.19	0.85 ± 0.31	0.75
Right catheterisation, n (%)			
mPAP (mm Hg), median [IQR]	23.0 [19.0-26.0]	23.0 [20.0-31.0]	0.50
PCP (mm Hg), mean ± SD	13.3 ± 2.7	12.0 ± 4.7	0.32
Treatment pre-transplant			
Glucocorticoids, n (%)	20 (76.9)	23 (88.5)	0.22
Immunosuppressive drugs, n (%)	7 (26.9)	21 (80.8)	**0.001**
Allograft dysfunction			
Acute rejection	15 (62.5)	8 (32.0)	**0.032**
Chronic rejection	2 (8.3)	5 (20.0)	0.417

CMV: cytomegalovirus; CTD-ILD: interstitial lung disease related with connective tissue diseases; DLCO: diffusing capacity of lung for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; IFP: idiopathic pulmonary fibrosis; IQR: interquartile range; KCO: transfer coefficient of the lung for carbon monoxide; n: number; RA-ILD: interstitial lung disease related with rheumatoid arthritis; mPAP: mean pulmonary arterial pressure; PCP: pulmonary capillary pressure; SD: standard deviation.

Results

In our centre, up to May 2018, a total of 585 patients underwent lung transplantation. Among them, only 26 transplants were performed to CTD-ILD patients. Therefore, it represented a 4.44% of the total of lung transplants performed in our institution. For the purpose of the present study we included 52 patients (all the patients with CTD-ILD and 26 patients with IPF diagnosis) with a mean age of 58.5±4.2 years.

The underlying diseases in the CTD-ILD cohort were RA in 9 patients (34.6 %), SSc in 6 (23.1%), primary SjS in 4 (15.4%), ANCA-v in 3 (11.5%), ASS in 2 (7.7 %), DM in 1 (3.7%) and SLE in 1 (3.7%).

The baseline characteristics and clinical variables of the two groups are shown in Table I. There were no differences in the age between both groups. Compared with IPF patients, the group of CTD-ILD included a slightly lower percentage of smokers but they were predominantly women. Time on waiting list of transplants was similar in both groups.

With regard to the transplant features, no significant differences were seen in the type of transplant (unilateral or bilateral) and CMV-mismatch in both groups. One third of the patients in both groups received basiliximab induction therapy prior to transplant.

With respect to the baseline pulmonary function tests at the time of transplant, there were no significant differences between the two groups in forced vital capacity (FVC) nor forced expiratory volume in one second (FEV1)/FVC ratio. Decreased diffusing capacity of lung for carbon monoxide (DLCO) and transfer coefficient of the lung for carbon monoxide (KCO) were observed in both groups (Table I).

Right catheterisation was performed in most patients before lung transplanta-

tion to identify the presence of pulmonary hypertension. The mean pulmonary artery pressure and pulmonary capillary pressure were similar in both groups (Table I).

Most patients from both groups were receiving glucocorticoids at the time of transplantation. However, a significantly higher percentage of patients with CTD-ILD received immunosuppressive drugs before transplantation. The immunosuppressive drugs used in the CTD-ILD cohort were methotrexate (15.6%), mofetil mycophenolate (15.6%), TNF-α inhibitors (15.6%), azathioprine (15.6%), cyclophosphamide (15.6%), rituximab (9.4%), leflunomide (9.4%) and antimalarial drugs (3.1%).

In assessing lung histology of pulmonary explants, we found that all patients with a diagnosis of RA who underwent lung transplantation showed the histological subtype of usual interstitial pneumonia (UIP) whereas non-specific interstitial pneumonia (NSIP) was the most common histological subtype of ILD associated with the remaining CTD patients (Fig. 1).

Patients with CTD-ILD experienced acute graft rejection less commonly that those with IPF (32.0% *vs*. 62.5%; p=0.032). However, a non-statistically significant increased frequency of chronic graft rejection was observed in the group of CTD-ILD patients when compared with those with IPF (20.0% *vs*. 8.3%; p=0.417) (Table I). In this regard, the 5-year cumulative survival rates after transplantation was reduced in CTD-ILD when compared to IPF (42.4% *vs*. 65.8%) but the difference did not achieve statistical significance (p=0.075)] (Fig. 2).

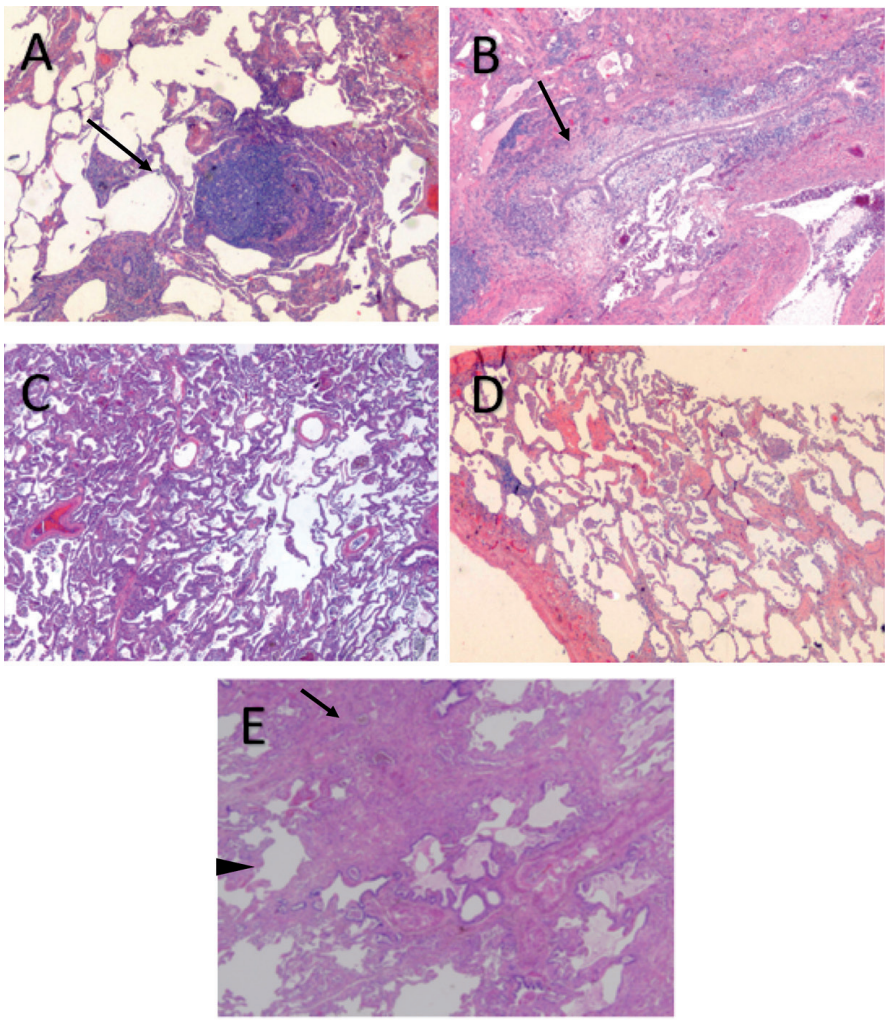

Fig. 1. Lung pathology specimens.
A: Interstitial lung disease related to rheumatoid arthritis. Collagen fibrosis with peribronchiolar lymphoid hyperplasia (follicular bronchiolitis) (arrow) (H&E original magnification 10x).
B: Interstitial lung disease related to rheumatoid arthritis. Immature collagen fibrosis with peribronchiolar lymphoid infiltrate and luminal stenosis (arrow) (H&E original magnification 10x).
C: Cellular non-specific interstitial pneumonia (NSIP) in CTD-ILD characterised by diffuse expansion of interstitium by a cellular infiltrate of lymphocytes (H&E original magnification 10x).
D: Fibrotic NSIP in CTD-ILD showing a diffuse pattern with interstitial thickening due to mature collagen fibrosis (H&E original magnification 10x).
E: Usual interstitial pneumonia (UIP) in a patient with idiopathic pulmonary fibrosis showing mature collagen fibrosis (arrow) with areas of fibroblast proliferation (arrowhead), distortion of lung architecture and few inflammatory cells (H&E original magnification 10x).

Discussion

Despite lung transplantation has been established as a safe and effective treatment for end-stage ILD, patients with CTD-ILD are often considered suboptimal candidates for this therapeutic procedure for fear of their overall risk profile as well as uncertainty about the outcomes and management of the CTD after transplantation.

Literature about the outcomes of lung transplant for CTD-ILD is scarce and most data are based on studies in SSc. Up to now, the only large series focused on the outcomes of lung transplant in patients with CTD-ILD was published by Takagishi *et al*. in 2012 (14). In this work, the authors conducted a retrospective review and compared the survival outcomes of 284 patients with CTD-ILD, 6720 patients with chronic obstructive pulmonary disease (COPD) and 4190 cases with IPF. The cohort of CTD-ILD included patients with SSc (61.2%), RA (12.7%), PM/DM (12%), mixed connective disease (7.7%), SLE (4%) and SjS (2.5%). The cumulative survival of patients with CTD-ILD was lower than that for patients with COPD at 30 days and 6 months, and 1, 2, 3 and 5 years. However, when patients with CTD were compared with those with IPF, the only difference was observed at 1 year. No significant differences were seen in survival rates at 5 years between patients with CTD-ILD and IPF (46.1% *vs*. 46.6%).

In keeping with these results, a recent study published by Park *et al*. (15) reported similar survival rates between patients with CTD-ILD and IPF at 5

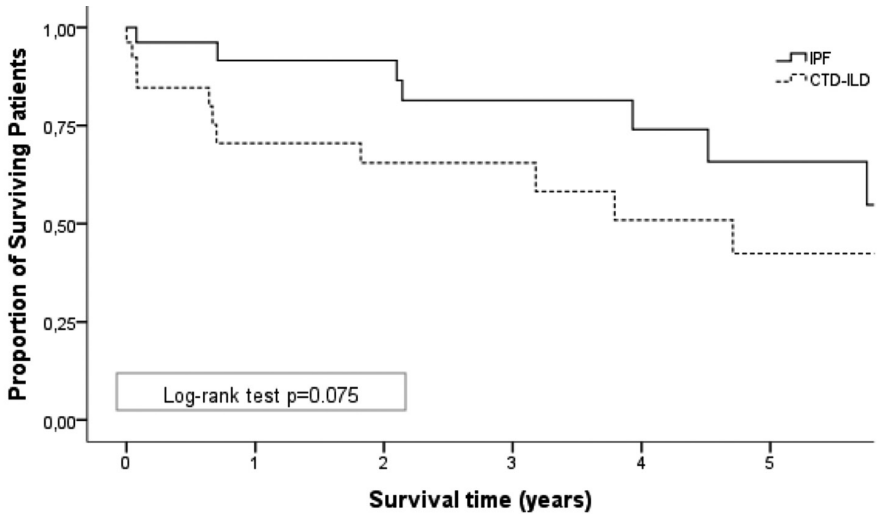

Fig. 2. Kaplan-Meier survival curves 5 years after lung transplantation. CTD-ILD: connective tissue disease-interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

years. The authors compared retrospectively 15 patients with CTD-ILD with 15 patients with IPF matched by age and sex from a single care centre of South Korea in a 6-year period. The CTD-ILD cohort included patients with DM/PM (33.3%), RA (26.7%), SSc (20.3%) and SLE, SjS and undifferentiated connective disease (6.7% each one). There were no differences in the cumulative survival rates between patients with CTD-ILD and those with IPF over the subsequent 60 months after transplantation (log-rank p=0.613). They also reported no significant differences in the incidence of primary graft dysfunction between both groups. There are also some comparative studies on non-SSc-CTD-ILD patients. In this regard, Courtwright *et al*. conducted a retrospective study comparing the cumulative survival in patients with non-SSc-CTD-ILD and patients with IPF (16). They assessed 275 patients with non-SSc-CTD-ILD and 6346 patients with IPF who underwent lung transplantation in the United States between 2005 and 2016. The non-SSc-CTD-ILD cohort included patients with mixed connective disease (29.8%), RA (24.7%), PM (18.5%), SjS (9.5%), SLE (8.7%), DM (2.5%) and other CTDs (4.4%). No significant differences in survival, acute o chronic rejection, or extrapulmonary organ dysfunction between patients with non-SSc-CTD-ILD and IPF were found. The adjusted survival by age, sex, mechanical respiratory/ECMO support at transplant and procedure type did not show differences between both groups.

In our study, the 5-year cumulative survival rate after lung transplantation for CTD-ILD patients was reduced. Patients with CTD have higher comorbidity than the general population and it is possible that it may be an explanation for our results. In this regard, CTD are associated with increased risk of cardiovascular disease. Higher awareness of this complication among clinicians may lead to better management of comorbidities and to an increased survival of these patients. In keeping with our findings, a trend to lower survival in patients with CTD-ILD was also observed within the first 6 months after lung transplant in the above-mentioned study by Takagishi *et al*. (14). In this study, the authors also speculated that increased rate of comorbidities among CTD-ILD patients may predispose to higher risk of transplant failure or death. In addition, they stated that an increased early mortality after lung transplantation in CTD could be due to a higher requirement of immunosuppressive drugs prior to transplant, leading to increased rate of infection in the immediate post-operative period.

In line with the above, there are some concerns about worse outcomes in terms of allograft dysfunction, and a higher risk of allograft rejection in patients with CTD-ILD after lung transplantation due to the underlying immune dysregulation in this population. These concerns came from renal transplantation studies that disclosed increased rates of allograft rejection in patients with SLE (17, 18). However, previous studies on lung transplantation did not show increased risk of allograft rejection in patients with CTD-ILD (14, 16). Although in our series patients with CTD-ILD experienced acute graft rejection less commonly that those with IPF, other apparent differences between CTD-ILD and IPF were not statistically significant. With respect to this, the frequency of chronic graft rejection was non-significantly increased in CTD-ILD patients when compared with those with IPF. This fact may be a possible explanation for the non-significantly decreased long-term survival rates in our patients with CTD-ILD. In this regard, it is known that chronic lung allograft dysfunction is associated not only with the frequency and severity of acute rejection episodes but also with graft infection/colonisation by several difficult organisms such as pseudomonas or aspergillus. In this sense, it would have been interesting to know whether these infections were more frequent in CTD patients who reached lung transplantation after different immunosuppressive treatment courses than in IPF patients who required lung transplantation. Unfortunately, due to the retrospective nature of our study, this information was not available.

The relatively small number of patients with CTD included in the present report may be a potential limitation. However, we matched our patients for relevant confounding factors to a very similar population of IPF patients, which strengthened the comparative power of our study. In addition, the monocentric design of the study with the inclusion of homogeneously evaluated consecutive patients with CTD who underwent lung transplant reinforces the relevance of our study.

In conclusion, Spanish patients with CTD-ILD showed a trend for lower long-term post-transplant survival compared with those with IPF. Nevertheless, lung transplantation appears to be feasible in patients with CTD. Prospective studies with group-matched

populations are needed to determine outcomes in patients with CTD-ILD with respect to other lung diseases with well-established indications for lung transplantation.

Acknowledgements

We thank all the staff, physicians, nurses and assistants of the Thoracic Surgery and Transplant Unit for their interest and collaboration during all these years.

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