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Steroid Avoidance After Adult Living Donor Liver Transplant: A Cohort Analysis

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Background. Although steroid avoidance (SA) has been studied in deceased donor liver transplant, little is known about SA in living donor liver transplant (LDLT). We report the characteristics and outcomes, including the incidence of early acute rejection (AR) and complications of steroid use, in 2 cohorts of LDLT recipients. **Methods.** Routine steroid maintenance (SM) after LDLT was stopped in December 2017. Our single-center retrospective cohort study spans 2 eras. Two hundred forty-two adult recipients underwent LDLT with SM (January 2000–December 2017), and 83 adult recipients (December 2017–August 2021) underwent LDLT with SA. Early AR was defined as a biopsy showing pathologic characteristics within 6 mo after LDLT. Univariate and multivariate logistic regressions were performed to evaluate the effects of relevant recipient and donor characteristics on the incidence of early AR in our cohort. **Results.** Neither the difference in early AR rate between cohorts (SA 19/83 [22.9%] versus SM 41/242 [17%]; $P=0.46$) nor a subset analysis of patients with autoimmune disease (SA 5/17 [29.4%] versus SM 19/58 [22.4%]; $P=0.71$) reached statistical significance. Univariate and multivariate logistic regressions for early AR identified recipient age to be a statistically significant risk factor ($P<0.001$). Of the patients without diabetes before LDLT, 3 of 56 (5.4%) on SA versus 26 of 200 (13%) on SM needed medications prescribed for glucose control at the time of discharge ($P=0.11$). Patient survival was similar between SA and SM cohorts (SA 94% versus SM 91%, $P=0.34$) 3 y after transplant. **Conclusions.** LDLT recipients treated with SA do not exhibit significantly higher rates of rejection or increased mortality than patients treated with SM. Notably, this result is similar for recipients with autoimmune disease.(Transplantation Direct 2023;9: e1488; doi: 10.1097/TXD.0000000000001488.)

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Traditionally, corticosteroids have been prescribed in immunosuppression (IS) regimens for liver transplant recipients. However, as chronic corticosteroid use is associated with many side effects, including obesity, hypertension, diabetes, and infection, it has led many to question whether steroids are necessary for adequate IS in deceased donor liver transplant recipients. Little is known about the effects of steroid avoidance (SA) after adult-to-adult living donor liver transplant (LDLT), and data surrounding the need for steroid maintenance (SM) in LDLT recipients with multiple risk factors for rejection after transplant, such as in autoimmune (AI) disease, are conflicting.[1-7] Given the steady increase in LDLT during the past 2 decades[8] and the frequency of risk factors for rejection in LDLT candidates, the impact of SA on these transplant recipients needs to be determined.

We stopped routine SM for 2 reasons. First, the risk of bile leak after LDLT is not insignificant.[9] Second, the success of SA in kidney transplantation was established.[10,11] In this study, we sought to evaluate the relationship between SA and early acute rejection (AR) in a cohort of LDLT recipients at our single center. Because we stopped routine SM after LDLT in 2017, we compared transplant outcomes in LDLT recipients who received SA versus those who received SM. Additionally, we performed a subgroup analysis to evaluate the safety of SA in transplant recipients with AI liver disease, such as primary biliary cholangitis, primary sclerosing cholangitis, and AI hepatitis.

PATIENTS AND METHODS

Patient Cohorts

The Institutional Review Board at the University of California, San Francisco, approved this study. All adult-to-adult LDLT recipients who underwent transplantation between 2000 and 2021 at the University of California, San Francisco, were included. A total of 24 patients in our SM cohort were excluded. Nine patients were excluded on the basis of the remote nature of their transplant and the resultant missing data in our electronic health record, 7 patients received a domino liver transplant, and 8 patients were retransplanted after LDLT within the first 6 mo. Of the 8 patients who were retransplanted, 7 patients had early hepatic artery thrombosis and 1 patient experienced primary nonfunction. A total of 5 patients in our SA cohort were excluded. One patient was excluded because they received simultaneous-liver kidney transplantation, 2 patients received steroids routinely before transplant for a medical condition that were continued post-transplantation, and 2 patients were retransplanted within the first 6 mo because of early hepatic artery thrombosis.

All patients, irrespective of the planned postoperative steroid plan, received a uniform intraoperative dose of intravenous steroids (methylprednisolone 500 mg) for induction with no other immunosuppressive induction adjuncts. Patients in the SA cohort were given a single dose of 500 mg of methylprednisolone in the operating room and then no steroids after transplant. The recipients before this systems change also received SM after transplant (a steroid taper postoperatively down to 5 mg of prednisone daily). Maintenance IS for both cohorts also included a relatively uniform dose of mycophenolate mofetil (1000 mg twice a day) started on postoperative day 1 and tacrolimus (serum trough goal 8–10 μg/L) started on postoperative day 1 or 2. The doses of these medications were reduced as needed in response to intolerances. Generally, during the first 6 mo maintenance, IS was gradually reduced to achieve a tacrolimus goal closer to 6 to 8 μg/L and mycophenolate mofetil dose of 500 to 750 mg BID. Maintenance IS goals were not different for patients in the SM versus SA cohorts.

Data Collection

The following recipient characteristics were collected: age, gender, body mass index, cause of liver disease, history of diabetes, and relationship to the donor. Donor-specific information, including age and gender, was also collected. Pathologic specimen notes were reviewed to determine whether a biopsy had been performed. All biopsies were performed on the basis of clinical indication only. Surveillance biopsies for patients with hepatitis C in the predirect acting antiviral era were done 1 y after transplant and thus fell outside the window of this analysis.

Early AR was defined as the presence of a biopsy demonstrating histologic features of rejection within 6 mo after transplant. Rejection was classified as mild, moderate, or severe by the reading pathologist. The number of biopsies each recipient underwent within the first 6 mo after transplant and the duration from transplant to biopsy-proven early AR, if indicated, were collected. Secondary outcomes included the need for treatment of diabetes with oral antihyperglycemics or insulin, acute cytomegalovirus (CMV) infection, and recipient survival at 6 mo. Duration of hospital stay was defined as the time of transplant to discharge.

Statistical Methods

Continuous variables were summarized using means and standard deviations and categorical variables were summarized using counts and percentages. Two-sample *t* tests with equal variances were used to compare continuous variables and Pearson's chi-square tests were used to compare categorical variables. For subgroup analysis of recipients with AI disease, nonparametric tests were used, given the small sample size. Kruskal-Wallis tests were used to compare continuous variables and Fisher exact tests were used to compare categorical variables. Univariate logistic regressions were performed to evaluate the association between relevant clinical characteristics and early AR. Multivariate logistic regression was performed using variables with a P value of <0.1 in the univariate logistic regression. Unadjusted and adjusted odds ratios (ORs) were reported along with 95% confidence intervals (CIs). Survival analyses were performed using Kaplan-Meier curves, and differences were assessed using log-rank tests.

RESULTS

Recipient and Donor Characteristics

Three hundred fifty-four adult-to-adult LDLTs were performed during the study period. A total of 325 LDLTs met the inclusion criteria: 83 patients (25.6%) with SA and 242 patients (74.4%) with SM. Baseline donor and recipient characteristics for each cohort are presented in Table 1. Recipient

TABLE 1.

LDLT recipient and donor characteristics

	SA; n = 83	SM; n = 242	*P*
Age (y)	56 (11.8)	54 (10.9)	0.15
Sex			
Male	41 (49.4%)	120 (49.6%)	0.98
Ethnicity			0.98
White, non-Hispanic	51 (61.4%)	147 (60.7%)	
Black, non-Hispanic	2 (2.4%)	7 (2.9%)	
Asian, non-Hispanic	8 (9.6%)	19 (7.9%)	
Hispanic, Latino	21 (25.3%)	65 (26.9%)	
Other	1 (1.2%)	4 (1.7%)	
Cause			<0.001
NASH	27 (32.5%)	14 (5.8%)	
Alcoholic cirrhosis	14 (16.9%)	51 (21.1%)	
Hepatitis C	13 (15.7%)	60 (24.8%)	
PSC	12 (14.5%)	28 (11.6%)	
PBC	4 (4.8%)	20 (8.3%)	
AIH	1 (1.2%)	10 (4.1%)	
Other	12 (14.5%)	59 (24.4%)	
BMI	27.2 (5)	27 (4.9%)	0.80
Liver lobe received			<0.001
Right	76 (91.6%)	154 (63.6%)	
History of diabetes	27 (32.5%)	41 (16.9%)	0.003
Related to donor	43 (51.8%)	171 (70.7%)	0.002
Donor age (y)	37.6 (12)	35.8 (10.3)	0.17
Donor sex			
Male	36 (43.4%)	121 (50%)	0.30

Quantitative variables are presented as mean ± standard deviation. Qualitative variables are presented as n (%).

AIH, autoimmune hepatitis; BMI, body mass index; LDLT, living donor liver transplant; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SA, steroid avoidance; SM, steroid maintenance.

age, sex, body mass index, and donor age and sex were similar between both groups. Patients in the SA cohort were more likely to receive a right lobe (SA 91.6% versus SM 63.6%, $P<0.001$), as expected because of the transplant era. Patients treated with SA were more likely to have a history of diabetes before transplant (SA 32.5% versus SM 16.9%, $P=0.003$) and less likely to receive a liver from a related-family member (SA 51.8% versus SM 70.7%, $P=0.002$). Additionally, as expected on the basis of the date of the transplant era, recipients with SA were more likely to have nonalcoholic steatohepatitis, whereas recipients with SM were more likely to have hepatitis C.

Early AR

The difference in the incidence of early AR between the SA and SM groups did not reach statistical significance (22.9% versus 17%, respectively; $P=0.46$; Table 2). Mild rejection was the most common classification of rejection among both groups (SA 13.2% versus SM 8.7%). Among those with early AR, the average time to rejection was 49.5 d in the SA group and 44 d in the SM group ($P=0.69$). The incidence of early AR in recipients with AI disease in each cohort (17 in the SA group and 58 in the SM group) revealed similar findings (SA 29.4% versus SM 22.4%, $P=0.58$; Table 3). The incidence of early AR in recipients with non-AI disease was not different between cohorts (SA 21.2% versus SM 15.2%, $P=0.26$).

With univariate logistic regression analyses, the only statistically significant factor was recipient age at the time of transplant (OR 0.95; 95% CI, 0.93-0.98; $P<0.001$; Table 4). Additionally, although not statistically significant, the odds of early AR were 40% lower if the donor and recipient were related (OR 0.6; 95% CI, 0.34-1.07; $P=0.08$). In the multivariate logistic regression model, the recipient's age at the time of transplant remained significant. There was a 5% reduction in the odds of early AR for every year increase in age at baseline, controlling for relation to the donor (adjusted OR 0.95; 95% CI, 0.93-0.98; $P<0.001$; Table 4). As with AI, age is commonly cited as a risk factor for AR. Subanalysis of recipients by age demonstrated similar rates of early AR between SA and SM if patients were <65 or ≥ 65 y of age (Table S1, SDC, http://links.lww.com/TXD/A529).

TABLE 2.

Outcomes comparing SA and SM in LDLT recipients

	SA; n = 83	SM; n = 242	P
Biopsies <180 d	0.76 (1.1)	1.14 (1.3)	0.02
Rejection	19 (22.9%)	41 (17%)	0.46
Mild	11 (13.2%)	21 (8.7%)	
Moderate	7 (8.4%)	19 (7.9%)	
Severe	1 (1.2%)	1 (0.04%)	
Time to rejection (d)	49.5 (48.6)	44 (49.1)	0.69
Length of stay (d)	12.3 (9.1)	13.9 (12.9)	0.28
<180 d			
Readmissions	1.2 (1.4)	1.5 (1.6)	0.19
CMV infection	5 (6.3%)	11 (3.5%)	0.12
New-onset diabetes at discharge	3 (5.4%)	26 (13%)	0.11

Quantitative variables are presented as mean ± standard deviation. Qualitative variables are presented as n (%).
CMV, cytomegalovirus; LDLT, living donor liver transplant; SA, steroid avoidance; SM, steroid maintenance.

TABLE 3.

Outcomes comparing SA and SM in LDLT recipients with AI liver disease

	SA; n = 17	SM; n = 58	P
Biopsies <180 d	0.8 (1.2)	0.9 (1.1)	0.51
Rejection	5 (29.4%)	13 (22.4%)	0.58
Mild	2 (11.8%)	4 (6.9%)	
Moderate	2 (11.8%)	8 (13.8%)	
Severe	1 (5.9%)	1 (1.7%)	
Time to rejection (d)	41.6 (34.2)	33.3 (47.4)	0.73
Length of stay (d)	10.6 (3.9)	12.9 (10.2)	0.44
<180 d			
Readmissions	1.4 (1.2)	1.3 (1.4)	0.38
CMV infection	1 (6.2%)	3 (5.6%)	0.99
New-onset diabetes at discharge	0 (0%)	6 (11.1%)	0.32

Quantitative variables are presented as mean ± standard deviation. Qualitative variables are presented as n (%).
AI, autoimmune; CMV, cytomegalovirus; LDLT, living donor liver transplant; SA, steroid avoidance; SM, steroid maintenance.

TABLE 4.

Univariate and multivariate analysis for AR in LDLT recipients

Characteristic	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Steroid use	0.67 (0.36-1.25)	0.20		
Recipient				
Age	0.95 (0.93-0.98)	<0.001	0.95 (0.93-0.98)	<0.001
Female	0.94 (0.53-1.65)	0.82		
Alcoholic liver disease	1.40 (0.54-3.73)	0.49		
NASH	1.42 (0.47-4.14)	0.52		
Hepatitis C	1.15 (0.43-3.30)	0.78		
PBC	1.28 (0.33-4.57)	0.71		
PSC	1.84 (0.64-5.56)	0.26		
AIH	1.08 (0.14-5.57)	0.93		
Other cause of liver disease	0.71 (0.24-2.13)	0.52		
Right lobe received	1.41 (0.75-2.79)	0.31		
Donor				
Related	0.60 (0.34-1.07)	0.08	0.64 (0.35-1.15)	0.13
Age	1.00 (0.98-1.03)	0.79		
Female	1.13 (0.64-2.00)	0.67		
Length of stay	0.99 (0.96-1.02)	0.53		

AIH, autoimmune hepatitis; AR, acute rejection; CI, confidence interval; LDLT, living donor liver transplant; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Postoperative Outcomes

The overall length of hospitalization after transplant, the number of readmissions within the first 6 mo, and the percentage of patients with CMV infection within the first 6 mo were similar among both cohorts (Table 2). Recipients in the SM cohort had a trend toward increased risk of requiring medications for glucose control after transplant compared with recipients with SA, even when excluding recipients with a known diagnosis of diabetes before transplant (SA 5.4% versus SM 13%; $P=0.11$). Similar findings were seen in recipients with AI disease (SA 0% versus SM 11.1%; $P=0.32$; Table 3).

Patient Survival

Patient survival did not differ at 1 and 3 y after transplant between SA and SM cohorts ($P=0.34$; Figure 1A). Subanalysis of

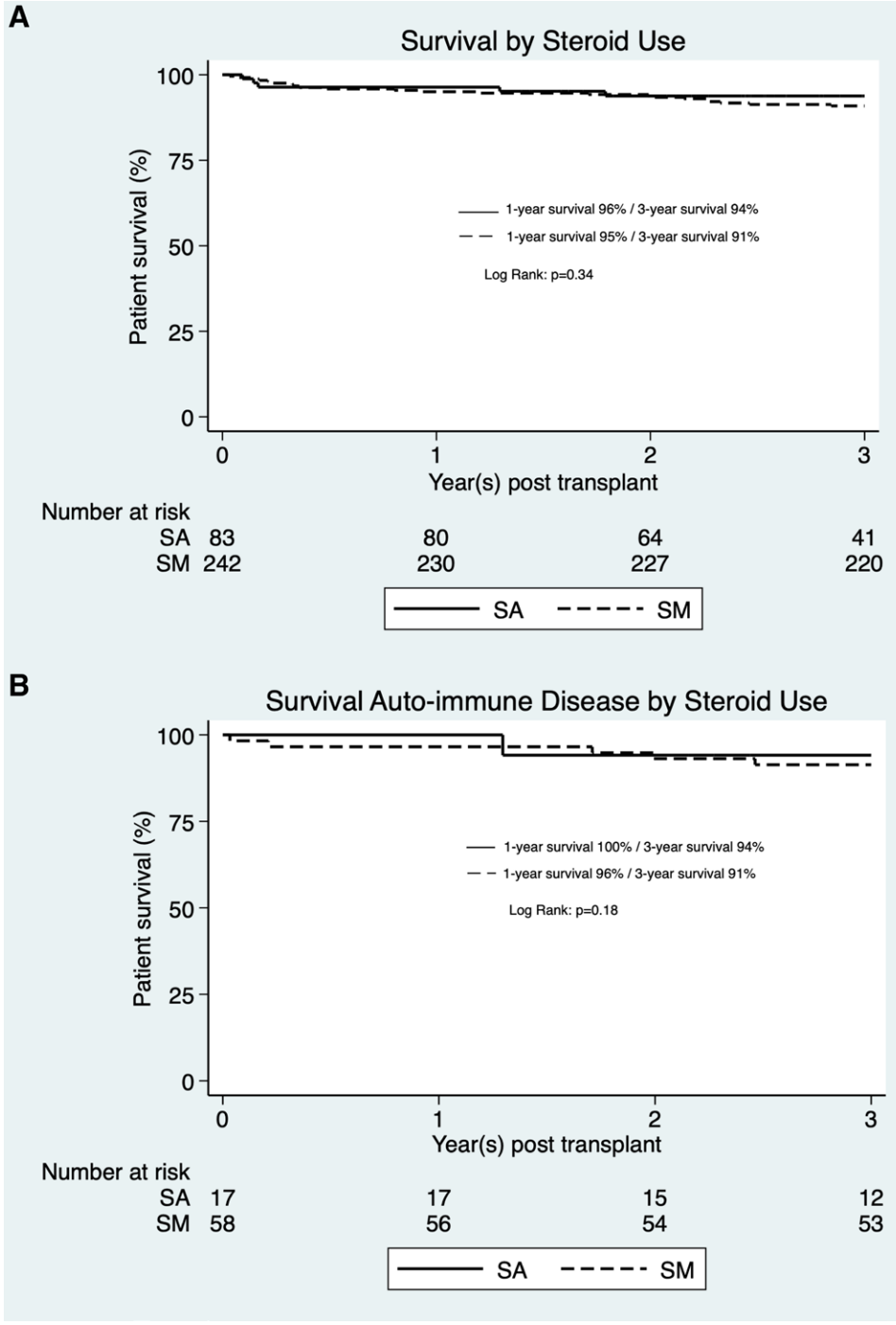

FIGURE 1. Kaplan-Meier curves for 3-y survival after transplantation. A, All transplant patients. B, Only patients with AI disease. The numbers in the bottom part of the figure depict the "number at risk." SA, steroid avoidance; SM, steroid maintenance.

patient survival between SA and SM cohorts for only recipients with AI disease revealed similar findings ($P = 0.18$; Figure 1B).

CONCLUSION

The purpose of this study was to compare the rate of early AR among recipients who underwent LDLT followed by SA or SM. The incidence of early AR in our cohort is similar to existing reports, including a large multi-institutional study showing biopsy-proven early AR in approximately 27% of LDLT recipients.[12] We report 3 main findings. First, SA after transplantation did not significantly affect the incidence of early AR in our cohort of LDLT recipients, and when rejection occurred, the time to rejection and severity were similar to recipients who received SM. Furthermore, no patient in either cohort experienced graft loss during the study period secondary to rejection. Second, SA after transplant did not significantly influence the incidence of early AR in recipients with AI liver disease. Third, patients on SA and SM had similar survival 3 y after transplantation.

Data from previous studies suggest that SA may be as safe as a steroid-based regimen.[13-15] However, most studies investigating SA after liver transplantation have focused on recipients

who receive deceased donor organs. In 2008, Segev et al[13] published a meta-analysis and meta-regression of over 19 randomized trials comparing SA with SM IS regimens after liver transplantation. All 19 trials included only recipients who received deceased donor organs. When steroids were avoided, there were no differences in death, graft loss, or infection, and there was a significantly decreased risk of recipients developing hypertension and elevated cholesterol levels posttransplant. Additionally, Fairfield et al[15] published a Cochrane review, which included data from 17 randomized trials comparing SA with SM IS regimens after liver transplantation. This study revealed similar findings to Segev et al[13] in that there were no differences in death, graft loss, or infection when steroids were avoided, but there was a decreased risk of developing diabetes and hypertension. This study also evaluated the risk of AR and concluded that there was low-quality evidence of increased rejection with SA versus SM-based IS. One limitation of these comprehensive reviews is the small number of patients with AI disease in these randomized control trials, making it difficult to infer if this practice of SA is safe for recipients with AI disease.

To our knowledge, there are few studies demonstrating the safety of SA after LDLT. These studies, however, are limited in disease cause, including few patients with AI disease.[1-4] Two studies on SA after LDLT come from Marubashi et al. Their group focused on the efficacy of a SA protocol for hepatitis C LDLT recipients before receiving direct-acting antiviral therapy.[2,3] Their findings demonstrated that SA is safe and protective of new-onset diabetes, CMV infection, and renal dysfunction in transplant recipients with hepatitis C cirrhosis. More recently in 2020, a randomized control trial was performed that included 104 patients (52 SA, 52 SM), which evaluated the effects of long-standing steroid use after LDLT.[4] There was no statistical difference in early AR between groups (19.2% SA versus 21.2% SM) and SM increased the risk of metabolic complications, including diabetes, hypertension, and hyperlipidemia at 6 mo compared with recipients with SA. In summary, these studies demonstrated similar rates of early AR irrespective of ongoing steroid use after transplant.

Our findings in this study are similar with respect to the incidence of early AR. Additionally, there was a trend toward decreased risk of requiring treatment for glucose control at time of discharge in patients treated with SA. Although our study is limited to a single center, it describes our LDLT program over 20 y and includes the incidence of early AR in 2 IS cohorts, yielding the largest study on this topic to date. Notably, our study includes an analysis of patients with AI liver disease and shows that the frequency of early AR remains similar irrespective of steroid use after transplantation in these patients. This is important because patients with AI liver disease frequently have limited access to deceased donor organ offers in this country.

With the ongoing obesity pandemic in the United States, and projections suggesting that nonalcoholic steatohepatitis will become the most common indication for liver transplant,[16] it is important to prevent further metabolic complications posttransplant. We saw an increased trend of recipients requiring treatment for glucose control in our SM cohort, as seen in previous studies.

One concern about SA is that without the use of steroids, providers may be inclined to increase tacrolimus doses to achieve higher serum trough levels, which could cause kidney dysfunction over time. Given the short-term nature of our study, we did not investigate this, but we see from findings from Kathirvel et al[4] that there was no difference in kidney function at 3 and 6 mo of follow-up between recipients on SA and SM.

Our study has several limitations. First, it is a single-center, retrospective, nonrandomized study subject to some degree of era effect and bias. Second, the follow-up period is limited to 6 mo to avoid confounding issues influencing the primary outcome of early AR. Thus, longer-term outcomes such as the recurrence of liver disease need to be studied. Third, we did not perform glucose tolerance testing to diagnose new-onset diabetes after transplant and have used the requirement for treatment of glucose control after transplant as a surrogate. Finally, the long-term nature of the study has limited our ability to reliably collect some data of interest because of the evolving local medical record during the study period, such as hemoglobin A1c, lipid profiles, incidence of hypertension, and weight changes.

In summary, these data show that the risk of early AR was not significantly influenced by SA after LTDT, even in patients with AI disease as the cause of their liver disease. Additionally, when rejection does occur, the timing and severity are unchanged.

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