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Research Article

Obeticholic acid- an FXR agonist following living donor liver transplantation: Hope or hype?

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Abstract

Liver transplantation (LT), the only lifesaving procedure for patients with liver failure due to acute or chronic diseases, is expensive. Following LT, a major morbidity mitigating long-term liver functions is intrahepatic cholestasis, which occurs for a multitude of reasons. Prolonged cholestasis following LT can result in graft dysfunction and is associated with increased morbidity and mortality. Indeed, the fiscal drain on the patient for managing cholestasis can be significant. The current study is aimed at the management of cholestasis in liver transplant patients in the first 12 months following surgery. Ursodeoxycholic acid (UDCA) is the only drug currently used as a protective agent against cholestatic liver injury. Unfortunately, scientific data regarding the efficacy of UDCA in this regard is sparse. We aim to study the effect of the new Farnesoid receptor(FXR) molecule, obeticholic acid (OCA) as a protective agent against cholestasis following liver transplantation. There is sufficient evidence of the superiority of OCA over UDCA in other cholestatic liver diseases like Primary Biliary Cholangitis, being an FXR agonist with 100 times more potent than UDCA. Furthermore, the drug may improve graft survival by decreasing rejection and biliary complications. We hypothesize that a low dose of obeticholic acid will have superior efficacy than UDCA in ameliorating post-transplant cholestasis, improving graft function, reducing rejection& and biliary complications, and overall quality of life following liver transplantation. Additionally, glycaemic control may be better with obeticholic acid due to the involvement of FXR in glucose hemostasis.

Keywords: FXR, cholestasis, obeticholic acid, ursodeoxycholic acid, FXR agonist, liver transplantation.

Introduction

Liver failure affects over 1.5 billion people worldwide. Liver diseases are listed as the 11th leading cause of mortality globally[1],[2]. Transplantation is the only curative treatment for liver failure due to acute or chronic liver disease. Currently, liver transplantation (LT) has a success rate of 85% in the first year and 75% in 5 years. Although an expensive surgical procedure, on health care economic analysis, LT is still recommended as a cost-effective treatment, given that, people in their prime of life with many years of active work ahead, are being saved by this procedure. Notwithstanding the lifesaving nature of liver transplant surgery, morbidity following it can be significant, consequently leading to extended intensive care and hospital stay. This adds to the already substantial financial burden associated with the primary procedure. Reducing post-transplant morbidity is thus an important goal for the transplant community.

Intrahepatic cholestasis constitutes major morbidity following liver transplantation. The reasons for post-liver transplant cholestasis are manifold [3].

Firstly, ischemia affecting the organ during retrieval followed by perfusion in the new recipient leads to the inevitable ischemia-reperfusion injury. This causes cellular damage, often presenting subsequently as postoperative cholestasis. Secondly, sepsis secondary to bacterial, viral, or fungal infections, is a common accompaniment following transplantation and often worsens cholestasis due to inflammatory cytokine response and consequent cellular damage. Thirdly, many drugs essential in the post-transplantation period such as immunosuppressants, antifungals, antibiotics, or antivirals may cause cholestatic liver injury due to interference with bile formation and biliary transport. Fourthly, immunological responses to the "foreign organ" by the recipient, such as T-cell mediated cellular rejection, B- cell-mediated humoral rejection, and CD8-mediated lymphocytic cholangitis, may all lead to cholestasis.[4] Finally, surgical complications affecting the biliary and vascular anastomosis such as stenosis or obstruction may cause intra and extrahepatic cholestasis. These changes, interestingly, appear to be more common in living donor LT than deceased donor LT, plausible due to the smaller size of the grafts and technically complex biliary anastomosis. Furthermore, some of the changes observed in post-LDLT cholestatic livers are, in many ways similar to those observed in patients with other chronic liver diseases such as Primary Biliary Cholangitis (PBC) or Non-Alcoholic Steato Hepatitis (NASH) [5][6].

Medical management for cholestasis is currently limited by the lack of effective agents. Ursodeoxycholic acid (UDCA) is being used by many practitioners as a hepatoprotective agent [7]. In many transplant centers, UDCA is prescribed in post-transplant patients for 3 months at a dose of 10-15mg/kg twice daily, although its effectiveness in ameliorating cholestasis following liver transplant is debatable. A novel selective FXR agonist, obeticholic acid (OCA), a semisynthetic hydrophobic bile acid analog that is similar to UDCA but 100 times more potent, obtained FDA approval to treat PBC in combination with UDCA in 2016[8][9][10].

Currently, there is an FDA warning on the use of OCA at a dose of 10-50mg in patients with advanced liver diseases. OCA was initially considered to treat fibrosis caused by NASH and then later denied its approval by FDA. [11]. However, no evidence currently exists in this regard. These findings and facts have inspired investigators to consider the use of OCA as a hepatoprotective agent following living donor LT to improve graft functioning and ameliorate intrahepatic cholestasis. Moreover, there are limited publications from India other than a meta-analysis &and systematic review published by Kulkarni AV et al on 'Efficacy and safety of obeticholic acid in liver disease'[12]. They analyzed the reports of seven RCTs and concluded that lower doses of OCA are effective and safe in NASH and cholestatic liver disease.

A case-control study performed in our uniton 234 patients who underwent LDLT from 2014 to 2021 revealed that patients taking OCA (5mg OD dosing) had a statistically significant median reduction compared to patients with UDCA in ALP and GGT from baseline to end of the study (74.5 v/s 32 & 104.9 v/s 8 respectively; P < .000). The OCA-treated patients also showed a significant median reduction in AST (29.85 v/s 5; P<.000), ALT (63.05 v/s 2; P<.000), total bilirubin (0.74 v/s .11; P<.001) and direct bilirubin (0.6 v/s 0.01; P<.002) levels when compared with UDCA. The occurrence of biliary stricture in patients with OCA was significantly lower than UDCA group (8.6 v/s 27.4; P <.001).however, this was a retrospective analysis with all its attendant biases. We, therefore designed this randomized controlled trial to assess the efficacy of OCA compared to UDCA in the management of cholestasis following LDLT.

In addition to the assessment of clinical efficacy, we intend to delve into the basic pathophysiological aspects of cholestasis by studying various biological markers, such as levels of bile salt excretory pump, serum autotaxin, Cytokeratin 18, fibroblast growth factor 19, bile acids and TGF beta.

Hypothesis

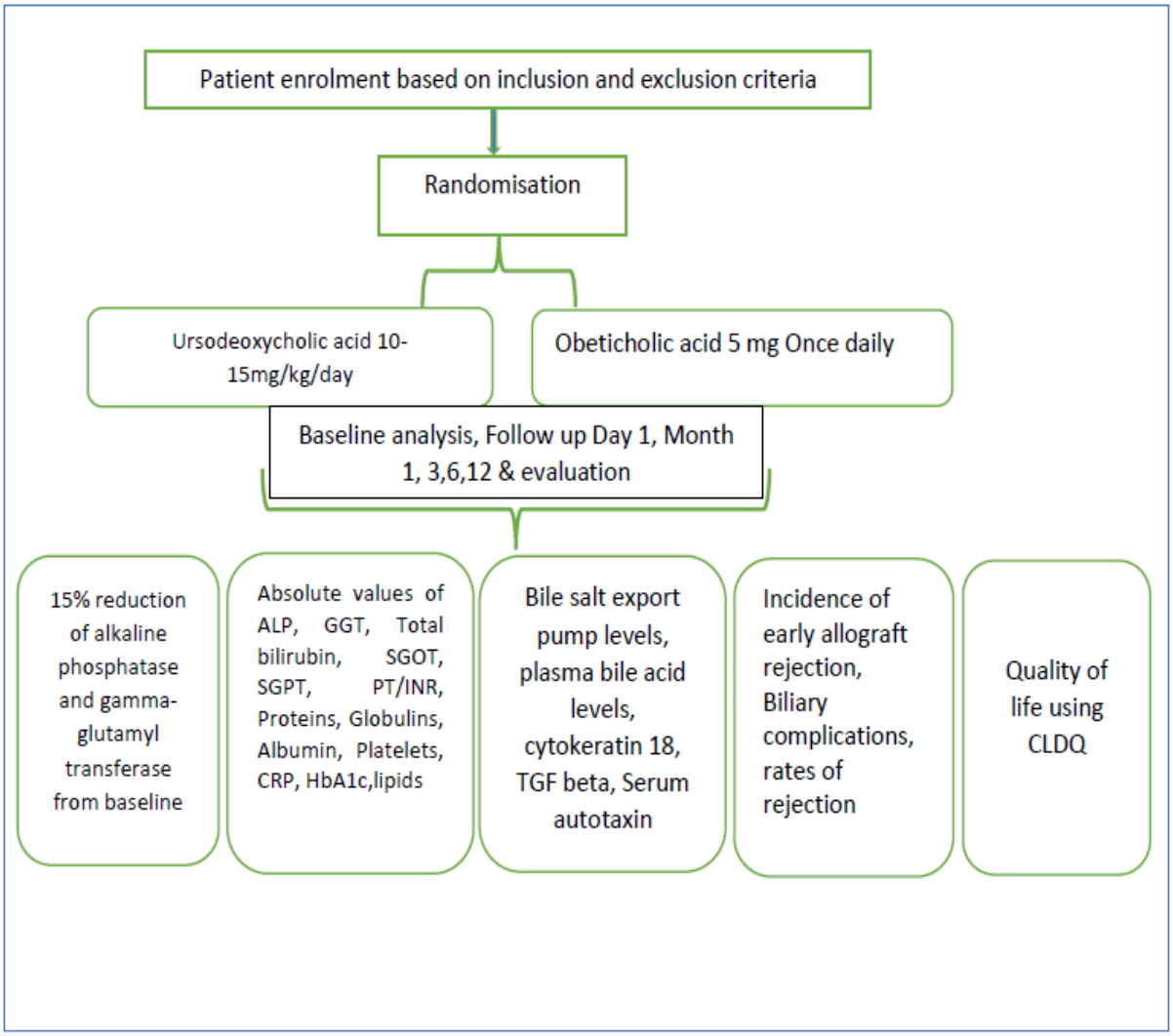
Following liver transplantation, Obeticholic acid is better than ursodeoxycholic acid in ameliorating cholestatic liver injury as evidenced by biochemical and molecular level markers. Additionally, a low dose of obeticholic acid will have superior efficacy

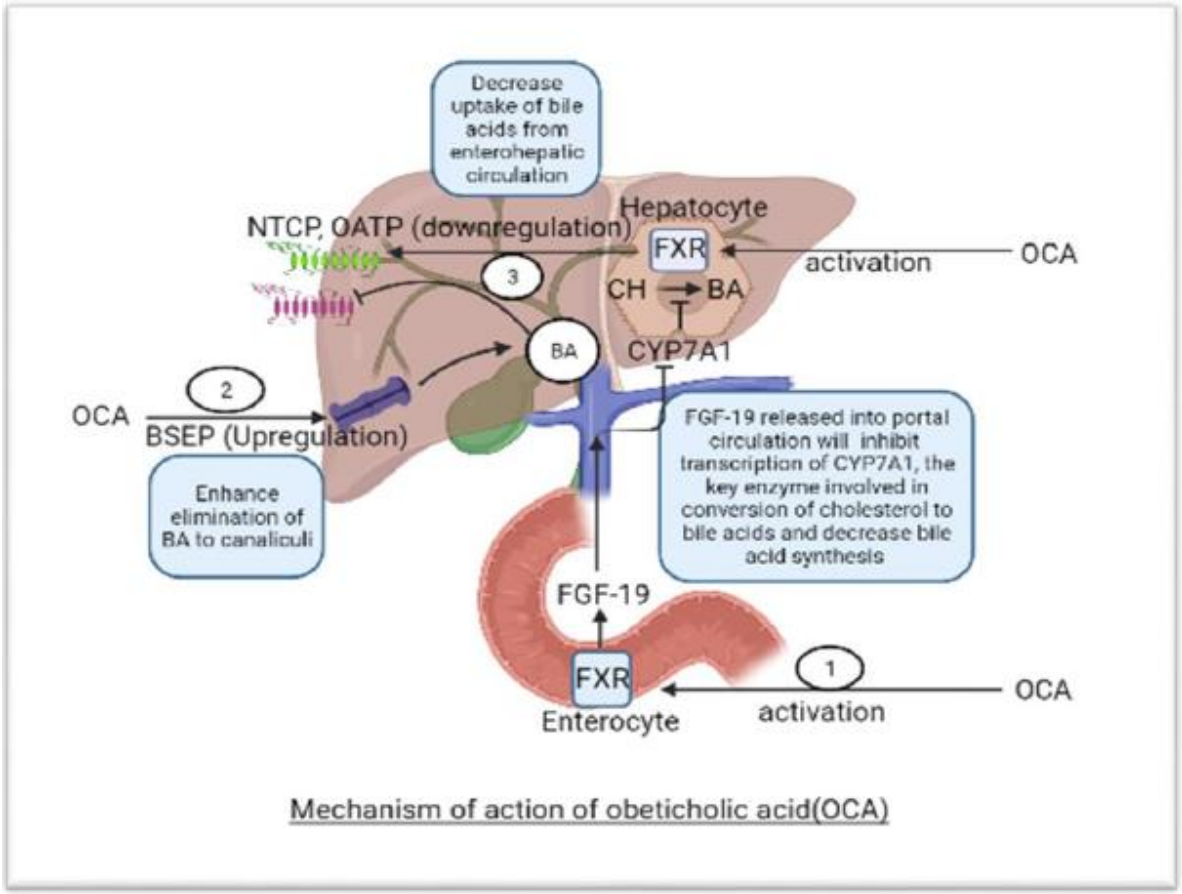
than UDCA in improving graft function, reducing rejection & biliary complications, and overall quality of life following liver transplantation. Glycaemic control may be better with obeticholic acid due to the involvement of FXR in glucose hemostasis.

Evaluation of Hypothesis

Stalling of bile flow through the biliary system leads to cholestatic disorders. Ursodeoxycholic acid and obeticholic acid are two bile acid-based hepatoprotective agents that render their role via different mechanisms. UDCA protects hepatocytes from toxic bile acids (BA), Stimulates impaired biliary secretion &and detoxifies hydrophobic BA, inhibits apoptosis of hepatocytes, and thus delays the progression of the histologic stage [13],[14]. Furthermore, it improves the Cholangiographic appearance and prolongs the projected survival of patients. Obeticholic acid being an FXR agonist effectively regulates bile hemostasis and protects hepatocytes by bile acid synthesis reduction, bile salt export pump stimulation, and inhibition of Enterohepatic bile acids [figure1] and may achieve better amelioration in cholangitis progression. OCA triggers the FXR in both hepatocytes and enterocytes when exposed to cholestatic stimulation [15] [16]. Apart from the aforementioned effects, better glycaemic control is expected due to the effect of FXR in improving insulin sensitivity and enhanced PPAR alpha coactivation [17].

Figure 1: Brief representation of the study methodology





Mechanism of action of obeticholic acid(OCA)

Alkaline phosphatase and gamma-glutamyl transferase, the two liver enzymes that are elevated in cholestatic circumstances, are regarded as the best indicators/biomarkers for assessing the prognosis and course of treatment for the condition and hence the primary endpoints of our study [18]. At time points, three months, six months, and twelve months after transplant, we are expecting at least for a 15% reduction of these markers in the OCA group compared to UDCA. An absolute reduction in all other liver functions is also considered an improvement in the condition. Reduction in intrahepatic cholestasis further may plausibly reduce the incidence of biliary complications and rejection episodes. Biochemical and biopsy-proven rejection episodes are counted for evaluation.

Numerous molecular markers are expressed during treatment and those which can quantitatively describe the mechanism of the molecules are chosen as secondary endpoints in our study.

Estimation of plasma bile acids: Quantitative assessment and comparison of bile acids expression in the study population is carried out. Potent FXR agonists have better control over the impaction of bile acids into the hepatocytes in the prevailing cholestatic condition. Excessive hydrophobic bile acids are cytotoxic and need to be drained off on a feedback basis. Cholic acid and chenocholic acid are primary bile acids whereas deoxycholic acid and lithocholic acids are the secondary bile acids [19]. Plasma bile acid levels help to understand the effective concentration of both drugs in the total bile acid pool.

Estimation of bile salt excretory pump (BSEP): The rate-determining canalicular bile salt export pump (BSEP) is a unidirectional, ATP-dependent efflux transporter, that is stimulated by FXRs found in the hepatocytes [20]. To move bile salts from the hepatocyte into the bile canaliculi for export into the gut, this pump is crucial [21]. This test is essential to understand the extent of the release of BSEP protein via a low dose of OCA.

Fibroblast growth factor 19 (FGF 19): FGF-19 is an enterokinase released after FXR activation. This protein will bind to receptor fibroblast growth factor

receptor 4 and inhibits the transcription of the crucial CYP7A1 (cholesterol 7 alpha-hydroxylase) enzyme required for the hepatocytes to convert cholesterol to bile acids [22]. FGF 19 estimation helps to assess the extent of FXR activation by the drugs.

Serum autotaxin levels: Serum autotaxin also known as ectonucleotide pyrophosphatase-phosphodiesterase 2 (ENPP2) is an inflammatory and fibrotic marker. Liver transplant patients need to be followed up and monitored frequently to guarantee good graft function. Post-LT de novo injury and fibrosis may occur due to many unidentified factors. Allograft biopsies are used as part of post-LT surveillance to detect these malfunctions. Noninvasive biomarkers at a molecular level provide apprehension on the fibrotic changes of the new graft.[23],[24]

Cytokeratin 18 (CK18) levels: This is a marker for liver necrosis and apoptosis. Although ubiquitously expressed in epithelial tissue, CK18 is frenetically liberated from necrotic hepatocytes. Following transplantation, the allograft may develop necrosis due to intrahepatic cholestasis, preservation/reperfusion injury, acute nonfunction, rejection, ischemia, and hepatitis; the severity of the underlying cause will determine the pattern and degree of the necrosis. This non-invasive biomarker can quantify the extent of apoptosis in liver cells.[25],[26].

TGF beta: Transforming growth factor-β (TGF-β), being a profibrogenic cytokine, could be a good biomarker throughout liver injury progression to failure[27]. Assessment of TGF beta in addition to serum autotaxin will provide better data about inflammation and fibrosis of the liver.

Quality of Life Assessment

Liver transplantation is probably known to be one of the most expensive treatments in modern medicine, considering the cost of surgery and the cost of medicine following surgery. This standard of care confers an overall improvement in quality of life (QOL). Any complications following the surgery will affect the substantial QOL. The term "health-related QOL" (HRQOL) refers to a multifaceted evaluation of how illness and treatment impact a patient's perception of overall function and well-being [28]. There are different tools/scales to assess HRQOL in chronic liver disease /liver transplant patients. Here the evaluation of HRQOL is done using the Chronic Liver Disease Questionnaire (CLDQ) question.

Materials and Methods

This is an open-labeled randomized control study that would be carried out in the Department of GI Surgery, Amrita Institute of Medical Sciences, Kochi for 3 years.

Selection, enrolment, and Randomization Process

All the patients who are planning for liver transplantation in the GI surgery, AIMS, and those who fulfil the study inclusion criteria will be invited to participate in the study. A detailed consent form will be provided and after obtaining consent, the patient will be enrolled in the study.

Inclusion Criteria

All adult patients undergoing live donor liver transplantation.

Exclusion Criteria

- Recipients less than 18 years of age
- Deceased donor liver transplants
- ABO-incompatible transplants
- Recipients who did not survive beyond 30 days.

Study Interventions:

- Control arm: Ursodeoxycholic acid 10-15mg/kg/day
- Intervention arm: Obeticholic acid 5 mg Once daily

Baseline data like demographics, patients' characteristics, vital information about the study like medication history, medical history, social habits, family history, regarding use of other systems of medicine, details of transplantation, important blood tests like Liver function tests, lipid profile, blood sugars, renal function tests, CRP, platelets, PT/INR, platelets will be collected.

Study participants will be randomized by statistician by permuted block sequence of computer-generated random numbers, to enroll into either the control arm (C) or the study arm (T) i.e., either to receive the standard liver protectant ursodeoxycholic acid 10-15mg/kg TID (control) or obeticholic acid 5mg OD. The sequence will be kept in sealed opaque envelopes. Following the transplantation and process of randomization, the study drug will be administered to the patient on the 3rd or 4th-day post-transplantation, once the patient can tolerate oral intake. The drug will be continued for 12 months initially with the same dose. The difference in the size of tablets and the difference in dosing frequency (three times for UDCA vs once daily for OCA), blinding is not planned.

Blood sample tests for Biochemical markers include (Carried at baseline- before drug administration/before transplant, 3, 6, and 12 months)Alkaline phosphatase (ALP) & Gamma Glutamyl Transferase (GGT); Alanine aminotransferase (ALT), Aspartate aminotransferase (AST); Total bilirubin; Direct bilirubin, total proteins, globulin, albumin; PT/INR, platelet count; Lipid profile, Renal function tests; Blood sugars; C-reactive protein (CRP). Blood Samples from patients will be collected in the first month post-transplant and 12th month, and stored appropriately for analysis.

Secondary endpoints like Level of fibroblast growth factor 19 (FGF-19), Transforming growth factor β (TGF-β) level, Cytokeratin 18 level, Serum autotaxin level, Bile Salt Export Pump (BSEP) levels, Plasma bile acid levels will be assessed using specific ELISA testing kits once sufficient samples are achieved.

Any suspected rejection (unexplained elevation of transaminases) will be confirmed by biopsy (graded according to Banff criteria and Rejection Activity Index score). Data regarding the incidence of and time to 1st biopsy-proven acute rejection (BPAR) episode (within 6 months of transplantation) that required treatment will be noted. Any biliary complications like strictures, leaks, and anastomosis will be noted down. Early allograft rejection is assessed using criteria by Olthoff et al[29]. The data from the enrolled patients will be collected on day 1 and all parameters relevant to measure the primary endpoint will be calculated at 3 months, 6, and 12. Follow-up will be attempted for 1 year. The improvement in molecular markers and other relevant parameters to measure secondary endpoints will be tested through follow-up investigations. Following interim analysis, if negative reactions are found more in the intervention arm, the study may be discontinued.

Quality of life will be assessed using a validated Chronic Liver Disease Questionnaire (CLDQ) questionnaire through patient interviews. (Pre-transplant and 12-month post-transplant). Copyright of the questionnaire was obtained from the authors. English or Malayalam version questions will be administered to patients before transplantation and follow up at the 12th month.

The questionnaire includes 6 domains [(Abdominal symptoms (AB) 1, 5, 17 Fatigue (FA) 2, 4, 8, 11, 13 Systemic symptoms (SY) 3, 6, 21, 23, 27 Activity (AC) 7, 9, 14 Emotional functions (EM) 10, 12, 15, 16, 19, 20, 24, 26 Worry (WO)]. The CLDQ overall score is calculated by adding up all the chosen answers in the completed CLDQ coming to a final universal Liver disease quality of life total. The total CLDQ score can range from 0 – 203. Low scores equate to poor quality of life [30].

Clinical implications and future consideration

The lack of sufficient scientific literature regarding the effective management of post-LT cholestasis is an unmet need. This is particularly so following living donor LT. Recently FDA issued a black box warning of the Dose-dependent risk of increased liver injury in patients with decompensated liver or rare chronic liver diseases. But this was concerning high doses above 10mg,and mostly above 15 mg. In our study, we are exclusively using 5 mg of OCA. Amelioration of post-liver transplant cholestasis will improve graft function. There may be additional benefits in biliary leaks and biliary strictures, especially in marginal grafts, due to the effects of FXR agonists on bile synthesis and transport. We will

furthermore know any interaction with immunosuppressive drugs.The proposed study if found useful following liver transplantation may become standard of care. Subsequent studies can be aimed at identifying appropriate dosage, duration, and long-term effects for more efficient use in the real-world scenario. Additionally, other FXR receptor molecules can be researched.

Conclusion

OCA has a novel mode of action on FXR, with a multitude of effects in liver hemostasis, and is 100 times more potent than the existing standard of careUDCA. Although the drug is proven to have beneficial effects in cholestatic liver diseases, its effects following LT are unknown due to the absence of good-quality trials. Our study is evaluating the hypothesis that obeticholic acid, pertainingtoits potent FXR agonism, is likely to be beneficial in post-LT cholestasis. Additionally, this drug is expected to improve graft function, reduce biliary complications& fiscal burden; and thus, overall appraisal in quality of life and survival in post-liver transplant patients.

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