Original Article

Retrospective analysis of the role of Ulinastatin in reducing mortality in severe pancreatitis in critical care unit in Nepal

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Abstract

Background: Acute pancreatitis sequelae require a multidisciplinary approach and ICU care. Ulinastatin is a serine proteases inhibitor that reduces inflammation by suppressing the infiltration of neutrophils and elastase release and inflammatory mediators that help improve clinical symptoms and reduce mortality. This study aims to evaluate the clinical utility of Ulinastatin.

Methods: Fifty-two patients admitted to ICU with acute pancreatitis were divided into; Ulinastatin group who received a 3 to 5 days course of 200,000IU, and Control Group who didn't receive ulinastatin. Pearson's Chi-square and Fisher's exact test were used and a p-value < 0.05 was considered statistically significant.

Results: Mean age was lower among the Ulinastatin group at 43 years(p-Value 0.014) and Hepatic dysfunction was more among this group(p-value 0.04). Among new onset of organ dysfunction, only CVS dysfunction was significant among the Control group(p-value 0.044) while respiratory function recovery(p-value 0.04) and coagulation profile improvement(p-value 0.017)was statistically significant among the Ulinastatin group. The mean duration of hospital stay was shorter among control group,9.65 days vs 14 days, a p-value of 0.05and also the average duration of stay in MDICU was lower, 4 days vs 8.5 days, p-value 0.0044 in comparison to Ulinastatin group. Overall mortality incidence was 15.38%, 19% in Ulinastatin group vs 11.5% in Control group.

Conclusion: This retrospective study is our experience in the use of Ulinastatin which has shown little efficacy in declining mortality and/or hospital stay duration though it helps prevent new organ dysfunctions.

Introduction

Acute pancreatitis(AP) is the sudden inflammation of the pancreas, clinically characterized by sudden onset of abdominal pain and elevated levels of pancreatic enzymes. The mechanism underlying the pathogenesis of severe acute pancreatitis is commonly believed to involve the abnormal activation of internal pancreatin due to various causes, resulting in damage to the pancreatic acinar cells and the release of inflammatory factors leading to a systemic inflammatory response.[1]

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Gallstone is one of the most common causes of pancreatitis. In Nepal, one study suggests it to be as common as alcoholic pancreatitis, together accounting for about 66 % of all causes. [2] Although the majority of patients with biliary pancreatitis recover without significant sequelae, 15–30 % of cases have severe episodes requiring multidisciplinary care.[3] The common complications are local (necrosis, pseudocyst formation, abscesses, hemorrhage) and systemic (pleural effusion, adult respiratory distress syndrome, renal insufficiency, multiorgan failure).[3, 4] If organ failure is not addressed within 48 hrs of onset it may lead to multi-system involvement and failure most commonly lung, kidney, and heart.

Ulinastatin inhibits various serine proteases, involved in the development of inflammation (both local and systemic) and dysregulated coagulation.[5] These proteases include trypsin, thrombin, chymotrypsin, kallikrein, plasmin, elastase, cathepsin G, and factors IXa, Xa, XIa, and XIIa.[5] It inhibits inflammation by suppressing the infiltration of neutrophils, the release of elastase and inflammatory mediators from neutrophils, also inhibiting the production of TNF-α, IL-1, and IL-6, possibly through suppression of the MAPK signaling pathway.[6]

Ulinastatin helps to suppress the elevated intra-abdominal pressure and acute lung injuries, decrease the Acute physiology And Chronic Health Evaluation (APACHE)-II score, improve clinical symptoms (time to abdominal pain relief and time to recover a normal heart and respiratory rate), and reduce serological marker levels (blood glucose, C-reactive protein, and Whole blood cell count) and hence reduce the 1-week mortality rate.[7]

This study aims to evaluate the clinical utility of Ulinastatin, a multifunctional serine protease inhibitor, in the management of severe acute pancreatitis and also to evaluate for improvement on multiorgan dysfunction after the use of Ulinastatin

Methods

After approval from Institutional Review Committee, all adult patients up to 70 years of age, diagnosed with AP, and admitted to the Intensive Care Unit (ICU) from April 1st 2019 to March 31st 2021 were included in the study as depicited in consort flow diagram of figure 1 below. All patients with or without organ dysfunction were included in the study. Organ dysfunction was defined as a score of 2 or more any organ systems using the Sequential Organ Failure Assessment (SOFA) scoring system. Those patients who took discharge against medical advice, patients receiving Ulinastatin for less than 3 days, and those patients whose all medical records couldn't be retrieved were excluded from the study.

Figure 1: Consort flow diagram

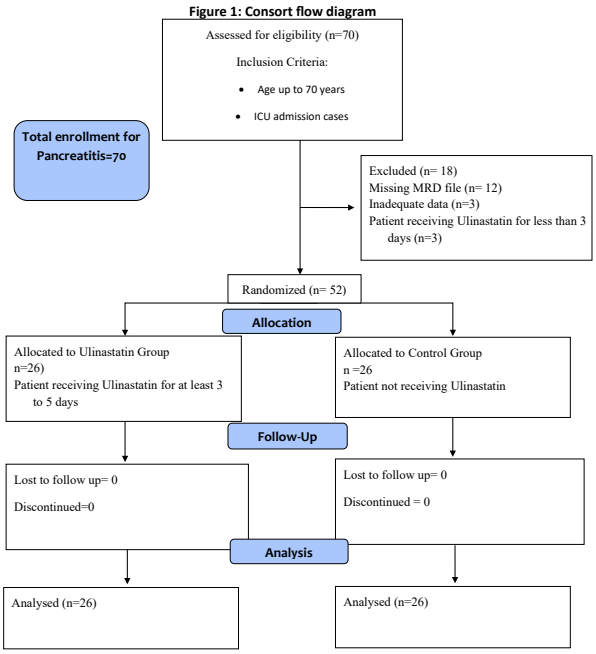

Figure 1: Consort Flow diagram for study conduction

The patients were divided into two groups depending on whether they did or did not receive Ulinastatin. The patients who received a 3 to 5-day course of Ulinastatin infusion in addition to standard care constituted the Ulinastatin group whereas patients who had received all other standard care but did not receive Ulinastatin constituted the Control group. Ulinastatin dosage of 200,000 I. U. was used as per ICU management protocol.

Standard care

Patients in both groups had received standard care according to the hospital protocol and Surviving Sepsis Campaign: 2012 guidelines[8]. The initial care had included non-surgical and solely supportive measures including fluid resuscitation, enteral feeds, and pain management. Antibiotics were administered for identified infections.

Statistical analysis

Data was collated in a Microsoft Excel spreadsheet and statistical analysis was performed using SPSS software version 20. The demographic and baseline variables were summarized using descriptive statistics such as the number of patients (n), mean, and standard deviation (SD) and were compared using either Pearson's Chi-square test or Mann-Whitney test, as appropriate. Mortality and organ dysfunction data has been summarized using frequency counts (n) and/or percentages (%) and compared using Pearson's Chi-square or Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant value.

RESULTS

1.Population characteristics

Fifty- two patients diagnosed with pancreatitis admitted to ICU were included in this study. Twenty-six patients had received the 5-day course of Ulinastatin in addition to standard supportive treatment; these comprised the Ulinastatin group. Twenty-six patients had not received Ulinastatin and comprised the Control group. The mean age of patients in the Ulinastatin and Control groups was 43.96±15.225 and 56.04±14.05 years,

respectively. The male: female ratio in the Ulinastatin and Control groups were16:10 and 16:10, respectively. The etiology of AP was predominantly alcoholic pancreatitis in both groups, followed by biliary pancreatitis. The mean APACHE II score, CT score,Glasgow Coma Scale (GCS) score, PaO2/FiO2 ratio, leucocyte count, platelet count, serum creatinine, and serum bilirubin values at baseline in both groups have been provided in table 1.

Respiratory dysfunction was the most common organ dysfunction present during admission among both groups followed by coagulation dysfunction, cardiovascular, renal, and hepatic dysfunction respectively. Five out of twenty-two patients had more than 3 organ dysfunction at the time of admission in Ulinastatin group in comparison to Control group.

2. Organ function status

2.1 Cardiovascular function

Seven out of twenty-six patients in the Ulinastatin group had cardiovascular (CVS) dysfunction at the time of admission in comparison to five from Control group and also required vasopressor support at baseline, among which four patients were weaned off the vasopressors by day 5. New-onset CVS dysfunction had developed in 3 patients in Ulinastatin group compared to 8 patients in the Control group (p 0.044) as shown in Table 2.

2.2 Respiratory function

Twelve patients from Ulinastatin group and eight from Control group had respiratory dysfunction, requiring oxygen support during admission, the majority presenting with pneumonia and/or pleural effusion. Mechanical ventilation (MV) were required among 9 patients, 34.6% of Ulinastatin group out of which only 2 patients could be weaned off from MV by day 5 and 7 patients, 26.9% of Control group out of which 4 patients could be weaned off of MV, respectively. New-onset respiratory dysfunction had developed among 7 patients from Ulinastatin group in comparison to 4 from Control group (p 0.5)as shown in table 2.

2.3 Hepatic function

Eight patients had hepatic dysfunction among Ulinastatin group in comparison to 3 from Control group which was statistically significant with a p-value of 0.04 meanwhile 7 and 5 patients had new onset of impaired hepatic function by day 5, respectively. Serum bilirubin and aspartate aminotransferase(AST),Alanine transaminase(ALT) enzymes were raised among these patients. Five patients (71.42%) and 3(75%) patients from Ulinastatn and control groups, respectively, who had impaired hepatic function had improved functional status by D5 as shown in table 2.

2.4 Renal function

Six patients from each group had impaired renal functional status during admission among which 5 from the Ulinastatin group and 3 from the Control group had resolved functional status by day 5. Seven patients from the Ulinastatin group and 5 from the Control group had new onset of renal impairment characterized by a rise in serum creatinine level.

2.5 Coagulation function

Seven patients from the Ulinastatin group and 8 from the Control group had impaired baseline coagulation profile (decreased platelet count or raised Prothrombin time PT,International normalized ratio INR values) with a p-value of 0.379, out of which 4(57.14%) and 2 patients(25%) had improved profile by day 5 from respective groups which were statistically significant with a p-value of 0.017 as shown in table 2. New-onset of coagulation derangement was noticed among 4 patients from the Ulinastatin group and 7 from the Control group by the end of day 5.

2.6 Overall organ dysfunction

Five patients from Ulinastatin group had ≥ 3 organ dysfunction during admission, of which 3 required MV and only 3 survived while 3 patients from Control group had ≥ 3 organ dysfunction, of which all 3 required MV and two patients could be weaned off with 1 mortality.

3. Laboratory parameters

Laboratory parameters comparison is depicted in table 1.

4 CT Severity Index Score

The mean CT severity index score among Ulinastatin and control group was 4 and 3.04, respectively, as shown in table 1. Those patients whose CT score was not mentioned in CT reporting were taken as Zero, which might have influenced the results as a total of 12 and 14 patients had a score of 0.

5 Laboratory Parameters

Laboratory parameters as shown in table 1, had improved by day 5 among Ulinastatin group except for random blood sugar levels whose mean value was increased. All parameters among Control group had shown improvement by day 5. Serum procalcitonin level, blood culture, and ABG analysis for PaO2/FiO2 ratio data couldn't be retrieved from MRD files, thus were not analyzed.

6 Operative procedures

The majority of the patients had undergone Necrosectomy(15.4% vs 19.2%) and /or Whipples procedure (26.9% vs 15.4%) among Ulinastatin and Control group, respectively is shown in table 1, both were not statistically significant.

7 Hospital Stay

The mean duration of hospital stay, as shown in table 1, was shorter among Control group with 9.65 days which was significant (p-value of 0.05) in comparison to 14 days among Ulinastatin group. The average duration of stay in ICU was also lower among Control group with 4 days in comparison to 8.5 days of ulinastatin group was also statistically significant (p 0.0044) while the duration of stay in ward among the Control group was lower though it wasn't significant statistically.

8 Mortality

Overall mortality was 15.38% of study sample where mortality incidence among Ulinastatin group was 19.2% in comparison to 11.5% of Control group which was not statistically significant (p-value 0.221)

Discussion

Ulinastatin inhibits various serine proteases such as trypsin, thrombin, chymotrypsin,

kallikrein, plasmin, elastase, cathepsin G, and factors IXa, Xa, XIa, and XIIa involved in the development of inflammation (both local and systemic) and dysregulated coagulation thus it plays a beneficiary role. [9] Chun-Chia Chen et al. suggested a potential role for antiproteases such as ulinastatin, aprotinin, nafamostat mesilate, and gabexate mesilate in the modulation of inflammatory cytokine response for treating acute pancreatitis. [10]

Regulatory T cells (Tregs), a critical immune cell lineage, develops and matures in the thymus to regulate immune response and maintain the immune homeostasis and they have been characterized with high expression of CD25 in CD4+ T cells. These Treg cells are also believed to help control the progression of inflammation. Ulinastatin can enhance immunological function and reduce the injury in SAP rats by inhibiting the apoptosis of CD4+ T cells.[11] Another study by Yu Pan et al in the rat model showed a significant decrease in CD4+CD25+ T cells in the ulinastatin group.[12] this study demonstrated that in the SAP rat model, pro-inflammatory cytokines TNF-α and IL-1α and anti-inflammatory cytokine IL-10 all were increased significantly, while TGF-α was decreased and treatment of ulinastatin led to decreased levels of TNF-α, IL-1α, and increased level of IL-10, thus attenuated the acute inflammatory response and improved the survival rate in the SAP rats.

The four most common causes of SAP were biliary causes, hyperlipidemia, alcohol, and other factors.[7] 26.9 % of the cause for pancreatitis was alcohol-induced and 19.2% were biliary causes, the most common causes in our study.

Organ failure may develop early in the course of the disease, present at admission, or within 24 hrs which includes respiratory, renal, hepatic, cardiovascular, digestive, neurologic, coagulation, endocrine, or immunologic dysfunction. Resolution of organ dysfunction within 48 h suggests a good prognosis.[13] Thus taking measures to treat and prevent these organ dysfunctions early in the course of acute pancreatitis might improve the patient outcome.

Respiratory dysfunction was the most common organ dysfunction among both groups, the overall incidence is 38.46%, followed by coagulation impairment 28.8%, renal dysfunction 23.07%, cardiac dysfunction 23.07%, and hepatic dysfunction 21.15% but none of them were statistically significant when compared among two groups. The presence of ≥ 3 organ dysfunction was among 15.38% of total patients, among which incidence was higher among the ulinastatin group(19.23%) than the control group(11.53%). This incidence of multiorgan dysfunction was lesser than in a study where it was as high as 79% and high APACHE II scores (N15; 60%) at baseline that led to a higher mortality rate.[9]

The new onset of organ dysfunction was comparatively lower among the Ulinastatin group, especially respiratory, cardiovascular, and coagulation dysfunction. The incidence of new-onset CVS dysfunction was statistically higher in the control group,30.76% with a P-value of 0.044. The new onset of renal and hepatic dysfunction was almost similar among both groups. In a study by Lagoo et al including forty-eight patients, a total of 6 (24%) subjects had developed 8 new-onset organ dysfunctions in the ulinastatin group by day 5, while 17 (73.9%) subjects had developed 29 new-onset organ dysfunctions in the control group, 20 out of 24 patients in the ulinastatin group had improved coagulopathy profile by day 5, fewer new-onset respiratory dysfunction i.e. 1 (4%) patient, improved renal function status by day 5 and 9 out of 16 patients requiring vasopressor support at baseline, had improved by day 5 and had been weaned off the vasopressors.[5]

The mean duration of the hospital was 14.307 days among the Ulinastatin group in comparison to 9.65 days in the Control group, p-value 0.05. ICU stay was also higher, 8.5 mean days vs 4 days with a p-value of 0.0044, and ward stay was 6.58 days vs 5.65days with a p-value of 0.68 among the Ulinastatin and the Control group respectively. This finding showed no beneficiary role of Ulinastatin to decrease the hospital stay duration which was in contrast to the finding of the mean duration of hospital stay is lower in the Ulinastatin group (15.3 days) compared to the Control group (19 days).[5]

A recent meta-analysis, which included 10 studies evaluating the effect of Ulinastatin in Asian patients with AP revealed that the serum levels of CRP, IL-6, and TNF-αsignificantly decreased after Ulinastatin therapy.[14]

Fujishiro et al. investigated the preventive effect of ulinastatin, high-dose (450,000 units) and low-dose (150,000 units) on post-ERCP pancreatitis, as compared to gabexate mesilate (900mg) and found out Post-ERCP pancreatitis observance of two (4.3%), three (6.5%), and four (8.5%) cases in the gabexate mesilate, high-dose ulinastatin, and low-dose ulinastatin groups, respectively.[15] The administration of low- and/or high-dose ulinastatin may help prevent post-ERCP pancreatitis.

Overall mortality incidence was 15.38%, 5(19.23%) from the Ulinastatin group, and 3(11.53%)from the Control group, a p-value of 0.22. This finding of mortality was higher when compared to the Ulinastain group from a study by Abraham et al., in a multicentre randomized controlled trial that included 70 patients with severe acute pancreatitis, 2.8% compared to 18.7% in the placebo group.[16] Our Study finding of mortality was comparatively lower when compared with an overall mortality of 41.7% in the ulinastatin group and 69.6% in the control group in a study by lagoo et al. [9] Similarly mortality was lower in comparison to another study where the mortality rate was 26.92%, 33.33% in the control group and 200,000 IU Ulinastatin groups, respectively.[7] Median hospitalization was shorter by one day in the ulinastatin group; the difference being insignificant.[17]

A study by P Abraham et al, which included 135 patients in which subjects had received at least 3 days (6 doses) of Ulinastatin/ placebo showed one vs six deaths in the ulinastatin group, and the placebo group died (p = 0.048) and 5 ulinastatin vs 4 placebo group subjects with new organ dysfunction (p = 0.744). [17] Adverse events were significantly lower in subjects with severe pancreatitis in the Ulinastatin group as compared to the placebo group (p = 0.00001).[17] These findings are statistically significant in comparison to our study.

A study in china by Hai wang found that Ulinastatin treatment can reduce the 1-week mortality rate and APACHE-II score of SAP patients; the best results were seen in the 600,000 IU group. [7] Our study group of Ulinastatin received 200,000 IU doses, which could be a reason for the higher mortality rate incidence and longer hospital stay duration.

Limitations

A small sample size might be a limiting factor for statistically insignificant results. The exact duration of onset of disease may play a role in prognosis which was not processed during data analysis. All biomarkers couldn't be evaluated such as PaO2, procalcitonin level, and blood culture, which could have been more relevant in defining the severity and prognosis of the disease. The cost of the Ulinastatin drug increases the financial burden which might be a limiting factor for regular usage. Also, several studies where higher doses were used showed positive outcomes meanwhile we had low dose recommendations being followed which might have an impact on patient outcome.

Conclusion

Pancreatitis in the ICU setting is common, which if not addressed on time may present with multiple organ dysfunction with a higher mortality rate. There are several guidelines derived from

many literature reviews but none has strongly recommended for regular use of trypsin inhibitor for the management of acute pancreatitis as many clinical trials have failed to show any benefits. This study is our experience in the use of Ulinastatin in our setting which has shown little efficacy in declining mortality and/or hospital stay duration though it helps prevent new organ dysfunction and help resolute previous organ dysfunctions.

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Table 1: Demographic data along with Lab parameters and Operative procedure, hospital stay, and mortality incidence and organ dysfunction data (n = total number).

Demographic data and incidence of organ dysfunction			
	Ulinastatin Group (n=26)	Control group (n=26)	P value
Age(mean± SD)	43.96 ± 15.225	56.04± 14.05	0.014
Sex (M:F)	16:10	16:10	0.487
Etiology			0.183
Alcohol induced (n)	9	5	0.105
Biliary (n)	6	4	0.240
Malignancy (n)	0	3	
Idiopathic (n)	11	14	0.202
APACHE II (mean± SD)	10.27± 6.744	11.23± 6.784	0.657
APACHE score ≥20	5	3	
APACHE score ≥15	5	4	
GCS (mean± SD)	14.38± 1.023	14.27± 1.151	0.748
CT Score(mean± SD)	4 ± 4.157	3.04 ± 3.802	
Renal Dysfunction (n)	6	6	0.240
Hepatic Dysfunction (n)	8	3	0.04
Respiratory Dysfunction (n)	12	8	0.127
CVS Dysfunction (n)	7	5	0.255
Coagulation Dysfunction (n)	7	8	0.379
≥ 3 Organ Dysfunction (n)	5	3	0.221
Operative procedure, hospital stay, and mortality incidence (n= number)			
	Ulinastatin group (n=22)	Control group (n=23)	P value
Operative Procedure			
Lap Cholecystectomy (n%)	0	1 (3.8%)	
Necrosectomy (n %)	4 (15.4%)	5 (19.2%)	0.356
Whipple's procedure (n%)	7 (26.9%)	4 (15.4%)	0.154
MRCP/ERCP (n %)	1 (3.8%)	0	
None (n %)	14 (53.8%)	13 (61.5%)	0.390
Vasopressors Use (n %)	9 (34.6%)	9 (34.6%)	0.5
Mechanical Ventilator Use (n%)	9 (34.6%)	7 (26.9%)	0.273
ICU days (n)	8.5 ± 5.736	4 ± 1.960	0.0044
Ward Days (n)	6.58 ± 6.008	5.85 ± 4.664	0.680
Total days (n)	14.307 ± 8.71	9.65 ±4.882	0.05
Mortality (n %)	5 (19.2%)	3 (11.5%)	0.221

Laboratory parameter comparison between two groups (D1= day first, D5= day fifth)			
Lab parameters	Time – point	Ulinastatin Group (mean± SD)	Control group (mean± SD)
Serum Creatinine	D1	1.81 ± 2.209	1.38 ± 0.983
	D5	1.46 ± 2.213	1.46 ±1.140
Serum Bilirubin	D1	1.73 ± 0.962	3.08 ± 5.939
	D5	1.54 ± 0.905	2.81 ± 4.290
TLC	D1	14260 ± 1.408	13076.54 ± 1.237
	D5	13181.46 ± 0.951	11122.15 ± 1.724
Platelets	D1	221849.96 ± 0.692	241669.62 ± 0.802
	D5	234384.62± 1.292	184301.15 ± 0.400
INR	D1	1.42 ± 0.578	1.58 ± 1.238
	D5	1.27 ± 0.452	1.27 ± 0.667
Serum Sodium	D1	139.77 ± 9.043	137.69 ± 7.822
	D5	139 ± 5.953	140.04 ± 5.532
Serum Potassium	D1	4.12 ± 0.816	4.19 ± 0.801
AST	D1	92.19 ± 1.458	117.42 ± 3.359
	D5	90.85 ± 1.861	64.88 ± 1.250
ALT	D1	88.73 ± 4.270	110.38 ± 2.855
	D5	79.31 ± 1.365	93.81 ± 3.148
RBS	D1	152.35 ± 3.317	170.46 ± 3.771
	D5	164.15 ± 1.049	134.85 ± 1.954

Table 2: New onset of organ dysfunction and resolution of organ dysfunction data

Resolution of organ dysfunction by day 5.					
	Ulinastatin Group (n=26)		Control Group (n=26)		
	Pt with Organ Dysfunction in D1 (n %)	Pt with resolution of Organ Dysfunction in D5 (n %)	Pt with Organ Dysfunction in D1 (n %)	Pt with resolution of Organ Dysfunction in D5 (n %)	Fishers' exact
P value					
Renal Dysfunction	6 (23.07%)	5(83.33%)	6 (23.07%)	3(50%)	0.221
Hepatic Dysfunction	8(30%)	5(71.42%)	4 (15.38%)	3(75%)	0.221
Respiratory Dysfunction	12(46.15%)	8(66.66%)	8 (30.76%)	3(37.5%)	0.04
CVS Dysfunction	7(26.92%)	4(57.14%)	5 (19.23%)	2(40%)	0.192
Coagulation Dysfunction	7 (26.92%)	4(57.14%)	8 (30.76%)	2(25%)	0.017
New-Onset organ dysfunction (n=number, D5= day fifth)					
New Onset (till D5)	Ulinastatin Group (n=22)	Control Group (n=23)	P value		
Renal Dysfunction (n)	7	5	0.255		
Hepatic Dysfunction (n)	6	5	0.367		
Respiratory Dysfunction (n)	4	4	0.5		
CVS Dysfunction (n)	3	8	0.044		
Coagulation Dysfunction (n)	4	7	0.154		

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