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Clinical and Biochemical Effectiveness of Ursodeoxycholic acid and S-adenosylmethionine in Intrahepatic Cholestasis of Pregnancy: An Observational Study in Kashmiri population

Naser Shaheen[1], Sameena Farhat Hakak[1], Athar Shabir[1], Shagufta Rather[2], Nisar Ahmad Shah[3], Shagufta Parveen[1]

[1]*Department of Pharmacology, Government Medical College, Srinagar, Jamu & Kashmir, India*
[2]*Department of Obsterics and Gynaecology, Government Medical College, Srinagar, J&K, India*
[3]*Department of Medicine, Government Medical College, Srinagar, J&K, India*

Corresponding Author: Athar Shabir (atharshabir786@gmail.com)

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) occurs in the last trimester of pregnancy1 and is characterized by pruritus and raised biochemical markers. Currently, used drugs for treating ICP include ursodeoxycholic acid (UDCA) and S-adenosyle methionine (SAMe). In our study we are comparing both the drugs in pregnancy induced cholestasis in terms of clinical effectiveness, biochemical changes, as no such study has been done so far in our setup.

Materials And Methods: Patients were divided into two groups A and B. Group A was given 300 mg of (UDC) twice daily. Group B was given 400 mg (SAM) twice daily. Both the groups were first evaluated for clinical and biochemical changes at day one and record was kept. Patients in both the groups were given the drugs as described above. After two weeks both the groups were monitored for clinical improvements and after four weeks both groups were investigated for clinical and biochemical improvements. The efficacy of two drugs was established.

Results: In our study we discover that both the drugs used in the study were effective in terms of both clinical and biochemical improvement in ICP. The bilurubin, ALT, AST and ALP levels in SAM group before treatment were 1.70 ± 0.17 mg/dL, 39.31 ± 8.45 IU/L, 54.1 ± 9.09 IU/L and 175.96 ± 22.12 IU/L, respectively. After treatment, the respective values were 1.54 ± 0.66, 36.67 ± 7.67, 56.17 ± 7.45, and 169.67 ± 19.98. The bilurubin, ALT, AST and ALP levels in UDC group before treatment were 1.80 ± 0.07, 49.25 ± 4.92, 54.35 ± 5.13, and 166.5 ± 18.23, respectively. After treatment the values were 0.84 ± 0.06, 36.25 ± 7.67, 35.67 ± 5.64, and 95.55 ± 23.12, respectively. Pruritus improved in both the groups, but more in UDCA group.

Conclusion: UDCA is a better drug for improving biochemical and clinical parameters as compared to SAM.

Keywords: Adenosylemethionine, Intrahepatic cholestasis of pregnancy (ICP), Ursodeoxycholic acid.

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a condition whose cause is poorly understood and may occur in the last trimester of pregnancy.[1] ICP is characterized by mild to severe pruritus and disturbed liver function.[2,3] ICP may be triggered by the cholestatic effects of pregnancy hormones and their metabolites in genetically predisposed women.[4] Multiple factors have been implicated in the pathogenesis of ICP, including environmental influences, nutritional deficiencies, hormonal changes and genetic variations.[5,6]

ICP may seriously affect the fetus, and is associated with complications such as premature delivery, meconium-stained amniotic fluid, fetal distress, sudden intrauterine fetal death, stillbirth and even neonatal death. Thus, women with ICP should be considered high-risk and the fetus should be carefully monitored during the third trimester.[7,8] ICP is characterized by its occurrence in the last trimester, higher incidence in twin pregnancies, resolves promptly after delivery and recurrence in 45–70% of the patients.[9] The higher incidence in third trimester and in multiple pregnancies and the induction of cholestasis by oral contraceptive pills containing estrogen

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in high dose or progesterone treatment indicate a major role of sex hormones.[10] Furthermore, specific alterations in progesterone and bile acid metabolism have been defined. It has been suggested that there is a combination of increased synthesis and impaired biliary excretion of sulfated progesterone metabolites.[11]

Incidence of intrahepatic cholestasis of pregnancy varies in different countries, like in USA the incidence of intrahepatic cholestasis of pregnancy is 70/10000,[2] in Canada 10/10000,[3] and in India 1.24%.[12] The clinical features of intrahepatic cholestasis of pregnancy are itching all over the body, abnormal liver function tests, sleep deprivation and sometimes jaundice,[13] but most of the authorities accept even only elevation of liver enzymes during pregnancy as intra hepatic cholestasis of pregnancy after other causes of elevation of these enzymes have been ruled out.[14]

Bile acids are the most sensitive indicator of ICP and ICP-specific changes, though their role as pruritogens is unclear. Serum bile acid levels only weakly reflect the degree of itch.[14] Transaminases (alanine aminotransferase/aspartate aminotransferase [AST/ALT]) are elevated in about 80% of cases in ICP.[3] In normal pregnancy serum concentrations of bile acids remain unaltered, but in intrahepatic cholestasis of pregnancy, there is 10–100 times increase of serum bile acid concentrations.[15] Though the clinical importance of intra hepatic cholestasis of pregnancy lies in the potential fetal risk that include small for gestational age, premature delivery, still birth and neonatal death,[16] but the symptoms experienced by the mother, as well as the psychological burden on the mother also needed to be taken into consideration. In view of its effect on foetus, regular tests of feto-placental function in late pregnancy are advised.[17] Currently, the major goal of ICP treatment is to improve symptoms in mother, decrease bile acid level, restore liver function and decrease the rate of neonatal asphyxia and even perinatal death. Primarily the aim of the treatment should be to relieve her symptoms without causing any harm to her foetus. A major goal of pharmacologic therapy in ICP is to provide relief from pruritus. An optimal therapeutic strategy against ICP has not yet been identified. The drugs that have so far been used in the treatment of ICP include ursodeoxycholicacid, S-adenosyl methionine, dexamethasone and some chinese herbs.[18,19] Previous studies have shown that both S-adenosylmethionine and Ursodeoxycholic acid are beneficial in intrahepatic cholestasis of pregnancy.[20,21]

Clinical trials and observational studies conducted over the last 20-years have indicated that ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) can improve pruritus and serum biochemical abnormalities, further improving perinatal outcomes.[20-23] UDCA is a hydrophilic bile acid that detoxifies hydrophobic bile acids, preventing injury to the bile ducts. SAMe is the principal glutathione precursor and methyl group donor involved in the synthesis of phosphatidylcholine. SAMe not only influences the composition and fluidity of hepatocyte plasma membranes, but it also increases the methylation and biliary excretion of hormone metabolites.[24]

Currently, used drugs for treating ICP include Ursodeoxycholic acid (UDCA) and S-adenosine methionine (SAMe),[22,23] and they need to be compared in terms of their effectiveness, cost benefits and foetal outcome. Since 1992, UDCA has become the standard medication for ICP.[25] Although having remarkable efficacy in treating ICP by these drugs, further substantiation is required due to inherent different scenarios in these previous studies and due to lack of any such study having been done in our setup. In addition to this, the different efficacies of these two therapies may be attributed to their different pharmacological effects. Further studies should examine how both of these drugs influence ICP, as well as the differences in the mechanisms by which these therapies improve symptoms in ICP patients.

MATERIALS AND METHODS

The study was conducted by the department of pharmacology in collaboration with the department of gastroenterology and the department of obstetrics and gynaecology, Government Medical College Srinagar, over a period of 2-years on 38 patients after seeking a proper clearance from institutional ethical committee. Patients with the diagnosis of ICP who were attending the Gastroenterology department (either directly or referred by the department of obstetrics and gynaecology) were prescribed the drugs under study and were observed and followed up 2 weekly for clinical, and monthly for biochemical improvement, as well as for monitoring adverse drug reactions, if any, for the drugs under study.

Patients after proper examination and all relevant investigations had been divided into two groups, A and B. Group A was given 300 mg of Ursodeoxycholic

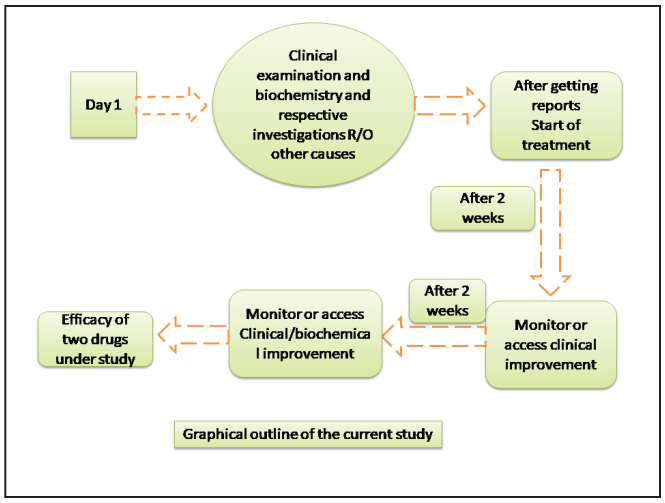

Figure 1: The graphical outline of whole study.

acid (UDC) twice daily. Group B was given 400 mg of S-Adenosyl menthionine (SAM) twice daily. The graphical outline of whole study is shown in Figure 1.

Statistical Analysis

Continuous variables were expressed as Mean ± S.E; while as categorical variables were expressed as count/percentage. Comparison for continuous variables was estimated by Mann-Whitney U-test and categorical data was compared by Chi-square test. Time dependent events in groups were compared by two-sided log-rank test (Hazard Ratio and 95% CI). *p-value* of less than 0.05 was considered Statistically significant and statistics was performed with IBM SPSS Statistics, version 20 and statographics.[18]

RESULTS

From 2017 to 2019, a total of 39 pregnant women met the inclusion criteria and chose to participate in the study, and they were randomized to Groups U and Groups S on a (n = 19) 1: (n =19) 1 ratio.

Table 1: Mean ± S.E of Biochemical parameters in clinical cases with ICP after randomization in two groups.

Parameter	Group U (N = 19)	Group S (N = 19)	p-Value
Bilirubin (mg/dL)	1.8 ± 0.20	1.73 ± 0.17	0.987
ALT (IU/L)	49.25 ± 4.92	39.31 ± 2.89	0.571
AST (IU/L)	54.35 ± 5.13	54.1 ± 4.13	0.897
ALP (IU/L)	166.5 ± 18.23	175.96 ± 14.13	0.345

Table 2: Comparison of Biochemical levels before and after treatment in ursodeoxycholic acid treatment group.

Parameters	Groups		p-value
	Before treatment	After treatment	
Bilirubin (mg/dL)	1.80 ± 0.07	0.84 ± 0.06	<0.001
ALT (IU/L)	49.25 ± 4.92	36.25 ± 7.67	<0.01
AST (IU/L)	54.35 ± 5.13	35.67 ± 5.64	0.06
ALP (IU/L)	166.5 ± 18.23	95.55 ± 23.12	<0.001

Table 3: Comparison of Biochemical levels before and after treatment in S-adenosylmethionine treatment group.

Parameters	Groups		p-value
	Before treatment	After treatment	
Bilirubin (mg/dL)	1.70 ± 0.17	1.54 ± 0.66	0.09
ALT (IU/L)	39.31 ± 8.45	35.67 ± 7.67	0.78
AST (IU/L)	54.1 ± 9.09	56.17 ± 7.45	0.79
ALP (IU/L)	175.96 ± 21.12	169.67 ± 19.98	0.67

Tables 2 and 3, show the mean changes in liver function tests and bilirubin before and after treatment with the different treatment protocols, in each group and between the two groups.

DISCUSSION

Liver diseases unique for pregnancy are not uncommon and may have a serious impact on fetal and/or neonatal outcomes.[26] One of the major areas of progress over the last decade in the hepatology field is the recognition and understanding of the pathogenesis of ICP.[27] Intrahepatic cholestasis of pregnancy is the most common liver disease during pregnancy with reported incidence rates between 0.2 and 12% in different countries.[12] ICP is characterized by otherwise unexplained pruritus in late second and third trimester of pregnancy, elevated bile acids and/or elevated transaminases and spontaneous relief of symptoms and complete normalization of biochemical aberrations within a few weeks after delivery.[2]

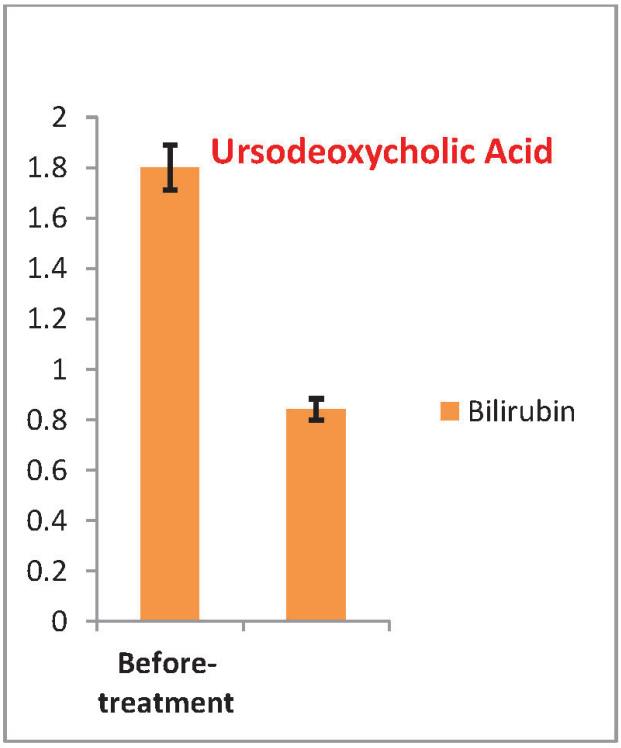

Figure 2 A: comparison of bilirubin levels before and after treatment in ursodeoxycholic acid treatment group.

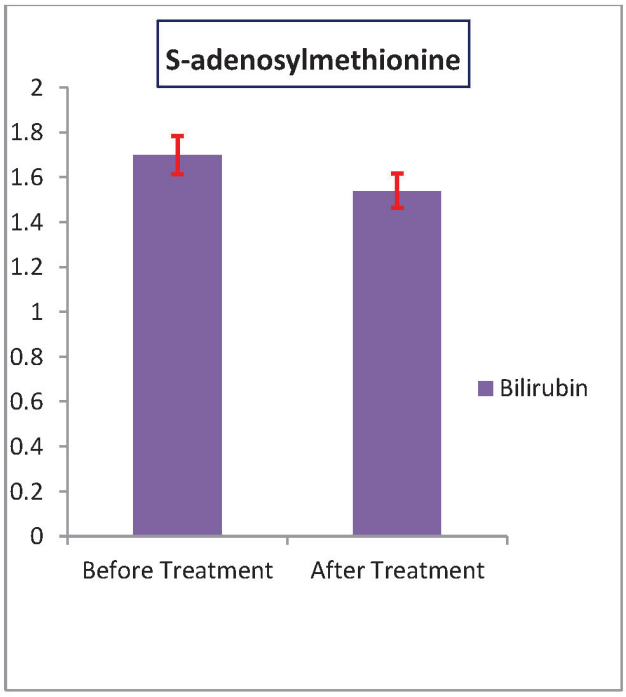

Figure 2B: Comparison of bilirubin levels before and after treatment in S-adenosylmethionine group.

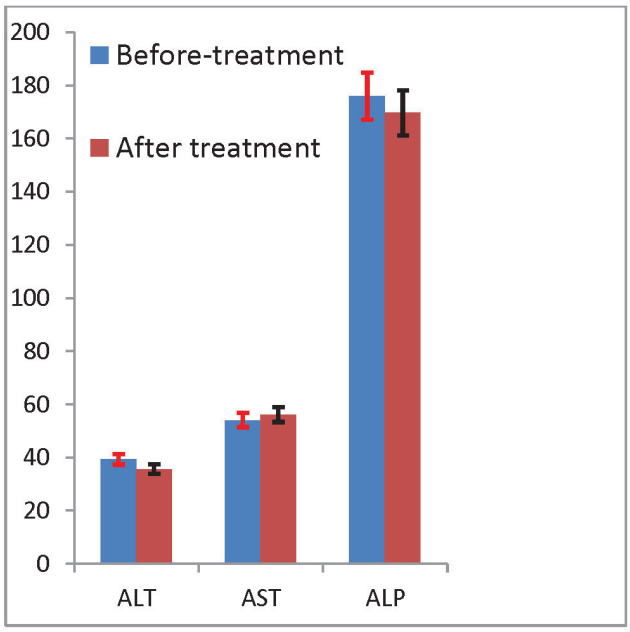

Figure 3A: Comparison of Liver specific biomarkers before and after treatment in S-adenosylmethionine group.

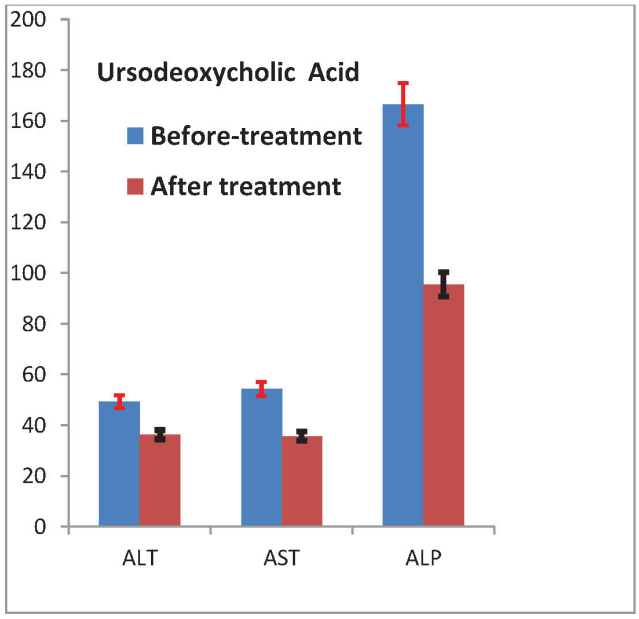

Figure 3B: Comparison of Liver specific biomarkers before and after in ursodeoxycholic acid treatment group.

Transaminases (alanine aminotransferase/aspartate aminotransferase [AST/ALT]) are elevated in about 80% of cases.[28] There are reports of ICP with debut of pruritus already in the first trimester, but majority (about 80%) of the patients present with itching in gestational weeks 30–32.[17] A major goal of pharmacologic therapy of ICP is to provide relief from pruritus. The gold standard for ICP treatment is drugs capable of reducing itching

and normalizing liver function tests and improving the outcome of pregnancy with minimal side effects on the mothers and the fetuses.[2,3]

The guidelines of the European Association for the Study of Liver (EASL) recommend ursodeoxycholic acid (10–20 mg/kg per day) as the first-line treatment for ICP as it also improves liver function tests in many cases.[29] S-adenosylmethionine (SAMe) aiming to enhance methylation and biliary excretion of hormone metabolites has also been reported to ameliorate symptoms of ICP.[30]

The present study was conducted in the Department of Pharmacology, Government Medical College, Srinagar in collaboration with the Department of Gastroenterology, Obstetrics and Gynecology, GMC Srinagar after getting approved by Institutional Ethics Committee, from January 2018 to June 2020, to compare the efficacy of S-adenosyl-L-methionine and ursodeoxycholic acid in the treatment of ICP. In our prospective unicentric study carried out on a sample size of 38 pregnant women with deterioration of liver function tests, we were able to prove that ursodeoxycholic acid administered to ICP patients was therapeutically efficient and not associated with serious side effects for pregnant women, fetuses, or neonates. Our data are consistent with all previous clinical studies published thus far,[28-31] but compared to the others, our study strongly supports the therapeutic potency as well as safety of this drug in ICP patients. In fact, the first case report on pregnant woman with ICP, treated with ursodeoxycholic acid was published as early as 1999.[32] Palma *et al.* reported that the administration of ursodeoxycholic acid to patients with ICP significantly improved pruritus, serum levels of bile acids, and ALT activities without adverse effects for mother or fetus,[33] with further studies following subsequently. Furthermore, the Cochrane review on treatment of ICP,[34] concluded that ursodeoxycholic acid treatment significantly improves pruritus, with the potential to decrease fetal distress and asphyxia. Together with the results from our large prospective clinical observation, all the available data strongly suggests the therapeutic efficacy as well as safety of ursodeoxycholic acid in ICP patients, which calls for a revision of the current obstetrics guidelines, changes of the current information, which should lead to wider use of ursodeoxycholic acid in pregnant patients.

UDCA and SAMe have been applied in the treatment of ICP for decades.[5,7] Previous reports have shown that both drugs are effective and safe, but available data are limited hitherto. We, therefore, performed a single-centered, randomized controlled, open clinical trial to compare the efficacy of UDCA, and SAMe, monotherapy. So, we compared ursodeoxycholic acid treatment with S-adenosylmethionine treatment in clinical series of 18 patients in each group. There are some clinical trials in the published literature however, the sizes of these studies are small, and the results are inconsistent. Thus, to our knowledge, we have completed the largest randomized clinical trial comparing the efficacy of UDCA and SAMe in the treatment of ICP to date. In our study, both UDCA and SAMe were equally effective at alleviating pruritus. We also found that the treatment by UDCA, in monotherapy is more effective than SAMe monotherapy in the improvement/normalization of bilirubin level. Our results based on statistical analysis shows ursodeoxycholic acid treatment was significantly more effective than S-adenosylmethionine (SAMe) in amelioration of biochemical anomalies observed in intrahepatic cholestasis of pregnancy. Furthermore, in the present study in the group treated by SAMe, no appreciable improvement was observed in the biochemical parameters, except in few isolated cases. In majority of cases, the values remained unaffected or increased. The group treated by the ursodeoxycholic acid recorded a marked improvement of the values; hence the comparative data indicate that treatment by ursodeoxycholic acid, in the form of monotherapy improves significantly the values of the biochemical manifestations of ICP whereas SAMe monotherapy has no significant effect on ICP biochemical symptoms. These findings are in accordance with recently published researcher results which reported similar effects in open series and case reports, and until 2019, a total of 11 randomized controlled trials have been published that compared ursodeoxycholic acid to other drugs, placebo or no treatment. The first meta-analysis reviewed nine randomized controlled trials,[32] which compared the effects of ursodeoxycholic acid to other drugs, placebo, or no treatment. Altogether, 454 patients were analyzed: 207 received only ursodeoxycholic acid, 70 only placebo, 42 cholestyramine, 36 dexamethasone (1 week, followed by placebo for 2 weeks), 65 SAMe, and 34 no treatment. Ursodeoxycholic acid compared with all controls was associated with reduced or resolved pruritus, decrease or normalization of ALT, and reduced serum levels of total bile acids. Results similar to ours have been reported by other randomised trials comparing

ursodeoxycholic acid and S-adenosyl-L-methionine.[35] Previous studies compared the effects of therapy only in women who completed at least 10 days of therapy; however, in our study treatment was conducted for 30 days. Although, S-adenosyl-L-methionine appeared to be less effective than ursodeoxycholic acid at improving laboratory parameters, there is contrasting evidence in the literature regarding its efficacy in comparison with placebo. A clinical trial of 18 women randomised to receive either S-adenosyl-L-methionine or placebo did not find a significant difference between the two groups in any of the laboratory measurements considered.[36] It is possible that these contrasting findings may reflect different dosages and routes of administration, as well as differences among populations in their response to the therapy. Similar findings have been reported in another small trial of ursodeoxycholic acid and S-adenosyl-L-methionine.[9] Our study was not large enough to assess whether either therapy had an effect on the risk of fetal mortality associated with gestational cholestasis. However, several lines of indirect evidence suggest that lowering serum bile acids may reduce foetal mortality.

CONCLUSION

We have completed the randomised clinical trial to compare the efficacy of S-adenosyl-L-methionine and ursodeoxycholic acid in the treatment of ICP. We have found that ursodeoxycholic acid is more effective than S-adenosyl-L-methionine at improving the maternal laboratory findings associated with ICP. In the prospective trial of SAMe vs. UDCA in ICP the most impressive results are (i) a positive effect of UDCA in reversing pruritus and in reducing total bile salts and liver specific biomarkers compared with SAMe; (ii) UDCA was found to be superior in restoring liver function tests to normal; (iii) UDCA monotherapy market value is 600 rupees for two week treatment, whereas SAMe monotherapy market value is approximately 2000 rupees. Thus, UDCA costs not more than SAMe, and oral medication is more convenient than intravenous route. In conclusion, with a view to the potential use of UDCA as an effective treatment for ICP, we believe that these results deserve to be confirmed in other case controlled randomized clinical trials.

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