Tohoku J. Exp. Med., 2014, **234**, 51-56

Safety of Tacrolimus Treatment during Pregnancy and Lactation in Systemic Lupus Erythematosus: A Report of Two Patients

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects women of childbearing years. Pregnancy with SLE is associated with an increase risk of adverse maternal and fetal outcomes. Recently, tacrolimus has been used for steroid-resistant SLE. However, because of limited information regarding the use of immunosuppressants during pregnancy, many SLE patients give up pregnancy. We report two SLE patients receiving tacrolimus who hoped to become pregnant. Patient 1 was a 31-year-old woman diagnosed with SLE 6 years earlier and treated with tacrolimus for 3 years because her symptoms were not controlled with other immunosuppressants. Patient 2 was a 28-year-old woman diagnosed with SLE 13 years earlier and treated with tacrolimus for 3 years because her symptoms were not controlled with prednisolone alone. The medical ethics board in our hospital approved the use of tacrolimus during pregnancy and lactation, and informed consent was obtained from the patients. Both patients were well controlled during pregnancy with prednisolone (Patient 1: 12 mg/day and Patient 2: 10 mg/day) and tacrolimus therapy (3 mg/day). They had healthy newborns and continued breastfeeding with tacrolimus therapy. The blood concentrations of tacrolimus 12 hours after taking tacrolimus was 3.0 ng/ml in Patient 1 and 2.9 ng/ml in Patient 2, and their newborns' blood concentrations of tacrolimus 1 hour after breastfeeding were 0.2 ng/ml and 0.5 ng/ml, respectively. Both newborns are healthy for at least 3 years after birth. This is the first report on the safety of tacrolimus for pregnancy and lactation in patients with SLE.

Keywords: lactation; lupus nephritis; pregnancy; systemic lupus erythematosus; tacrolimus
Tohoku J. Exp. Med., 2014 September, **234** (1), 51-56.

Introduction

Pregnancy with systemic lupus erythematosus (SLE) is associated with many complications, such as fetal loss, preterm delivery, preeclampsia, intrauterine growth retardation, and neonatal lupus syndrome (Ruiz-Irastorza and Khamashta 2004; D'Cruz et al. 2007). Lupus activity during pregnancy is a major predictor of poor gestational outcome (Clowse 2007). Therefore, the patient's SLE disease activity needs to be managed as low as possible during pregnancy. Many pregnancies with SLE are limited to patients whose disease activity can maintain remission with a low dose of prednisolone. Some SLE patients can maintain remission with immunosuppressants and desire pregnancy. However, because of limited information regarding the use of immunosuppressants during pregnancy, many SLE patients give up pregnancy.

Tacrolimus, targeted against the calcineurin pathway of T-cells, is an immunosuppressant drug used orally for organ transplantation or autoimmune disease. Recently, tacrolimus has been used for steroid-resistant SLE. This fact raises the possibility of the use of tacrolimus during pregnancy in SLE. However, there is only a single report on the safety of tacrolimus for pregnancy and birth in a patient with SLE (Alsuwaida 2011). We report two SLE patients treated with tacrolimus who hoped to become pregnant.

Case Report

Patient 1

A 31-year-old SLE woman who has been visiting our hospital, desired to become pregnant in 2010. She was diagnosed with SLE in 2004 based on proteinuria and her renal biopsy showed lupus nephritis (WHO IV-B). Because her disease activity could not be controlled only with prednisolone, she was treated with mizoribine (150 mg/body weight) and three times of cyclophosphamide pulse therapy (2004/2005/2008). Although she was treated with cyclosporine (CSA) from 2006, her disease activity could not be controlled. She was treated with tacrolimus (3 mg/body weight), switching from CSA in 2007, and her disease activity was remission. The medical ethics board in our

Received February 17, 2014; revised and accepted August 7, 2014. Published online August 30, 2014; doi: 10.1620/tjem.234.51.
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hospital approved the use of tacrolimus during pregnancy and lactation, and informed consent was obtained from the patient and her family. Upon examination, no lymphadenopathy, cutaneous involvement, fever, or arthritis was observed, and her disease activity was almost controlled. A laboratory examination before pregnancy showed, that her SLE activity was controlled with prednisolone (12 mg/day) and tacrolimus (3 mg/day) (Table 1). She became pregnant in June 2010 and continued her previous medications without change. Her disease activity remained stable during pregnancy, without development of hypertension. Her tacrolimus trough level was around 3.0 ng/ml (1.9-5.0). Her proteinuria was 1 g/day or less, and her complement level and her serum creatinine were in the normal range during pregnancy. Although her serum anti-SSA/Ro antibody was positive, there was no abnormal sign with weekly fetal echocardiography. She was admitted to our hospital in the 35th gestational week for preparation for parturition. On admission, her proteinuria was 2 g/day. She was in labor at the 37th gestational week. She was diagnosed with non-reassuring fetal status because recurrent late deceleration appeared. A caesarean section was performed, with a healthy baby girl weighing 2,260 g. She was treated with an increase in dose of prednisolone of 40 mg/day and continued tacrolimus (3 mg/day). Her proteinuria 7 days after giving birth was 1 g/day or less (Fig. 1). She hoped to breastfeed her newborn. We measured her newborn's tacrolimus concentrations 10 days after giving birth. The newborn's whole-blood concentrations of tacrolimus 1 hour after breastfeeding was 0.2 ng/ml and the mother's level 12 hours after taking tacrolimus was 3.0 ng/ml. We considered that these levels were safe and she continued lactation, and she was then discharged. Three years after birth, her SLE activity is currently controlled with prednisolone (12.5 mg/day) and tacrolimus (3 mg/day) and her child is healthy.

Patient 2

A 28-year-old woman with SLE was referred to our hospital hoping to become pregnant in 2010. She was diagnosed with SLE in 1997 based on the development of proteinuria, and a renal biopsy showed lupus nephritis (WHO II). Although she was treated with prednisolone, her dis-

Table 1. Patient 1 Laboratory findings before pregnant.

		Normal range			Normal range
Peripheral blood			**Serological tests**		
White blood cells	10,900/μl	(3,500-9,100)	C-reactive protein	< 0.30 mg/dl	(< 0.30)
Neutriphil	91.40%	(40.0-60.0)	IgG	897 mg/dl	(870-1,700)
Lymphocyte	5.50%	(20.5-51.1)	CH50	32.0 mg/dl	(29.0-48.0)
Monocyte	2.80%	(3.0-14.0)	C3	88 mg/dl	(86-160)
Eosinophil	0.20%	(0.0-10.0)	C4	16 mg/dl	(17-45)
Red blood cells	$414 \times 10^4/\mu$l	(380-480)	Anti-SSA Ab	124 index	(0.0-9.9)
Hemoglobin	10.9 g/dl	(11.3-15.2)	Anti-SSB Ab	< 0.5 index	(0.0-14.9)
Hematocrit	33.20%	(34.0-43.0)	Anti-ss DNA Ab	50 IU/ml	(0-25)
Platlet	$46.0 \times 10^4/\mu$l	(13.0-36.9)	Anti-ds DNA Ab	< 10 IU/ml	(0-12)
			Anti-Caldiolipin Ab	< 0.8 U/ml	(0.0-9.0)
Blood chemistry			Anti-beta2-glycoprotein I Ab	< 0.7 U/ml	(0.0-3.5)
Total protein	6.4 g/dl	(6.7-8.3)	Lupus anticoagulant	1.1 Ratio	
Albumin	3.8 g/dl	(4.0-5.0)	Tacrolimus	2.8 ng/ml	
Blood urea nitrogen	12.1 mg/dl	(8.0-22.0)	(12 hours after intake)		
Creatinine	0.7 mg/dl	(0.4-0.7)			
Total bilirubin	0.5 mg/dl	(0.3-1.2)	**Coagulation**		
Asparate transaminase	11 IU/l	(13-33)	Prothrombin time	107.80%	(72.0-130.0)
Alanine transaminase	11 IU/l	(6-27)	APTT	28.2 s	(24.8-40.4)
Lactatedehydrogenase	173 IU/l	(119-229)			
Alkaline phosphatase	201 IU/l	(115-359)	**Urinalysis**		
Creatinine kinase	44 IU/l	(45-163)	Protein	(±)	
Na	139 mEq/l	(138-146)	U-TP/Cr	0.1	
K	2.7 mEq/l	(3.6-4.9)	Occult Blood	(−)	
Cl	106 mEq/l	(99-109)	Glucose	(−)	
			Ketone	(−)	
			Bilirubin	(−)	
			Clast	(−)	

APTT, activated partial thromboplastin time; CH50, total complement activity.

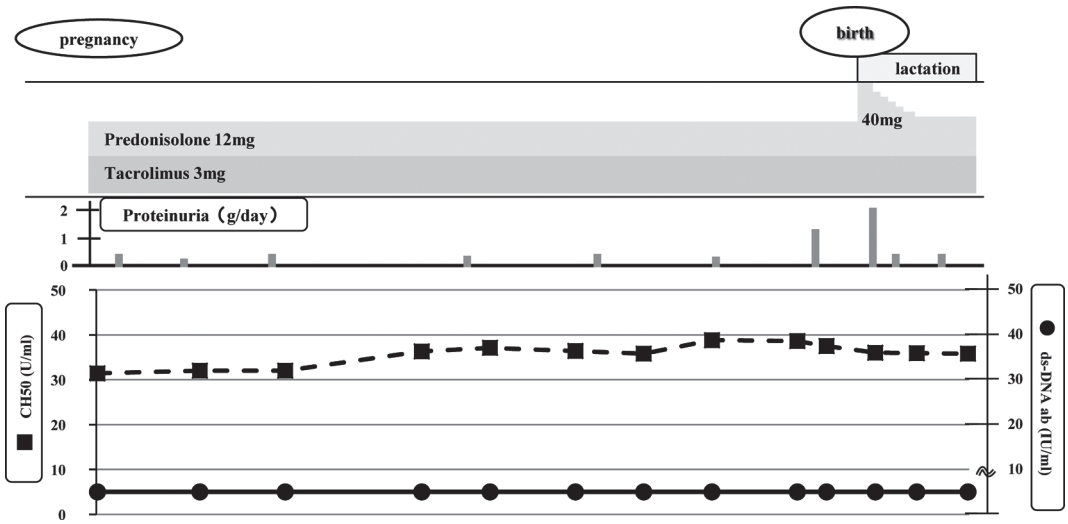

Fig. 1. Clinical courses of patient 1.
Patient 1 was treated with prednisolone (12 mg/day) and tacrolimus (3 mg/day) during pregnancy, and her disease activity did not become worse. Her proteinuria was 1 g/day or less and her complement level was in the normal range during pregnancy. She was admitted to our hospital in the 35th gestational week for preparation for parturition. On admission, her proteinuria was 2 g/day. She was treated with an increase in dose of prednisolone of 40 mg/day and continued tacrolimus after birth. Her proteinuria 7 days after giving birth was 1 g/day or less. She continued to breastfeed her baby.

ease activity could not be controlled only with prednisolone. She was treated with tacrolimus (3 mg/day) from 2007. Although her complement levels were low, other disease activity was remission. She stopped being treated with tacrolimus and her prednisolone dose was increased (5 mg to 10 mg/day). However, her proteinuria became worse and her complement levels decreased. She was referred to our hospital hoping to become pregnant in March 2010. She was treated again with tacrolimus (3 mg/day) and her proteinuria was soon in remission 1 month later. Her laboratory examination results before pregnancy are shown Table 2. The medical ethics board in our hospital approved the use of tacrolimus during pregnancy and lactation, and informed consent was obtained from the patient and her family. She became pregnant in June 2010 and continued her previous medications without change. Her disease activity remained stable during pregnancy, without development of hypertension. Her tacrolimus trough level was around 3.0 ng/ml (2.3-3.2). Her complement level and her serum creatinine were in the normal range during pregnancy. Although her serum anti-SSA/Ro antibody was positive, there was no abnormal sign with weekly fetal echocardiography. She did not have a previous history of thrombosis. Anti β-2 glycoprotein I antibody was positive when she was referred to our hospital and her activated partial thromboplastin time was longer than the normal range. She was treated with anticoagulation therapy according to pregnancy complicated by antiphospholipid syndrome. She was admitted to our hospital at the 40th gestational week for having labor pains. She vaginally delivered a healthy girl with a birth weight of 3,300 g on the next day. She was treated with increased prednisolone of 30 mg/day and continued tacrolimus (3 mg/day) (Fig. 2). She hoped to breastfeed her baby. We measured whole-blood concentrations of tacrolimus in the mother and newborn 7 days after giving birth. The newborn's tacrolimus concentration 1 hour after breastfeeding was 0.5 ng/ml and the mother's level 12 hours after taking tacrolimus was 2.9 ng/ml. We considered that it was safe for her to continue lactation, and she was discharged. Three years after birth, her SLE activity is currently controlled with prednisolone (5 mg/day) and tacrolimus (3 mg/day), and her child is healthy.

Discussion

SLE is a systemic autoimmune disease that affects women of childbearing years. Pregnancy with SLE is associated with an increase risk of adverse maternal and fetal outcomes (Ruiz-Irastorza and Khamashta 2004; D'Cruz et al. 2007; Stojan and Baer 2012). Many reports recommend that the disease activity of SLE needs to be in remission for a safe pregnancy (Stojan and Baer 2012). Some authors have reported that pregnancy outcomes are favorable in patients with a previous history of lupus nephritis, particularly if the renal disease is in complete remission and renal function is normal at the time of conception (Imbasciati et al. 2009; Wagner et al. 2009).

The frequency of pregnancy loss in SLE has declined over the last 40 years from levels as high as 43% in 1960-1965 to 17% in 2000-2003, a level now commensurate with that of the general US population (Clark et al. 2005). In Japan, Ideguchi et al. (2013) reported that the live birth rate in SLE with 55 pregnancies was 84% from 2000 to 2009. The best outcomes for a lupus pregnancy occur when the disease has been in remission for at least 6 months prior to

Table 2. Patient 2 Laboratory findings before pregnant.

		Normal range			Normal range
Peripheral blood			**Serological tests**		
Whit blood cells	5,800/μl	(3,500-9,100)	C-reactive protein	< 0.30 mg/dl	(< 0.30)
Neutriphil	81.70%	(40.0-60.0)	IgG	804 mg/dl	(870-1,700)
Lymphocyte	11.60%	(20.5-51.1)	CH50	23.1 mg/dl	(29.0-48.0)
Monocyte	6.20%	(3.0-14.0)	C3	66 mg/dl	(86-160)
Eosinophil	0.30%	(0.0-10.0)	C4	9 mg/dl	(17-45)
Red blood cells	483 × 10^4/μl	(380-480)	Anti-SSA Ab	20.3 index	(0.0-9.9)
Hemoglobin	13.8 g/dl	(11.3-15.2)	Anti-SSB Ab	< 0.5 index	(0.0-14.9)
Hematocrit	40.50%	(34.0-45.0)	Anti-SM Ab	< 0.5 index	(0.0-6.9)
Platlet	16.8 × 10^4/μl	(13.0-36.9)	Anti-RNP Ab	5.3 index	(0.0-14.9)
			Anti-ds DNA Ab	40 IU/ml	(0-12)
Blood chemistry			Anti-beta2-glycoprotein I Ab	2.2 U/ml	(0.0-3.5)
Total protein	6.3 g/dl	(8.3-6.7)	Lupus anticoagulant	1.2 Ratio	
Albumin	4.3 g/dl	(4.0-5.0)	Tacrolimus	3.6 ng/ml	
Blood urea nitrogen	10.1 mg/dl	(8.0-22.0)	(12 hours after intake)		
Creatinine	0.6 mg/dl	(0.4-0.7)			
Total bilirubin	0.5 mg/dl	(0.3-1.2)	**Coagulation**		
Asparate transaminase	14 IU/l	(13-33)	Prothrombin time	94.50%	(72.0-130.0)
Alanine transaminase	9 IU/l	(6-27)	APTT	46.7 s	(24.8-40.4)
Lactatedehydrogenase	129 IU/l	(119-229)			
Alkaline phosphatase	131 IU/l	(115-359)	**Urinalysis**		
Na	138 mEq/l	(138-146)	Protein	(−)	
K	3.8 mEq/l	(3.6-4.9)	U-TP/Cr	0.07	
Cl	105 mEq/l	(99-109)	Occult Blood	(−)	
			Glucose	(−)	
			Ketone	(−)	
			Bilirubin	(−)	
			Clast	(−)	

APTT, activated partial thromboplastin time; CH50, total complement activity.

conception (Stojan and Baer 2012). In our study, we allowed our patients to become pregnant 6 months after we confirmed that their disease activity was almost in remission by treatment with tacrolimus. Safe outcomes of pregnancy and birth were achieved. There are many reports describing that medications, including prednisolone (Petri 1998; Stojan and Baer 2012), azathioprine (Østensen et al. 2006; Alsuwaida 2011), CSA (Stojan and Baer 2012) and hydroxychloroquine (Levy et al. 2001), are effective for lupus flares during pregnancy. Although the efficacy of tacrolimus for SLE is well known (Szeto et al. 2008), there is only one report of successful management of lupus flare-up during pregnancy with tacrolimus (Alsuwaida 2011). Alsuwaida (2011) reported a case of successful management on lupus nephritis flare in the first trimester, showing the successful induction of remission of a lupus nephritis flare in the first trimester with steroids and tacrolimus. The patient reached full-term with no maternal of fetal complications. However, the patient was advised to avoid breast-feeding.

There are few reports regarding anatomical abnormalities or fetal growth disorders under treatment with tacrolimus during pregnancy and birth after organ transplantation. In female kidney recipients who are pregnant, there are less reports on tacrolimus than those for CSA, but fetal prognosis is not markedly different between tacrolimus and CSA (Armenti et al. 2003). In one study of 100 pregnancies in 84 organ-transplant patients treated with tacrolimus, four neonates presented with malformations without any consistent pattern of affected organs (Kainz et al. 2000). In their study, the maternal median dose of tacrolimus was 10 mg/day during pregnancy. Christopher et al. (2006) reported that, in female liver recipients treated with tacrolimus, there was no increased risk of miscarriage or congenital anomalies and that the maternal trough levels of tacrolimus were 4-8 ng/ml. There are many reports of successful pregnancies in various solid organ transplant patients treated with tacrolimus, and the number of congenital abnormalities is not higher than that in the general population (Bar et al. 2003; Armenti et al. 2008). The maternal tacrolimus dose

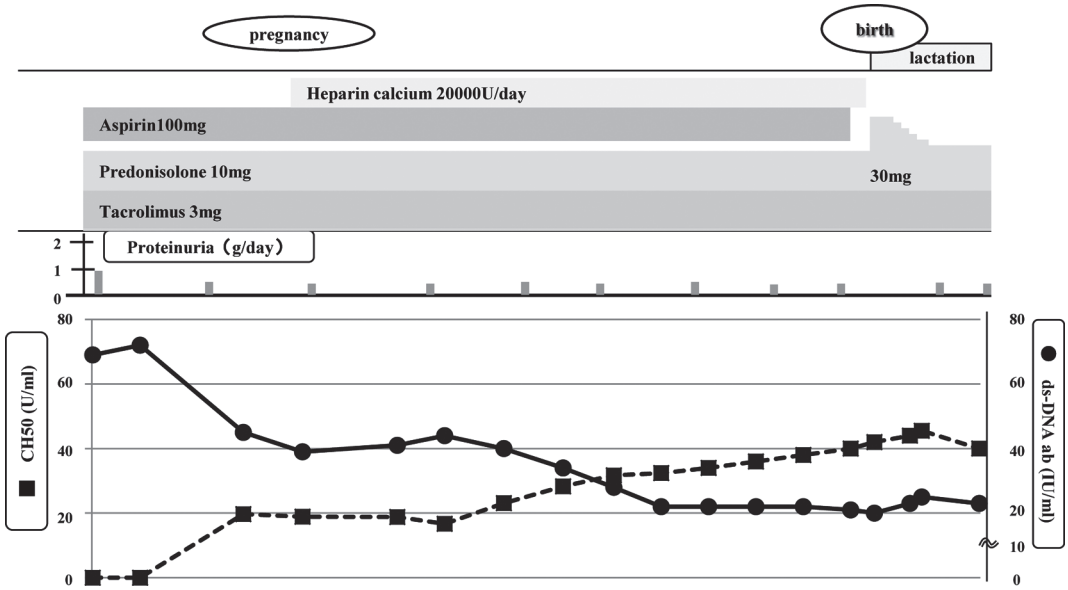

Fig. 2. Clinical courses of patient 2.
Patient 2 was treated with prednisolone (10 mg/day) and tacrolimus (3 mg/day) during pregnancy, and her disease activity did not become worse. Her complement level was in the normal range during pregnancy. She was treated with anticoagulation therapy according to pregnancy complicated by antiphospholipid syndrome. She was treated with increased prednisolone of 30 mg/day and continued tacrolimus after birth. She continued to breastfeed her baby.

for organ recipients is higher than the dose for SLE. We suggest that tacrolimus is safe during pregnancy in SLE patients. A review on immunosuppressive anti-rheumatic drugs showed that calcineurin inhibitors, including tacrolimus and CSA, may be continued during pregnancy when indicated (Østensen et al. 2008).

We considered that the SLE activity of our two patients was well controlled by treatment with tacrolimus. In Patient 1, her disease activity could not be controlled by other immunosuppressants, including mizoribine, cyclophosphamide and CSA. In Patient 2, she was not treated with any immunosuppressants other than tacrolimus, but her disease activity was well controlled with tacrolimus and low dose prednisolone for approximately 4 years. We considered that our patients should continue tacrolimus during pregnancy according to the above-mentioned review on immunosuppressive anti-rheumatic drugs (Østensen et al. 2008). We fully explained to our patients and their families about the maternal and fetal outcomes of pregnancy with treatment of tacrolimus by referring to previous reports in the field of organ transplantation (Kainz et al. 2000; Bar et al. 2003; Armenti et al. 2003, 2008; Christopher et al. 2006) and to the review describing that tacrolimus may be continued during pregnancy when indicated in rheumatic disease (Østensen et al. 2008). We also explained the possibility of disease flare-up by changing their medication from tacrolimus to other immunosuppressants that are safe for pregnancy in SLE.

The fetuses of women with anti-SSA/Ro antibodies are believed to be at risk for neonatal lupus. Congenital atrioventricular block is the most common cardiovascular abnormality, and approximately 1-3% of the fetuses and neonates whose mothers are autoantibody positive develop atrioventricular block. Many other cardiovascular manifestations of neonatal lupus have been recognized, including other cardiac conduction abnormalities, structural cardiac defects, and cardiomyopathies (Hornberger and Al Rajaa 2010). In our patients, they were performed weekly fetal echocardiography, because their serum anti-SSA/Ro antibodies were positive. Their fetuses had no cardiac manifestations of neonatal lupus and they delivered healthy newborns.

Our two patients also hoped to breastfeed their newborns while continuing to be treated with tacrolimus. We investigated the safety of tacrolimus for newborns by measuring tacrolimus concentrations. Armenti et al. (2008) reported five cases of kidney recipients who were breastfeeding while on tacrolimus, and there were no reports of problems in these children at the last follow-up. Two reports described that newborns who were breastfed by organ transplant mothers who were continuing tacrolimus treatment, ingested approximately 0.06% or 0.5% of the maternal tacrolimus dose (weigh-adjusted), by measuring the milk-to-blood ratio (French et al. 2003; Gardiner and Begg 2006). The authors concluded that infant exposure to tacrolimus in milk is low, suggesting that maternal tacrolimus therapy may be compatible with breastfeeding. Østensen et al. (2006) recommended that breastfeeding from mothers being treated with tacrolimus is possible in rheumatic disease, although the evidence was level IV. However, there are no reports regarding tacrolimus concentrations in infants breastfeeding in mothers treated with tacrolimus. In our study, we measured the newborn's tacrolimus concentrations approximately 1 hour after breastfeed-

ing, to detect maximum concentrations. Our data suggested that the exposure of tacrolimus in the newborn was at a low level. In the future, it is important to measure tacrolimus concentrations of newborns breastfed by mothers being treated with tacrolimus, and the long-term prognosis of these children should be investigated.

This is the first report of tacrolimus concentrations in newborns, and shows that tacrolimus concentrations are low. The two newborns of our study were breastfed for 1 year after birth, and they are healthy and developing normally at approximately 2 years. While more data are required, including the long-term prognosis of children, we consider that maternal therapy with tacrolimus for SLE may be compatible with pregnancy and breastfeeding.

Acknowledgments

We thank obstetricians and pediatricians in our hospital for their clinical support.

Conflict of Interest

The authors declare no conflict of interest.

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