Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy

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BACKGROUND. Administration of conventional antithrombotic treatment (low-dose aspirin plus low–molecular weight heparin [LDA+LMWH]) for obstetric antiphospholipid syndrome (APS) does not prevent life-threatening placenta insufficiency–associated complications such as preeclampsia (PE) and intrauterine growth restriction (IUGR) in 20% of patients. Statins have been linked to improved pregnancy outcomes in mouse models of PE and APS, possibly due to their protective effects on endothelium. Here, we investigated the use of pravastatin in LDA+LMWH-refractory APS in patients at an increased risk of adverse pregnancy outcomes.

METHODS. We studied 21 pregnant women with APS who developed PE and/or IUGR during treatment with LDA+LMWH. A control group of 10 patients received only LDA+LMWH. Eleven patients received pravastatin (20 mg/d) in addition to LDA+LMWH at the onset of PE and/or IUGR. Uteroplacental blood hemodynamics, progression of PE features (hypertension and proteinuria), and fetal/neonatal outcomes were evaluated.

RESULTS. In the control group, all deliveries occurred preterm and only 6 of 11 neonates survived. Of the 6 surviving neonates, 3 showed abnormal development. Patients who received both pravastatin and LDA+LMWH exhibited increased placental blood flow and improvements in PE features. These beneficial effects were observed as early as 10 days after pravastatin treatment onset. Pravastatin treatment combined with LDA+LMWH was also associated with live births that occurred close to full term in all patients.

CONCLUSION. The present study suggests that pravastatin may improve pregnancy outcomes in women with refractory obstetric APS when taken at the onset of PE or IUGR until the end of pregnancy.
Results

Twenty-one women with persistent aPL antibodies participated in this study. Most women met APS criteria before the current pregnancy, and a few of them met criteria during the current pregnancy (Tables 1 and 2). All women had a poor obstetric history, as can be observed in Tables 1 and 2. Regardless of the fact that some women did not fulfill the criteria for APS at the beginning of the current pregnancy, all women were treated with antithrombotic therapy from the time of the first positive pregnancy test (35). The live birth rate prior to this study in the control group was 3.5% and 8% in the group that received pravastatin. All women were treated with LMWH (enoxaparin or tinzaparin, 40 mg subcutaneously, once daily)plus LDA (80 mg orally, once daily). Despite treatment, all of the patients developed PE and/or IUGR (Tables 1 and 3). Most of the patients were diagnosed with early PE (21-23 weeks) and received methyldopa (MDP) to treat hypertension. None of the 21 patients had underlying chronic hypertension, and all presented normal blood pressure (BP) values prior to the onset of PE. Increased impedance to blood flow in the uterine arteries as shown by a pulsatility index (PI) above the 95th percentile — frequently associated with pregnancy complications associated with defective trophoblast invasion — (36, 37) was observed in all women during Doppler assessment of uteroplacental perfusion (Tables 1 and 2, and Figure 1). Presence of diastolic notching (a characteristic waveform indicating decreased early diastolic flow) in the uterine artery reflects low vessel elasticity (37). Bilateral diastolic notching in uterine arteries was observed in 7 patients.

Patients 1 through 10 continued to be treated with standard LMWH+LDA after PE and/or IUGR diagnosis. Doppler measurements in the uterine arteries remained abnormal with standard LMWH+LDA treatment. A slight decrease in BP was observed after the administration of MDP. After PE and/or IUGR was diagnosed, pregnancies continued for approximately 4 weeks (median, 4.5 weeks; interquartile range [IQR], 2-6). Three pregnancies ended in stillbirth at 25 to 26 weeks. Preterm cesarean delivery (C-section) was performed in 7 women due to fetal distress and or maternal health concerns (median C-section time, 26.3 weeks; IQR, 26-32). One neonate died 3 hours after birth. Because of prematurity (birth weight: median, 900 g; IQR, 580-1100) all neonates were admitted to the neonatal intensive care unit (NICU). Of the 7 neonates admitted to the NICU, 2 neonates died — one at 3 days and the other at 2 months of age — due to infection. The remaining 5 neonates were discharged from the NICU, and 3 of them currently present neurological and gastrointestinal developmental abnormalities.

In patients 11 to 21, pravastatin (20 mg) was added to the standard of care treatment as soon as signs of PE and/or IUGR were observed until delivery. This group also received MDP to treat hypertension. Following the addition of pravastatin to conventional therapy, uteroplacental blood flow improved (Figure 1) and proteinuria and BP diminished significantly (Table 3). To evaluate improvement of maternal signs of PE after pravastatin treatment, a threshold of BP of 130/90 mmHg or less and proteinuria of 300 mg/dl or less was set. The BP/proteinuria values that reached these thresholds after pravastatin treatment are shown in Table 3. After reaching the threshold values, BP and proteinuria remained within those values or improved until the end of pregnancy. Time
IUGR is an ominous finding that requires immediate delivery to prevent IUFD. In the control group that did not receive pravastatin, rEDV was observed in patients 1 and 8. Emergency C-sections were performed in both patients 1 week after the detection of abnormal Dopplers because of fetal distress. One of the neonates died 3 days after birth, and the other spent 4 months in the NICU. Abnormal Dopplers because of fetal distress. One of the neonates died 3 days after birth, and the other spent 4 months in the NICU.

Abnormal umbilical artery Doppler (absent end diastolic flow [aEDV] or reverse end diastolic flow [rEDV]) in the presence of IUGR is an ominous finding that requires immediate delivery to prevent IUFD. In the control group that did not receive pravastatin, rEDV was observed in patients 1 and 8. Emergency C-sections were performed in both patients 1 week after the detection of abnormal Dopplers because of fetal distress. One of the neonates died 3 days after birth, and the other spent 4 months in the NICU and currently shows neurological abnormalities.

In the pravastatin-treated group, patients 12 and 19 also showed rEDV and IUGR (Table 2). However, while fetal survival in this situation is very unlikely, fetal weight gain and normal cardiotocography (CTG) were observed with pravastatin treatment, and pregnancies continued for 8 and 12 weeks, respectively. Redis-

### Table 1. Antibody profile, obstetric and medical history, risk factors, characteristics of current pregnancy, and pregnancy/fetal outcomes in 10 APS patients (1–10) who were treated with standard LMW+LDA

<table>
<thead>
<tr>
<th>Patient no., age</th>
<th>Past medical history/risk factors</th>
<th>Current pregnancy</th>
<th>LMWH + LDA</th>
<th>Time of delivery</th>
<th>Latency time (from PE/severe IUGR diagnosis)</th>
<th>Neonatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 32 yr</td>
<td>APS (aCL IgM positive, 3 miscarriages)</td>
<td>12 wk: ↑ Ut art PI, 21 wk: ↑ Ut art PI, bilateral notching, 24 wk: PE and severe IUGR &lt; 5%, 25 wk: rEDV in umbilical artery</td>
<td>Yes</td>
<td>26 wk emergency C-section</td>
<td>2 wk</td>
<td>BW: 520 g, Time NICU: 4 mo, Current status of infant: abnormal neurodev</td>
</tr>
<tr>
<td>2, 27 yr</td>
<td>APS (LA positive, 3 miscarriages)</td>
<td>21 wk: ↑ Ut art PI, severe IUGR &lt; 5%</td>
<td>Yes</td>
<td>26 wk; stillbirth FW: 400 g</td>
<td>5 wk</td>
<td>–</td>
</tr>
<tr>
<td>3, 28 yr</td>
<td>APS (LA positive, aJ2GPI positive, stillbirth)</td>
<td>21 wk: ↑ Ut art PI, IUGR &lt; 10%, 32 wk: severe IUGR &lt; 5%</td>
<td>Yes</td>
<td>34 wk: emergency C-section</td>
<td>2 wk</td>
<td>BW: 980 g, Time NICU: 3 mo, Pseudomonas aeruginosa infection, Current status of infant: normal development</td>
</tr>
<tr>
<td>4, 38 yr</td>
<td>APS (aCL IgG, 3 miscarriages, 5 IVFs, age &gt; 35 yr)</td>
<td>21 wk: ↑ Ut art PI, 30 wk: severe PE, 31 wk: severe IUGR &lt; 5%</td>
<td>Yes</td>
<td>32 wk: emergency C-section</td>
<td>2 wk</td>
<td>BW: 1100 g, Time NICU: 3.5 mo, Current status of infant: normal development</td>
</tr>
<tr>
<td>5, 37 yr</td>
<td>APS (LA positive, 1 miscarriage &lt; 10 wk, 1 miscarriage &gt; 10 wk, SLE treated with HCQ, age &gt; 35 yr)</td>
<td>21 wk: ↑ Ut art PI, bilateral notching, severe IUGR &lt; 5%, 23 wk: severe PE</td>
<td>Yes</td>
<td>25 wk: stillbirth FW: 450 g</td>
<td>4 wk</td>
<td>–</td>
</tr>
<tr>
<td>6, 31 yr</td>
<td>APS (LA positive, HELLP syndrome 28 wk, postpartum DVT)</td>
<td>21 wk: severe IUGR &lt; 5%, 25 wk: fetal weight stagnation for 3 wk</td>
<td>Yes</td>
<td>26 wk: stillbirth FW: 430 g</td>
<td>5 wk</td>
<td>–</td>
</tr>
<tr>
<td>7, 32 yr</td>
<td>APS (triple positivity, DVT, severe early PE 24 wk, stillbirth 26 wk)</td>
<td>21 wk: ↑ Ut art PI, bilateral notching, 27 wk: severe IUGR &lt; 5%, PE</td>
<td>Yes</td>
<td>28 wk: emergency C-section</td>
<td>7 wk</td>
<td>BW: 700 g, Admitted to NICU 2 mo later, died of infection</td>
</tr>
<tr>
<td>8, 43 yr</td>
<td>APS (LA positive, ACA IgM positive, 3 miscarriages &gt; 10 wk, age &gt; 35 yr, IVF twin pregnancy)</td>
<td>21 wk: bilateral notching, severe IUGR (boy &lt; 1%, girl &lt; 5%) mild hypertension, 26 wk: PE, severe IUGR, rEDV in umbilical artery (boy)</td>
<td>Yes</td>
<td>27 wk: emergency C-section</td>
<td>6 wk</td>
<td>Born alive BW: 580 g (boy), 900 g (girl), Admitted to NICU, Boy died at 3 days, Girl spent 4 mo in NICU</td>
</tr>
<tr>
<td>9, 31 yr</td>
<td>APS (LA positive), HELLP syndrome, stillbirth (29 wk)</td>
<td>21 wk: ↑ Ut art PI, 26 wk: severe IUGR &lt; 5%, 32 wk: weight stagnation</td>
<td>Yes</td>
<td>33 wk: emergency C-section</td>
<td>7 wk</td>
<td>FW: 1100 g 1 mo at NICU, Developmental problems</td>
</tr>
<tr>
<td>10, 37 yr</td>
<td>APS (ACA IgM, aJ2GPI IgM, miscarriage &gt; 10 wk)</td>
<td>21 wk: ↑ Ut art PI, hypertension, IUGR, 22 wk: severe PE and IUGR, 24 wk: weight stagnation</td>
<td>Yes</td>
<td>25 wk: emergency C-section</td>
<td>4 wk</td>
<td>Baby died 3 hours after birth</td>
</tr>
</tbody>
</table>

Median age before the current pregnancy was 32 years (IQR, 31–37). aCL, anticardiolipin antibodies; aJ2GPI, anti–β2 glycoprotein antibodies; IVF, in vitro fertilization; Ut art PI, uterine artery PI; SLE, systemic lupus erythematosus; HCQ, hydroxychloroquine; BW, birth weight; FW, fetal weight; Time NICU, time spent in NICU; GI, gastrointestinal; neurodev, neurodevelopment; HELLP, syndrome characterized by hemolysis, elevated liver enzymes, and low platelet count; DVT, deep vein thrombosis.
after 37 weeks. Interestingly, 8 (73%) of the patients who received pravastatin treatment delivered close to term (median, 4.5 weeks; IQR, 2–6; P < 0.01) (Tables 1 and 3). With pravastatin delivery, women delivered close to term (median, 4.5 weeks; IQR, 2–6; P < 0.01) (Tables 1 and 3). With pravastatin treatment, women delivered close to term (median, 36 weeks; IQR, 35–36), increasing the chances of fetal maturation and survival. In the group that did not receive pravastatin, all premature neonates were admitted to the NICU and 3 perinatal deaths occurred preterm. All of the patients cotreated with pravastatin delivered after 34 weeks, thus diminishing substantially the chances for any prematurity-associated adverse neonatal outcomes.

The currently accepted first-line treatment for obstetric APS is thromboprophylactic treatment with LDA and heparinoids. However, in no evidence of maternal morbidity because of the use of pravastatin, adding to the growing evidence that statins are safe in pregnancy.

### Discussion

The currently accepted first-line treatment for obstetric APS is thromboprophylactic treatment with LDA and heparinoids. However, in

### Table 2. Antibody profile, obstetric and medical history, risk factors, and characteristics of current pregnancy of the 11 APS patients (11–21) who were treated with standard LMW+LDA treatment supplemented with pravastatin

<table>
<thead>
<tr>
<th>Patient no., age</th>
<th>Antibody profile</th>
<th>Fetal loss at &lt; 10 wk</th>
<th>Fetal loss at &gt; 10 wk</th>
<th>Past medical history/Risk factors</th>
<th>Current pregnancy</th>
<th>Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td>11, 38 yr</td>
<td>aCL, ANA, no SLE</td>
<td>1 HELLP</td>
<td>2 normal pregnancies on LMWH+LDA</td>
<td>Severe, 21 wk</td>
<td>Severe, 21 wk</td>
<td>22 wk: ↑Ut art PI, Bilateral notchling</td>
</tr>
<tr>
<td>12, 36 yr</td>
<td>LA</td>
<td>2, 1 ectopic</td>
<td>15 IVF</td>
<td>Twins, Severe, 22 wk (girl)</td>
<td>Severe, 26 wk, ↑Ut art PI, rEDV in Umb art (boy)</td>
<td></td>
</tr>
<tr>
<td>13, 39 yr</td>
<td>LA</td>
<td>1</td>
<td>1</td>
<td>Hashimoto, History of eclampsia (mother)</td>
<td>Severe, 30 wk</td>
<td>21 wk: normal 30 wk: ↑Ut art PI</td>
</tr>
<tr>
<td>14, 42 yr</td>
<td>aCL IgM, aP&lt;sub&gt;2&lt;/sub&gt;GPI IgM</td>
<td>1</td>
<td>1</td>
<td>Hyperlipidemia, Age &gt; 35 yr</td>
<td>Severe, 22 wk</td>
<td>21 wk: ↑Ut art PI</td>
</tr>
<tr>
<td>15, 28 yr</td>
<td>LA</td>
<td>–</td>
<td>Early PE (21 wk)</td>
<td>Postpartum DVT</td>
<td>Severe, 24 wk</td>
<td>21 wk: ↑Ut art PI, Bilateral notchling</td>
</tr>
<tr>
<td>16, 33 yr</td>
<td>LA</td>
<td>–</td>
<td>HELLP</td>
<td>Stillbirth</td>
<td>Severe, 24 wk</td>
<td>21 wk: ↑Ut art PI</td>
</tr>
<tr>
<td>17, 38 yr</td>
<td>LA</td>
<td>1</td>
<td>1</td>
<td>Type 1 diabetes, Hashimoto, Age &gt; 35 yr</td>
<td>22 wk, ↑Ut art PI, ↑Ut art PI, ↑Ut art PI</td>
<td></td>
</tr>
<tr>
<td>18, 36 yr</td>
<td>LA</td>
<td>–</td>
<td>1 PE, 1 placenta abruption</td>
<td>Vitamin D3 deficiency</td>
<td>Severe, 23 wk</td>
<td>23 wk: ↑Ut art PI</td>
</tr>
<tr>
<td>19, 36 yr</td>
<td>aCL IgM</td>
<td>1</td>
<td>1</td>
<td>IVF, Age &gt; 35</td>
<td>Severe, 21 wk</td>
<td>22 wk: ↑Ut art PI, rEDV in Umb art</td>
</tr>
<tr>
<td>20, 35 yr</td>
<td>aCL IgM</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>Severe, 30 wk</td>
<td>21 wk: normal 30 wk: ↑Ut art PI</td>
</tr>
<tr>
<td>21, 39 yr</td>
<td>LA</td>
<td>4</td>
<td>Age &gt; 35 yr</td>
<td>Severe, 21 wk</td>
<td>23 wk: ↑Ut art PI, Bilateral notchling</td>
<td></td>
</tr>
</tbody>
</table>

Median age before the current pregnancy was 38 years (IQR, 35–39). Antinuclear bodies (ANA); Umb art (umbilical artery).
Pravastatin ameliorates preeclamptic features in all APS patients. Threshold values (BP ≤ 130/90 mmHg, proteinuria ≤ 300 mg/dl) were set to evaluate treatment efficacy. Values after pravastatin correspond to the values less than or equal to the threshold that remained constant or improved until delivery. Median time of threshold achievement was 14 days (IQR, 10–15). Live births were observed in all of the patients. *10 days in NICU. †90 days in NICU. ‡Difference from before pravastatin, P < 0.0005. §Difference from before pravastatin, P = 0.002. ¶Difference from before pravastatin, P = 0.0011. BP and protein values before and after pravastatin treatment were compared using a paired t test. P < 0.05 is considered statistically significant.

Limitations of the present study include the small number studied.

MDP remains one of the most widely used drugs for the treatment of PE. The use of antihypertensive therapy might also contribute to the improvement of maternal signs of PE in this cohort of women. However, treatment of preeclamptic women remote from term with antihypertensive drugs showed limited benefits in prolonging gestation and improving perinatal outcomes (40). In fact, in 5 out of the 10 women in the control group who did not receive pravastatin, MDP did not decrease BP significantly and pregnancies were prolonged for a short time (median, 4 weeks; IQR, 2–5). Some women in this study were put on bed rest. While some studies suggest this might help control BP, there are no data to support the benefit of bed rest in prolonging gestation (41).

The rapid response to pravastatin observed in uterine artery hemodynamic parameters suggests that pravastatin might be targeting placental vasculopathy in APS patients who develop PE. It is tempting to speculate that pravastatin might increase placental blood flow by its antiatherogenic effects and by stimulating the release of vasoactive substances from the endothelium, such as nitric oxide or carbon monoxide (42, 43). Statins have also been shown to downregulate tissue factor, a crucial molecule in the crosstalk between inflammation and thrombosis in mice and humans with APS (29, 44). These protective effects of pravastatin on the endothelium together with its effect restoring angiogenic balance (24) might also explain the amelioration of placental and maternal preeclamptic signs.

approximately 20% of obstetric APS cases, good pregnancy outcomes cannot be achieved with this conventional treatment (38). In fact, women with APS that received LDA+LMWH treatment throughout pregnancy had higher rates of PE than control women without APS, as nitric oxide or carbon monoxide (42, 43). Statins have also been shown to downregulate tissue factor, a crucial molecule in the crosstalk between inflammation and thrombosis in mice and humans with APS (29, 44). These protective effects of pravastatin on the endothelium together with its effect restoring angiogenic balance (24) might also explain the amelioration of placental and maternal preeclamptic signs.

Considering the adverse outcomes in previous pregnancies and in patients who received LMWH+LDA without pravastatin supplementation, the present study suggests that women with refractory obstetric APS may have improved pregnancy outcomes with pravastatin taken at the time of onset of PE or severe IUGR.

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Considering the adverse outcomes in previous pregnancies and in patients who received LMWH+LDA without pravastatin supplementation, the present study suggests that women with refractory obstetric APS may have improved pregnancy outcomes with pravastatin taken at the time of onset of PE or severe IUGR.
Overall, the results obtained in this study in which pregnant women with APS who did not respond to conventional antithrombotic therapy responded satisfactorily to pravastatin appear encouraging in a patient population with frequent adverse pregnancy outcomes and warrant further investigation. Randomized clinical trials should be organized to confirm these observations.

Methods

Between 2013 and 2015, at the Hippokration General Hospital of Thessaloniki, twenty-one women with APS had been treated with LMWH (enoxaparin or tinzaparin, 40 mg subcutaneously, once daily) plus LDA (80 mg orally, once daily) from the first positive pregnancy test. APS was defined by the presence of clinical criteria and laboratory criteria as follows. Clinical criteria included 1 or more clinical episodes of thrombosis and pregnancy morbidity. Pregnancy morbidity was defined as 1 or more unexplained fetal deaths at or beyond the 10th week of gestation or 1 or more premature births before the 34th week of gestation because of placental insufficiency such as PE or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation. Lupus anticoagulant (LA) and/or anticardiolipin (aCL) and/or β2 glycoprotein-I IgG or IgM antibody present in plasma or serum on 2 or more occasions, at least 12 weeks apart, are included in the laboratory criteria for APS (45).

While some of the women met the criteria for obstetric APS before this study and others had persistent aPL antibodies and met criteria during the current pregnancy, all women received conventional LDA+LMWH treatment (35).

Despite the aforementioned antithrombotic treatment, all of the patients developed placental insufficiency-related complications such as PE and IUGR. Most of the patients were diagnosed with early PE (21–23 weeks).

PE was defined according to the report of the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy (46). PE was defined as BP elevation after 20 weeks of gestation with proteinuria or any of the following features: thrombocytopenia, impaired liver function, new development of renal insufficiency, pulmonary edema, or new onset of cerebral or visual disturbances. IUGR was defined as fetal weight below the 10th percentile, and severe IUGR was defined as fetal weight below the 5th percentile for gestational age and abdominal circumference below the 2.5th percentile (47).

The patients’ past obstetric and medical history, risk factors, and characteristics of current pregnancy, including Doppler studies, are presented in Table 1 (patients who were treated with LMWH+LDA) and Table 2 (patients who were supplemented with pravastatin). All women had a poor obstetric history with a low rate of live births. Eleven patients consented and were started on pravastatin (20 mg/d) from the time they were diagnosed with PE or IUGR, and 10 received only standard LMWH+LDA treatment.

Median age for the patients who were supplemented with pravastatin was 38 years (IQR, 35–39), and 32 years (IQR, 31–37) was the median age for the group that received only standard therapy. Women with PE were given MDP (1 g/d in 2 divided doses) to treat hypertension. All patients were admitted to the hospital, most of them until delivery. Because these were inpatients in the high-risk pregnancy unit, close maternal and fetal monitoring was undertaken. Maternal monitoring included measurement of BP 3 times a day, measurement of proteinuria, and blood tests to assess liver and kidney function and number of platelets twice weekly. Ultrasound assessment of fetal growth was performed every week, amniotic fluid volume was assessed twice weekly, and umbilical, middle cerebral artery, ductus venous, and uterine artery Doppler velocimetry were performed twice weekly to monitor fetal status. Daily monitoring of the fetus with CTG was also performed. Maternal and fetal progress were reviewed regularly. Patients with PE were discharged to the community when BP was less than 130/90 mmHg and blood results were stable or improving and, in the case of IUGR fetuses, when acceleration of fetal weight gain was observed along with stable or improved fetal and maternal Doppler measurements. After discharge, women were advised to check their BP twice daily and to visit the antenatal day assessment unit 3 times a week in order to have a CTG and to review their measurements. Blood tests were also performed during these visits, and the quantity...
of urinary protein was checked once a week. Doppler assessment after discharge was performed twice weekly. Despite improvement after pravastatin treatment, some patients chose to remain as inpatients in the high-risk pregnancy unit until delivery for close monitoring, mainly because of maternal anxiety.

Statistics. Statistical analysis to compare BP and proteinuria values before and after pravastatin treatment and time from diagnosis to delivery between pravastatin-treated women and control was conducted using a paired t test. \( P < 0.05 \) was considered statistically significant. Medians and IQRs are reported for all variables measured. All analysis was conducted with GraphPad Prism statistical software (GraphPad Software Inc.).

Study approval. This study was approved by the Ethical Review Committee at Hippokration General Hospital of Thessaloniki, and informed consent was obtained from all pregnant patients.

Author contributions
GG and EL conceived and designed the study. GG and EL analyzed and interpreted data. GG created graphs and wrote the manuscript. TD, CV, and AM collected data. DR was responsible for the overall supervision of the patients.

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