High-dose atorvastatin causes regression of endometriotic implants: a rat model

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BACKGROUND: This prospective randomized-controlled animal study was designed to determine the effects of atorvastatin on experimentally induced endometriosis in a rat model. METHODS: Thirty-seven Wistar-Albino rats in which endometriotic implants were induced were randomly divided into four groups. Group I (Low-dose atorvastatin group, eight rats) were given 0.5 mg kg\(^{-1}\) day\(^{-1}\) oral atorvastatin. Group II (High-dose atorvastatin group, 10 rats) were given 2.5 mg kg\(^{-1}\) day\(^{-1}\) oral atorvastatin. Group III were given a single dose of 1 mg kg\(^{-1}\) s.c. leuprolide acetate (GnRH agonist group, nine rats). Group IV were given no medication and served as controls (10 rats). All rats received the treatment for 21 days and were then euthanized to assess the implants’ size, vascular endothelial growth factor (VEGF) level in peritoneal fluid and histological score. RESULTS: At the end of the treatment, the mean areas of implants were smaller and VEGF levels in peritoneal fluid were lower in Groups II and III than those in Group I, and the control group (all \(P<0.05\)). The mean areas of implants decreased from 41.2 \pm 13.9 to 22.7 \pm 13.9 mm\(^2\) after medication in Group II and decreased from 41.2 \pm 18.1 to 13.1 \pm 13.8 mm\(^2\) in Group III (both \(P<0.05\)), whereas in Group I, the mean area increased from 43.0 \pm 12.7 to 50.5 \pm 13.9 mm\(^2\) (\(P<0.05\)). CONCLUSIONS: High-dose atorvastatin caused a significant regression of endometriotic implants.

Key words: atorvastatin/angiogenesis/endometriosis/statins/vascular endothelial growth factor

Introduction

Endometriosis is defined as the presence of endometrial tissue, consisting of both glandular epithelium and stroma, outside the uterine cavity (Kennedy et al., 2005). This condition is predominantly found in women of reproductive age and affects \(\sim 7–10\%\) of all women, \(71–87\%\) of women with chronic pelvic pain and 38\% of all fertile women (Amsterdam et al., 2005).

Retrograde menstruation is the mechanism most frequently suspected in the etiology of endometriosis (Groothuis et al., 1999). According to this theory, endometrial tissue retrogradely migrates into the peritoneal cavity, where it adheres to the peritoneal surface, invades the extracellular matrix and initiates angiogenesis in order to generate new blood vessels needed to survive (Groothuis et al., 1999). Therefore, early angiogenesis is mandatory for this process. In addition, to maintain the endometriotic implants, continuation of angiogenesis is required. Several studies confirmed that increased angiogenesis is found around peritoneal endometriosis implants (Nisolle et al., 1993; Wingfield et al., 1995; Maas et al., 1999).

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (Omar et al., 2001). They lower cholesterol synthesis by blocking conversion of HMG-CoA to mevalonate. In addition to their lipid lowering action, statins at high dose have been shown to have anti-inflammatory and anti-angiogenic activity (Vincent et al., 2001, 2002, 2003; Park et al., 2002). Therefore, we hypothesize that high-dose statins may inhibit angiogenesis and may regress endometriotic implants.

In this study, we aimed to compare the effects of low dose and high-dose atorvastatin, which is a statin, and leuprolide acetate on experimentally induced endometriosis in a rat model.

Materials and method

Animals

Forty mature female Wistar-Albino rats (250–300 g) were used for the experiment. All rats were provided by Baskent University Animal Reproduction Center and housed in the Animal Laboratory of Baskent University. They were caged in a controlled environment of 22°C with 12 h light/dark cycles. Standard rat feed and reverse-osmosis-purified water were provided ad libitum. All rats were allowed to have 1 week of acclimation to this environment before the experiment.
The Baskent University Committee on the Use and Care of Animals approved the experiments, and all investigations complied with the 1996 National Academy of Science’s Guide for Care and Use of Laboratory Animals.

**Surgical procedures**

All the rats were anesthetized with an i.p. administration of 50 mg kg\(^{-1}\) Ketamine hydrochloric acid (Ketalar; Eczacibasi Warner-Lambert Haş Sanayi, Levent, Istanbul, Turkey) and 7 mg kg\(^{-1}\) Xylazine hydrochloric acid (Rompun, Bayer Sisli, Istanbul, Turkey). They were immobilized on a standard rat surgery board. Using the aseptic technique, a ventral midline incision was made to expose the reproductive organs. All rats underwent three surgeries (laparotomies) as explained below.

*First surgery*

The ectopic endometrium was induced surgically as described by Rajkumar *et al.* (1990). Briefly, the left uterine horn was ligated at both the uterotubal junction and the cervical end using 4-0 silk and removed. A 7 mm segment of the excised horn was cut and placed in sterile isotonic saline. The endometrium was separated from the myometrium and trimmed to 5 × 5 mm. The trimmed section of the endometrium was then transplanted into the peritoneal cavity with the epithelial lining of the segment apposed to the ventrolateral body wall adjacent to a large vessel using sterile 4-0 silk. The midline abdominal incision was closed with chronic catgut sutures. The skin incision was closed with a horizontal mattress. After the first surgery, all rats were observed for 21 days in their cages without any medication.

*Second surgery*

Three rats died during 21 days after the first surgery. The remaining 37 rats underwent a second exploratory laparotomy to detect endometrial implants and collect peritoneal fluid to measure vascular endothelial growth factor (VEGF) levels.

To assess the level of VEGF in peritoneal fluid, peritoneal lavage with 3 ml saline was performed samples immediately sent to the laboratory at the beginning of the laparotomy.

The length and width (mm) of the implants were measured microscopically and the surface areas of the implants were calculated (length × width) and recorded. Then, the laparotomy was closed.

Following the second surgery, all rats were allowed a resting period of 3 days. Then, the rats were randomly allocated to four groups blinded to the surgeons. The rats in Group I (Low-dose atorvastatin group, eight rats) were given 0.5 mg kg\(^{-1}\) day\(^{-1}\) oral atorvastatin (Liptor tablet, Pfizer, Istanbul, Turkey). The rats in Group II (High-dose atorvastatin group, 10 rats) were given 2.5 mg kg\(^{-1}\) day\(^{-1}\) oral atorvastatin. The low (0.5 mg kg\(^{-1}\) day\(^{-1}\)) and high dose (2.5 mg kg\(^{-1}\) day\(^{-1}\)) of atorvastatin in rats were based on a previous animal study (Weis *et al.*, 2002). The rats in Group III [GnRH agonist (GnRHa) group, nine rats] were given single s.c. injection of leuprolide acetate depot formulation (1 mg kg\(^{-1}\) body weight; Lucrin; Abbott, Cedex, Istanbul, Turkey). The leuprolide acetate dose was based on a previous study in which 1 mg kg\(^{-1}\) was found to be optimal for female rats (Dogan *et al.*, 2004). The rats in Group IV (Control group, 10 rats) were given no medication. The oral medications were given via an orogastric tube by the laboratory personnel. All the rats were observed for 21 days.

*Third surgery*

After the end of the medical treatments, the rats were euthanized by ketamine anaesthesia and the third laparotomy was performed.

In that laparotomy, the length and width of the implants were measured microscopically and the surface areas of the implants were calculated again. The implants were then excised and fixed in 10% formalin for histopathological examination. Peritoneal lavage with 3 ml saline was performed again to assess the VEGF level in peritoneal fluid. All of the surgeries and measurements were performed by two physicians blinded to the groups.

**VEGF assessment.** The VEGF level in the peritoneal fluid was quantitatively assessed using a commercially available enzyme-linked immunosorbent assay kit (Bio Source International, Nivelles, Belgium) according to manufacturer’s instructions. The enzyme immunoassay measures with a sensitivity of < 5 pg ml\(^{-1}\); it has an intra-assay variability of ± 4.9% and an inter-assay variability of ± 8.5%.

**Histopathological examination.** The pathologist assessing the samples was blinded to the treatment groups. The formalin-fixed endometriotic foci were embedded in paraffin blocks, sectioned at ~5 μm thickness (four sections per sample), stained with hematoxylin and eosin and examined under a light microscope. The persistence of epithelial cells in endometrial implants was evaluated semiquantitatively as follows: 3 = well preserved epithelial layer; 2 = moderately preserved epithelium with leukocyte infiltrate; 1 = poorly preserved epithelium (occasional epithelial cells only) and 0 = no epithelium. This evaluation was based on a previous rat endometriosis study (Keenan *et al.*, 1999).

**Statistical analysis**

The statistical analyses were performed using Statistical Package for Social Sciences version 11.0 (SPSS, Chicago, IL, USA). Normally distributed (Shapiro-Wilk test) parametric variables were tested by the analysis of variance using the least significant difference test for *post hoc* analysis. Non-normally distributed metric variables were analysed by the Kruskal-Wallis test and Mann–Whitney U-test with Bonferroni correction. The mean surface areas of the endometriotic implants and VEGF levels in the same group (before and after the medical treatment) were analysed by paired sample t-test since they were normally distributed. P values of < 0.05 were considered statistically significant. Values were expressed as mean ± SD.

**Results**

Table I summarizes the basal characteristic and treatment results. At the beginning of the medical treatment, the mean surface areas of the endometriotic implants and VEGF levels in peritoneal fluid were comparable in all four groups. However, at the end of the treatment, the mean areas of implants were smaller and VEGF levels were lower in Groups II and III than those in Group I and the control group.

The mean areas of implants decreased from 41.2 ± 13.9 to 22.7 ± 13.9 mm\(^{2}\) in Group II (*P < 0.05*) and decreased from 41.2 ± 18.1 to 13.1 ± 13.8 mm\(^{2}\) in Group III (*P < 0.05*). Of note, the mean areas of implants in Group I increased from 43.0 ± 12.7 to 50.5 ± 13.9 mm\(^{2}\) (*P < 0.05*). There was no statistically significant change in control group.

VEGF levels in peritoneal fluid decreased from 22.4 ± 14.1 to 9.8 ± 3.9 pg ml\(^{-1}\) in Group II (*P < 0.05*) and decreased from 18.9 ± 7.1 to 10.3 ± 3.4 pg ml\(^{-1}\) in Group III (*P < 0.05*). However, there was no statistically significant
change in Group I and control group. Sample views of the endometriotic implants are shown in Figure 1.

The mean score of the histopathological examination of the implants at the end of the treatment was lower in Groups II and III, when compared with Group I and the control group (Table I). Sample views of the histological examination of the endometriotic implants are shown in Figure 2.

Discussion

Several studies confirmed that angiogenesis is markedly increased around peritoneal endometriosis implants (Nisolle et al., 1993; Wingfield et al., 1995; Maas et al., 1999). Previously, the agents that inhibit angiogenesis such as the soluble VEGF receptor, angiogenesis inhibitor and angiotatin were shown to be effective in the prevention of ectopic lesion formation in mouse models of endometriosis (Dabrosin et al., 2002; Hull et al., 2003). Nap et al. (2005) evaluated the vascularization and endometriosis-like lesion formation after the transplantation of human endometrium together with the effects of angiostatic agents on the chicken chorioallantoic membrane. Their findings suggested that the early implantation of endometrial tissue depends on an immediate angiogenic response. In different murine models, it was shown that angiogenesis also played an important role in supporting growth in the post-implantation period (Nap et al., 2005). After lesions were allowed to develop in these models, angiostatic treatment was shown to reduce the number of lesions (Hull et al., 2003; Nap et al., 2004). These studies confirm that also after implantation of the endometrium a continuous angiogenic process is required for survival of the tissue.

Recently, studies showed that statins directly affect angiogenesis independently from their effect of lipid lowering (Rutishauser, 2006). The effect of statins on angiogenesis is biphasic and dose-dependent (Weis et al., 2002; Rutishauser, 2006). It has been reported that statins can have both pro- and antiangiogenic activities (Weis et al., 2002; Rutishauser, 2006). It appears that low statin doses induce pro-angiogenic effects through Akt activation, leading to endothelial nitric oxide synthase phosphorylation and nitric oxide production (Goligorsky et al., 1999; Kureishi et al., 2000; Weis et al., 2002). On the other hand, high statin doses will appreciably inhibit the synthesis of the non-sterol products of mevalonate, resulting in decreases in protein prenylation and an inhibition of cell growth (Weis et al., 2002). In addition, high doses of statins induce reductions in geranylgeranyl pyrophosphate (GGP), which inhibits angiogenesis (Edwards and Ericsson, 1999). GGP is required for the membrane localization of small GTP-binding proteins such as Rho family members (Edwards and Ericsson, 1999). Other antiangiogenic effects of statins may include inhibition of the expression or activity of monocyte chemoattractant protein-1, metalloproteinase and angiotensin-2, preproendothelin gene and actin filament and focal adhesion formation (Aepfelbacher et al., 1997; Nickenig et al., 1999; Hernandez-Perera et al., 2000; Ikeda et al., 2000; Romano et al., 2000).

The dose-dependent effect of atorvastatin on endothelial cell (EC) migration and angiogenesis was investigated (Urbich et al., 2002). The results demonstrated that low doses of atorvastatin (0.01–0.1 µmol l⁻¹), which resemble the plasma concentrations in patients on low-dose chronic statin therapy, promote angiogenic processes in mature ECs. In contrast, higher concentrations of atorvastatin (40.1 µmol l⁻¹) exert antiangiogenic effects by inducing EC apoptosis. However, Weis et al., 2002; reported that proangiogenic effects were observed at statin concentrations between 0.005 and 0.05 µmol l⁻¹ (refers to low- to mid-range concentrations in humans), whereas angiostatic effects could be observed at 0.05 µmol l⁻¹ and higher concentrations of atorvastatin (refers to high-dose concentrations in humans). Serum levels

### Table I. Characteristics and results of the groups of rats treated with low (0.5 mg kg⁻¹ day⁻¹) or high (2.5 mg kg⁻¹ day⁻¹) dose oral atorvastatin for 21 days, or a single s.c. dose (1 mg kg⁻¹) of GnRH agonist

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (Statin Group I, low dose)</th>
<th>Group II (Statin Group II, high dose)</th>
<th>Group III (GnRH agonist Group)</th>
<th>Group IV (Control Group)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of rats</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>Non-significant (NS)</td>
</tr>
<tr>
<td>Weight of rats before the medication (g)</td>
<td>242.4 ± 24.5</td>
<td>236.8 ± 20.3</td>
<td>239.1 ± 21.8</td>
<td>246.1 ± 28.8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight of rats after the medication (g)</td>
<td>224.5 ± 12.5</td>
<td>218.8 ± 13.5</td>
<td>238.7 ± 16.9</td>
<td>227.2 ± 27.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean surface area of the implants at the second laparotomy before the medication (mm²)</td>
<td>43.0 ± 12.7</td>
<td>41.2 ± 13.9</td>
<td>41.2 ± 18.1</td>
<td>40.1 ± 17.4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean surface area of the implants at third laparotomy after the medication (mm²)</td>
<td>50.5 ± 13.9</td>
<td>22.7 ± 13.9</td>
<td>13.1 ± 13.8</td>
<td>38.3 ± 17.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF) level in peritoneal fluid before the medication (pg ml⁻¹)</td>
<td>21.6 ± 10.1</td>
<td>22.4 ± 14.1</td>
<td>18.9 ± 7.1</td>
<td>26.6 ± 10.6</td>
<td>NS</td>
</tr>
<tr>
<td>VEGF level in peritoneal fluid after the medication (pg ml⁻¹)</td>
<td>17.6 ± 9.4</td>
<td>9.8 ± 3.9</td>
<td>10.3 ± 3.4</td>
<td>22.9 ± 9.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Histopathological score of the implants at the end of the treatment</td>
<td>2.4 ± 1.2</td>
<td>1.4 ± 1.1</td>
<td>0.8 ± 1.1</td>
<td>2.6 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Statistically different from Group I and control group. Statistically different from values which were measured before the medication in same group (P < 0.05).

Statistically different from values which were measured before the medication in same group (P < 0.05).

Statistically different from Group I and control group.
of statins in humans range between 0.002 and 0.2 μmol l⁻¹ for atorvastatin (10–80 mg day⁻¹) (Cilla et al., 1996). Atorvastatin can be prescribed in humans at doses of 10, 20, 40 and 80 mg day⁻¹ to lower the serum lipids as deemed appropriate by the physician. Atorvastatin at 80 mg day⁻¹ is a high dose for humans. In a recent prospective randomized study including 10 001 patients, it was shown that intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable coronary artery disease provided significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day (LaRosa et al., 2005). However, high-dose atorvastatin (80 mg day⁻¹) resulted in a greater incidence of elevated aminotransferase levels when compared to low-dose atorvastatin (10 mg day⁻¹) (1.2% versus 0.2%, respectively) (LaRosa et al., 2005). Increased levels of aminotransferases do not lead to liver disease in women treated with high-dose atorvastatin (80 mg day⁻¹). The rate of other side effects is comparable between high dose and low-dose atorvastatin in humans [headache (5.4% versus 6.4%), flu syndrome (2.2% versus 3.2%), abdominal pain (2.8% versus 2.1%), back pain (2.8% versus 1.1%), constipation (2.1% versus 1.1%), diarrhoea (2.7% versus 5.3%), dyspepsia (2.3% versus 2.1%), flatulence (2.1% versus 1.1%) and rash (3.9% versus 1.1%), respectively] The exact effect of high-dose atorvastatin on the human female reproductive system is not understood. However, studies in rats performed at doses up to 175 mg kg⁻¹ (~15–20 times the human exposure) produced no changes in fertility. Safety for women in early pregnancy has not been established. Atorvastatin crosses the rat placenta and reaches a level in the fetal liver equivalent to that of maternal plasma Lipitor Manufacturer information (Pfizer, Istanbul, Turkey). Atorvastatin was not teratogenic in rats at doses up to 300 mg kg⁻¹ day⁻¹.

It was previously shown that treatment of rats with 100 mg kg⁻¹ day⁻¹ of atorvastatin for 3 months resulted in a plasma area under the curve (0–24 h) value of ~16 times the mean human plasma drug exposure after an 80 mg oral dose. In other words, the mean plasma drug exposure after an 80 mg oral dose in humans is approximately equivalent to 6.25 mg kg⁻¹ day⁻¹ atorvastatin in rats. Since 2.5 mg kg⁻¹ day⁻¹ atorvastatin administration in our study was sufficient to cause a regression of endometriotic implants in rats, we

Figure 1. (A) An endometriotic implant in the low dose atorvastatin group of rats (after medication with 0.5 mg kg⁻¹/day⁻¹ oral for 21 days). (B) An endometriotic implant in the high dose atorvastatin group (after medication with 2.5 mg kg⁻¹ day⁻¹ oral for 21 days). (C) An endometriotic implant in the leuprolide acetate (GnRH agonist) group [after a single s.c. injection of leuprolide acetate depot formulation (1 mg kg⁻¹)]. (D) An endometriotic implant in control group.
may hypothesize that, in humans, high-dose atorvastatin (80 mg day$^{-1}$) treatment may be sufficient to induce the angiostatic effects of atorvastatin. Therefore, further human studies should be performed to clarify the effect of high-dose atorvastatin (80 mg day$^{-1}$) on endometriosis.

To our knowledge, there is no study in the literature evaluating the effect of statins directly on endometriosis. Two studies have evaluated the effect of statins on endometrial cells (Kwintkiewicz et al., 2004; Esfandiari et al., 2005). Esfandiari et al. (2005) examined the inhibitory effect of a statin (lovastatin) on angiogenesis in a 3D culture of human endometrial fragments in vitro. They reported that angiogenesis was abolished and cell proliferation was inhibited in the presence of 5 μmol l$^{-1}$ lovastatin. In the presence of 1 μmol l$^{-1}$ lovastatin, angiogenesis was reduced but cell proliferation was not affected. Similarly, Kwintkiewicz et al. (2004) reported that statins induced dose-dependent inhibition of endometrial stromal cell proliferation. At the highest level (30 μmol l$^{-1}$) mevastatin inhibited proliferation by 73%. Even more potent was simvastatin, which at the highest level (30 μmol l$^{-1}$) decreased proliferation by 97%. However, in our study, we directly assessed the effect of atorvastatin on endometriotic implants. We noted that, low-dose atorvastatin (0.5 mg kg$^{-1}$ day$^{-1}$ oral) significantly increased the size of the endometriotic implants. On the contrary, high-dose atorvastatin (2.5 mg kg$^{-1}$ day$^{-1}$ oral) caused a significant regression of endometriosis implants.

In this study, we also noted that leuprolide acetate, a GnRHa, caused a significant decrease in the size of the endometriotic implants, as we expected. GnRHa causes regression of endometriotic implants via resulting hypoestrogenism (pseudomenopause). However, it was previously shown that GnRHa also had anti-inflammatory effects, which decrease pelvic endometriosis and adhesions. Wright and Sharpe-Timms (1995) investigated the effectiveness of GnRHa therapy on adhesion formation and reformation in established rat models for surgically induced adhesion formation and endometriosis. They reported that preoperative GnRHa therapy reduced adhesion scores in rats with surgically induced endometriosis. In our study, we noted that VEGF levels were significantly decreased when GnRHa (leuprolide acetate depot formulation [1 mg kg$^{-1}$ body weight]) was administered. This finding suggests to us that there is also an anti-inflammatory action of GnRHa, which results in regression of endometrial implant and decreases VEGF levels.

There are three limitations of our study. The first is that changes in serum estradiol and atorvastatin levels of the rats during the study period were not assessed. The second is that only two doses of atorvastatin were tested instead of concentration gradients including the mid-range doses. The third is that rats are different from women with respect to reproductive anatomy and physiology and they do not undergo menstruation or spontaneous endometriosis. Therefore, the next step in Figure 2. (A) Histologic section from a control rat indicating well-preserved viable epithelial tissue (score 3) (Hematoxylin-Eosin X4 original magnification). (B) Histologic section from rat treated with low dose Atorvastatin, also indicating viable epithelial tissue (score 3) (Hematoxylin-Eosin X4 original magnification). Histologic sections from rat treated with high dose atorvastatin (C) and leuprolide acetate (D) showing marked atrophy and regression of the epithelial tissue (score 0). Histologically marked hyalinizations are observed at the tissues. (Hematoxylin-Eosin X4 original magnification- insets-X10 original magnification).
evaluating the role of statins in the prevention or treatment of endometriosis should be to test these products in more relevant preclinical models such as the baboon model for endometriosis.

In baboon models, it has been shown that tumor necrosis factor (TNF)-alpha inhibitors may both prevent and treat endometriosis (D’Hooghe et al., 2006; Falconer et al., 2006). D’Hooghe et al. (2006) investigated the effect of a TNF-alpha inhibitor, recombinant human TNFRSF1A (r-hTBP1), on the development of endometriotic lesions in 20 baboons. He reported that baboons treated with r-hTBP1 had a lower endometriosis Revised American Fertility Society score, a lower surface area and estimated volume of peritoneal endometriotic lesions and a lower histological confirmation rate compared with the controls. No hypoestrogenic effects were observed in baboons treated with r-hTBP1. In another study, Falconer et al. (2006) reported that anti-TNF-monoclonal antibody (c5N) treatment significantly reduced the extent of endometriosis, mainly due to reducing both the number and surface area of red lesions in 18 adult female baboons. In our study, we noted that VEGF levels were significantly decreased in the high-dose atorvastatin and leuprolide acetate group. Our findings confirmed that VEGF contributes to the aetiology of endometriosis via angiogenesis. Inhibition of angiogenesis probably decreased the VEGF levels in peritoneal fluids.

In conclusion, we observed that high-dose atorvastatin (2.5 mg kg\(^{-1}\) day\(^{-1}\) oral) significantly reduced the size of experimentally induced endometriotic implants and VEGF levels in peritoneal fluids of rats. The findings of this study provide a basis for further studies aimed at assessing statins as potential therapeutic agents in the treatment of endometriosis.

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