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c-Jun NH_2-terminal kinase (JNK) inhibitor bentamapimod reduces induced endometriosis in baboons: an assessor-blind placebo-controlled randomized study

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Objective: To test the hypothesis that the c-Jun NH_2-terminal kinase (JNK) inhibitor (JNKI) bentamapimod (AS602801/PGL5001) can reduce induced endometriosis in baboons.
Design: Prospective randomized placebo-controlled study.
Setting: Nonhuman primate research center.
Animal(s): Twenty baboons each underwent four laparoscopies. Initial screening laparoscopy (L1) was followed after one rest cycle by an endometriosis-induction laparoscopy (L2). Fifty days after L2, the baboons were randomized just before staging laparoscopy (L3). Treatment lasted for 60 days, followed by a post-treatment staging laparoscopy (L4).
Intervention(s): Randomization before a 60-day treatment in four groups: daily placebo (n = 5), daily oral administration of 20 mg/kg JNKI (n = 5), concomitant daily oral administration of 20 mg/kg JNKI and 10 mg medroxyprogesterone acetate (MPA; n = 5), or subcutaneous administration of 3 mg cetrorelix every 3 days (n = 5).
Main Outcome Measure(s): Type, surface area and volume of endometriotic lesions, and revised American Society for Reproductive Medicine score and stage were recorded during L3 and L4. Menstrual cycle length and serum hormonal concentration were recorded before and after treatment.
Result(s): Compared with placebo, treatment with JNKI, JNKI + PMA, or cetrorelix resulted in lower total surface area and volume of endometriotic lesions. Remodeling of red active lesions into white lesions was observed more frequently in baboons treated with JNKI + MPA than in baboons treated with JNKI only. Menstrual cycle length and serum hormonal concentration were similar between placebo and JNKI groups.
Conclusion(s): JNKI alone was as effective as JNKI + MPA or cetrorelix in reducing induced endometriosis in baboons, but without severe side effects or effect on cycle length or serum reproductive hormones. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: JNK, endometriosis, baboons, endometriotic lesions, biomarkers

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Endometriosis is a benign gynecologic disease, defined by the presence of functional endometrial tissue fragments outside the uterine cavity, associated with chronic inflammation, pelvic pain, and subfertility. Studies have shown that chronic pelvic pain contributes to 10% of all outpatient visits to a gynecologist and is responsible for ~40% of laparoscopies and 10%–15% of hysterectomies (1). Current medical therapy is aimed at suppressing endometriosis lesions and minimizing endometriosis-associated pelvic pain, but existing therapies neither eliminate lesions or adequately suppress pain symptoms beyond the cessation of treatment. The ideal antiendometriosis drug should prevent the progression of endometriosis, cure existing disease and related adhesions, not interfere with the menstrual cycle, be safe regarding conception and pregnancy, and have no (or few) side effects. Such a drug does not exist today and would represent a major breakthrough in the management of endometriosis.

Over the past 20 years, the baboon model of endometriosis has been developed and validated as the best preclinical model for endometriosis (2). Although baboons have the full range of spontaneous endometriosis observed in humans (3), peritoneal endometriosis can also be induced after intrapelvic injection of menstrual endometrium, with laparoscopic and histologic aspects similar to spontaneous endometriosis in baboons or in humans (4). This experimental endometriosis model in baboons has been used to validate several candidate therapies. Among the endocrine agents evaluated in the baboon endometriosis model, aromatase inhibitors have been shown to reduce lesion volume without affecting menstrual cycle length in baboons (5), whereas GnRH antagonists, though effective, disrupt the menstrual cycle (6). Both aromatase inhibitors and GnRH analogues have demonstrated favorable lesion regression in women. Although there are abundant reports documenting benefit of GnRH analogues on lesion regression or pain, aromatase inhibitors have been evaluated in a only a limited number of premenopausal patients, and only in the presence of additional therapies (progestins, GnRH analogues); this combination treatment has been demonstrated to reduce endometriosis-related pain (7). In postmenopausal women, case reports have shown that aromatase inhibitors can be used as single agents to relieve pelvic pain (8, 9). GnRH antagonists have also been shown to cause endometriotic lesion regression in baboons (6), however at the doses used, they disrupt menstrual cycles. A recent study conducted in women with the use of elagolix, an orally active GnRH antagonist, demonstrated that nonmenstrual pain was reduced, but that menstrual pain (during progesterone withdrawal) was not superior to placebo (10). Progesterone responsiveness is linked with control of pain in endometriosis; pain management is the primary clinical trial objective, and lesion regression is a secondary clinical objective.

Several nonendocrine therapies have also been evaluated in the baboon model and were designed to reduce systemic inflammation in expectation that this could reduce the peritoneal impact of disease. A peroxisome proliferator–activated receptor (PPAR) γ agonist was shown to be partially effective at reducing typical and red lesions through its receptor-dependent pharmacology without interfering with steroid hormone effects on menstrual cycles (11), and a recombinant tumor necrosis factor (TNF) α–binding protein 1 was shown to prevent development of endometriotic lesions (6). Despite the demonstration of peritoneal endometriosis lesion regression with a species-adapted variant of infliximab (12) (c5N; anti–TNF-α antibody), infliximab failed to be effective in management of pelvic pain in patients with deep endometriosis awaiting surgery (13).

JNK inhibitor AS602801 has previously been evaluated for its mechanism of action in blood cells obtained from multiple sclerosis (MS) patients (14). In that disease, the response of motor neurons is impaired by excessive proliferation and activation of T cells that compromise the function of the myelin sheath. By analogy, endometriosis has been described over several years as an immune activation with multiple immune cell types reported to be elevated in the peritoneal fluid in combination with increased presence of sensory nerves (15). The parallel involvement of inflammation and neurons in these two diseases raised the intriguing possibility that JNK inhibitors may also be useful in treatment of endometriosis.

It has been hypothesized that progesterone resistance is a key mechanism in the development and progression of endometriosis (16, 17). Progesterone naturally antagonizes estrogen action in the uterus, but in women with endometriosis, progesterone receptor and Hic-5 coactivator levels have been reported to decline, and progesterone receptor function is reduced in eutopic and ectopic endometrium of patients compared with volunteers (18). From the foregoing, it would be reasonable to include the use of a progestin in studies that evaluate new candidate therapies that target different axes of the disease mechanism.

In a parallel study (19), we demonstrated that JNKI bentamapimod (also coded AS602801 or PGL5001) caused regression of experimentally induced endometriosis in the nude mouse model for endometriosis as well as in the surgically induced model of endometriosis in the rat. JNK inhibitor AS602801 improved the apparent progesterone resistance among in vitro cultures of human endometrial organ cultures, as measured by production of matrix metalloproteinases (MMPs) 3 and 7. Although neither rodent model provides a precise simulation of human endometriosis, these results raised the possibility that a JNK inhibitor, alone or in combination with hormonal modulation, could target both inflammatory and endocrine axes of the disease and provided the basis for a clinical trial design.

Modulation of endometriosis via the use of JNK inhibitors therefore represents a novel mechanism of action in the disease, because it targets both inflammation and proliferation cascades in endometriosis. Combination of AS602801 with a contraceptive progestin (in this case, medroxyprogesterone acetate [MPA], also approved for use in treatment of endometriosis) would enable assessment of the impact of contraceptive agents on the efficacy of AS602801 and provide a preliminary measure of recovery of progesterone resistance, if it developed, in baboons.

Based on new insights in endometriosis, it has become clear that pelvic inflammation, increased macrophage activation,