Selective estrogen receptor modulator and selective progesterone receptor modulator: Therapeutic efficacy in the treatment of uterine leiomyoma

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Summary

Recent advances in endocrinology open a door for clinical application of selective estrogen receptor modulator (SERM) and selective progesterone receptor modulator (SPRM) in the treatment of uterine leiomyoma. With regard to SERM, treatment with raloxifene is shown to reduce leiomyoma size in postmenopausal women. Although raloxifene causes shrinkage of leiomyomas in combination with gonadotropin-releasing hormone agonist in premenopausal women, the effects of monotherapy with raloxifene on leiomyoma growth in premenopausal women remain controversial. By contrast, tamoxifen may not be suitable for long-term treatment of leiomyomas due to an agonistic action on the endometrium. Treatment with progesterone antagonist (RU486) or SPRM (J867) has been demonstrated to inhibit leiomyoma growth and improve clinical symptoms in premenopausal women. No serious adverse effects associated with SERM or SPRM have been reported. In light of therapeutic efficacy and few adverse effects, SERM and SPRM may hold promise as novel treatment modalities for leiomyoma. Further studies are warranted to determine the optimal strategy for the treatment of leiomyoma with SERM and SPRM.

Key words: Selective estrogen receptor modulator (SERM); Selective progesterone receptor modulator (SPRM); Leiomyoma.

Uterine leiomyoma is a sex steroid hormone-related neoplasm that possesses estrogen receptors and progesterone receptors. Accumulating data support the concept that estrogen and progesterone play critical roles in regulating leiomyoma growth [1]. These sex steroid hormones activate the transcription of target genes through interaction with specific nuclear receptors. By contrast, selective estrogen receptor modulator (SERM) and selective progesterone receptor modulator (SPRM) bind to estrogen receptors and progesterone receptors, respectively, and exhibit tissue-selective agonist and antagonist properties [2, 3].

Preclinical data obtained from animal studies have demonstrated that SERMs such as tamoxifen and raloxifene inhibit leiomyoma growth [4-7], but what about the effect of SERMs on leiomyoma growth in the clinical setting? A small prospective randomized study demonstrated that treatment with tamoxifen 20 mg daily for six months did not affect leiomyoma size [8]. In addition to the discouraging results, tamoxifen is associated with an increased risk of endometrial cancer due to an agonistic action on the endometrium. Tamoxifen may not be acceptable as a therapeutic agent for leiomyoma. Unlike tamoxifen, raloxifene has no increased risk of endometrial cancer due to the lack of estrogenic activity in the uterus [2]. In a prospective randomized placebo-controlled clinical trial, Palomba et al. [9] first demonstrated that treatment with raloxifene 60 mg daily for one year significantly reduced leiomyoma size in postmenopausal women without affecting endometrial thickness. However, the results of therapeutic efficacy of raloxifene in premenopausal women remain inconsistent. Palomba et al. [10] reported that raloxifene at the doses of 60 mg or 180 mg daily for six months had no significant effect on leiomyoma size in premenopausal women, whereas Jirecek et al. [11] demonstrated that treatment with raloxifene 180 mg daily for three months inhibited leiomyoma growth in premenopausal women. The discrepancy between the results of these studies might be due to the difference in circulating estrogen levels and study design [12]. Moreover, a recent randomized study has demonstrated that estrogen receptor antagonist fulvestrant does not induce shrinkage of leiomyoma in premenopausal women [13]. The authors suggest that the lack of effect of fulvestrant on leiomyoma growth may be related to high circulating estradiol levels in premenopausal women [13]. Thus, it seems unreasonable to speculate that monotherapy with raloxifene is optimal for inhibiting leiomyoma growth. It may be necessary to render hormonal status hypoestrogenic for enhancing therapeuetic efficacy of raloxifene and fulvestrant in premenopausal women. This hypothesis has been tested in several clinical trials. Palomba et al. [14, 15] demonstrated that combined therapy with raloxifene at a dosage of 60 mg daily and gonadotropin-releasing hormone (GnRH) agonist for six months in premenopausal women provided more benefits in reducing leiomyoma size and in preventing bone loss compared with GnRH agonist alone. Moreover, the efficacy and safety of this combined therapy over 18 months has been confirmed [16]. Since raloxifene is an osteoporosis agent, it seems reasonable to use raloxifene for preventing bone loss during GnRH agonist therapy. However, the optimal dose of raloxifene and duration of treatment has not been determined. The adverse effects associated with raloxifene during the treatment of leiomyoma include hot flushes, nausea, gastralgia, leg cramps, and dry skin [9-11]. Although no serious complications have developed during the treatment of leiomyoma, it should be kept in mind that raloxifene is associated with thromboembolic diseases such as deep vein thrombosis and pulmonary embolism [2].
Progesterone receptor ligands exhibit a spectrum of activity ranging from pure progesterone antagonist to mixed agonist/antagonist. RU486 (mifepristone) behaves as a pure progesterone antagonist, whereas J867 (asoprisnil) behaves as a mixed agonist/antagonist [3]. Treatment with RU486 induces the regression of leiomyoma with a decrease in immunoreactivity for progesterone receptor [17]. Murphy et al. [17, 18] reported that treatment with RU486 at a dosage of 50 mg daily for three months in premenopausal women resulted in a 49% to 51% reduction of leiomyoma size with no changes in bone mineral density, and that a 25-mg dosage, but not a 5-mg dosage, was as effective as the 50-mg dosage in achieving regression of leiomyoma. Moreover, Eisenger et al. [19] have recently demonstrated that RU486 administration at lower doses of 5 mg or 10 mg daily for six months in premenopausal women resulted in a 48% and 49% decrease in leiomyoma size, respectively. However, these data on the therapeutic efficacy of RU486 should be interpreted with caution because they were not based on placebo-controlled studies. By contrast, a recent placebo-controlled parallel-group study demonstrated that J867 at doses of 5 mg, 10 mg, and 25 mg daily for three months reduces leiomyoma size and the duration and intensity of uterine bleeding in a dose-dependent manner [20]. The adverse effects associated with RU486 include hot flushes, mild elevations of hepatic enzymes, and endometrial hyperplasia [17-19]. The development of endometrial hyperplasia may be attributable to the unopposed estrogen effect on the endometrium resulting from the antiprogestrone activity of RU486. In contrast, J867 has been reported to induce endometrial atrophy accompanied by stromal compaction in female cynomolgus monkeys, although the mechanism of an antiproliferative effect of J867 on the endometrium is unknown [21].

Eisenger et al. [19] offered three possible applications of low dose RU486 in the treatment of leiomyoma, including 1) an alternative to GnRH analogues for preoperative use, 2) taking this medication until menopause in perimenopausal women with large, symptomatic leiomyomas, and 3) clinical application in younger women with large leiomyomas who wish to retain fertility. RU486 may be an effective therapeutic agent for the treatment of leiomyoma, but the development of endometrial hyperplasia may limit the long-term use of this agent. Although combined therapy with RU486 or J867 with GnRH agonists has not been tested in patients with leiomyoma, it may be another option for the treatment of leiomyoma. In combined therapy, hypoestrogenic status induced by GnRH agonists would suppress the occurrence of endometrial hyperplasia, but it may impinge on bone mineral density. As suggested by Eisenger et al. [19], the long-term effects of RU486 on fertility remain unknown. Further study is warranted to determine therapeutic efficacy and risks associated with combined therapy with SPRM and GnRH agonists in the treatment of leiomyoma.

Little information is available regarding the precise mechanism by which raloxifene and SPRM cause shrinkage of leiomyoma. It has been reported that raloxifene analog reduces Eker rat leiomyoma growth through inhibition of cell proliferation without induction of apoptosis [7], but cellular actions of SPRM on leiomyoma cells remain to be elucidated. A better understanding of the actions of SERM and SPRM on leiomyoma will contribute to the effective and safe usage of these compounds for the treatment of leiomyoma. Collectively, SERM and SPRM may hold promise as novel non-surgical therapeutic agents for the treatment of leiomyoma. However, prospective randomized placebo-controlled studies are necessary to determine the optimal strategy for the treatment of leiomyoma with SERM and SPRM.

References


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