[UCI]I804:24011-200000266126

2017년 2월
석사학위 논문

장기간 생식샘 자극 호르몬 방출 호르몬 작용제 치료를 하는 심각한 자궁내막증 환자에서 랄록시펜의 투여

- 골밀도에 미치는 영향 -

조선대학교 대학원

의 학 과

조 영 화

장기간 생식샘 자극 호르몬 방출 호르몬 작용제 치료를 하는 심각한 자궁내막증 환자에서 랄록시펜의 투여

- 골밀도에 미치는 영향 -

Raloxifene Administration in Women Treated with Long Term Gonadotropin-Releasing Hormone Agonist for Severe Endometriosis:Effects on Bone Mineral Density

2017년 2월 24일

조선대학교 대학원

의 학 과

조 영 화

장기간 생식샘 자극 호르몬 방출 호르몬 작용제 치료를 하는 심각한 자궁내막증 환자에서 랄록시펜의 투여

- 골밀도에 미치는 영향 -

지도교수 정 혁

이 논문을 의학 석사학위신청 논문으로 제출함

2016년 10월

조선대학교 대학원

의 학 과

조 영 화

조영화의 석사학위논문을 인준함

위원장 의과대학교 교 수 이 상 홍 (인)

위 원 의과대학교 교 수 정 혁 (인)

위 원 의과대학교 교 수 유 병 식 (인)

2016년 11월

조선대학교 대학원

목 차

표목차

초 록

장기간 생식샘 자극 호르몬 방출 호르몬 작용제 치료를 하는 심각한 자궁내막증 환자에서 랄록시펜의 투여

조 영 화
지도교수:정 혁
조선대학교 병원 산부인과

목표: 장기간 생식샘 자극 호르몬 방출 호르몬 투여를 하는 경우 랄록시펜이 골소실을 예방하는 효과에 대해 평가하였다.

설계: 전향적, 무작위, 관찰 추적 연구를 시행하였다.

환경: 조선대학교 병원 산부인과

결과 및 측정: 골밀도 변화

방법: 심각한 자궁내막증이 있는 22명의 폐경전 여성에서 루프로라이드 아세테이트 데포를 4주 간격으로 3.75mg 씩 48주 동안 투여하였다. 골밀도 측정은 치료 시작할 때와 12회 치료 완료 후 시행하였다.

결과: 생식샘 자극 호르몬 방출 호르몬과 랄록시펜 12회 치료 시작 전후 요추, 대퇴 전자, 대퇴 경부, 대퇴 근위부의 골밀도를 측정하였다. 요추와 대퇴 전자는 치료 시작 1년후 약간 감소하였으나(도표 2), 의미 있는 차이는 없었다.

결론: 본 연구 결과 폐경 전 심각한 자궁 내막증 환자에게 장기간 생식샘 자극 호르몬 방출 호르몬과 랄록시펜을 함께 투여하는 것은 골밀도 손실 예방에 효과적이었다.

중요 단어:장기간 생식샘 자극 호르몬 방출 호르몬 / 랄록시펜 / 심각한 자궁 내막증 / 골밀도

INTRODUCTION

Endometriosis, a common gynecological condition causing cyclical pain, dyspareunia, and infertility, affects 2-5% of women of reproductive age (1). Endometriosis commonly recurs after medical or surgical treatment; in the absence of a drug treatment that is safe for long-term use, recurrence can lead to hysterectomy and bilateral oophorectomy (2). Goals of therapy include relief of symptoms, resolution of existing lesions, and prevention of new lesions (3). GnRH-a are increasingly used to treat endometriosis (4).

Therapy with GnRH-a achieves hypoestrogenism and amenorrhea by suppressing pituitary gonadotropin secretion. Several studies have shown that use of GnRH-a promotes subjective and objective improvements in endometriosis symptoms (4-6).

Prolonged treatment is often required to achieve clinically significant effects on endometriotic symptoms. However, there is concern about the clinical, physical, and biochemical side effects of hypoestrogenism, particularly the rapid reduction in bone mineral density (BMD) that could increase the risk of osteoporosis. Thus, the use of GnRH-a is generally restricted to a 6-month course (7-10).

However, GnRH-a related hypoestrogenism frequently causes climacteric-like symptoms, such as vasomotor symptoms and overall severe bone loss (11, 12). Several drugs have been associated with GnRH-a to reduce these side effects and to allow prolonged treatment (11-18).

Raloxifene hydrochloride is a synthetic non-steroidal drug derived from benzothiophene and afferent to selective estrogen receptor modulators(SERM), a group of compounds that interact with estrogen receptors eliciting tissue-specific responses (19, 20).

Raloxifene acts on the metabolism, central nervous system, skeleton and

cardiovascular system as an estrogenic agonist (21-24), whereas it shows a weak estrogenic antagonist effect on reproductive organs, including the breast and uterus (25-27). Therefore, raloxifene has been used as a therapeutic agent for osteoporosis.

Continuous administration of GnRH-a inhibits the release of gonadotropins inducing a down-regulation of pituitary GnRH receptors and a state of hypogonadotropic hypogonadism (11, 12).

Thus far, there has been limited research regarding raloxifene administration for the prevention of the bone loss associated with GnRH-a. Therefore, the aim of this study was to evaluate whether the bone loss that occurs when using GnRH-a could be prevented. Raloxifene appears to be an effective add-back candidate to associate with GnRH-a. Consequently, the present study was designed to investigate the effect of adding 60 mg of raloxifene hydrochloride daily to women treated with GnRH-a for severe endometriosis on bone metabolism.

MATERIALS AND METHODS

Patient Selection

The present study was conducted in the Department of Obstetrics and Gynecology at Chosun University Hospital. From January 2012 to December 2015, 22 reproductive female patients from 25 to 51years old who suffered from endometriosis were enrolled in a non-randomized prospective study.

Exclusion criteria were as follows: patients with BMD below the age-matched normal range(z-score below -1.5), who had physical findings that affected the measurement of BMD, such as fracture or osteoarthritis of spine, and who were administered drugs that affected bone turnover, or who received therapy for endometriosis within 4 weeks prior to the start of the study. Written consent from the patient was obtained before enrollment.

Thirty-two patients were enrolled in this study. Four patients discontinued leuprolide administration due to adverse effects or undesirable complications. Two patients were excluded because hormone drugs(oral pill) had been administered within 4 months prior to the start of treatment, and four patients were excluded because BMD was not measured correctly. Thus, the analysis was performed on 22 patients.

Treatment protocol

At the start of the study, all subjects were randomized in a study design using a computer-generated randomization list. The subjects were assigned to 22 women. All women received leuprolide acetate depot (LAD) (Enantone; Takeda, Rome, Italy) at a dose of 3.75 mg/4 weeks combined with raloxifene hydrochloride (Evista; Eli Lilly, Sesto Fiorentino, Italy) at a dose of 60 mg/day p.o. The duration of the study was 12 cycles of 4 weeks each, and for this

period, the single-blinding was maintained.

Study protocol

BMD was measured at the beginning of the study and after cycle 12 treatment with GnRH-a plus raloxifene.

BMD measurement

The BMD was determined using a prodigy series X-ray tube housing assembly (LUNAR, GE Medical system, Madison, Wisconsin USA) at the posterior-anterior lumbar spine(vertebrae L1 to L4) and hip(trochanter, ward's and femoral neck).

The results of absorptiometry were examined by a single observer blind to different treatment regimens. The primary end-point was the lumbar spine BMD. Hip trochanter, ward, sand femoral neck BMD were considered secondary end-points.

Statistical analysis

In this study, the paired t- test was used to compare the BMD differences of the lumbar spine, trochanter, femoral neck, and ward's in women before and 1 year after treatment with GnRH-a plus raloxifene. A P value of $< .05$ indicated statistical significance. Statistical analysis was performed using SPSS (version 12.0, Korea).

RESULTS

Demographic data

Twenty-two enrolled patients completed the study. All the patients had endometriosis diagnosed by laparoscopy. The classification of patients is shown in Table 1.

Subjects in this study had a mean body weight of 62.2 ±10.2 kg; mean height of 159 ± 5.1 cm, and BMI of 24.7 ± 4.3 kg/m^2.

BMD measurements

We designed a prospective study and checked lumbar spine, trochanter, femoral neck, and ward's BMD in 22 patients at the start of the study and 1 year after treatment with GnRH-a plus raloxifene.

At cycle 12 of treatment with GnRH-a plus raloxifene, lumbar spine, trochanter, femoral neck, and ward's BMD differed from before treatment. The lumbar spine and trochanter decreased slightly at the 1 year after treatment than before (Table 2), but were not significantly different.

Side effects and drop-outs

Throughout the study, the treatment schedules were generally well tolerated. Raloxifene was well tolerated. No serious adverse experience was reported during the study. No drop-out was due to drug-related adverse experiences.

DISCUSSION

Use of GnRH-a has an established place in the medical treatment of endometriosis. These agents act by down-regulating pituitary gonadotropins, resulting in the suppression of gonadotropin production and secondary ovarian suppression. This ovarian suppression may lead to osteopenia by reducing the BMD.

Accordingly, treatment with GnRH-a alone is generally restricted to 6 month duration because of concern about continuing loss of BMD over longer treatment periods. All studies agree that bone loss occurs with continued use of GnRH-a for 6 months or more.

Circulating estradiol levels decrease to the post-menopausal range, producing important menopausal side effects, such as a reduction in BMD at the lumbar spine (28, 29) and proximal femur (30). Therefore, there is a need for the prevention of bone loss during long term treatment with GnRH-a.

Raloxifene at the standard dosage of 60 mg daily prevents postmenopausal bone loss in women without osteoporosis and is used also to treat established postmenopausal osteoporosis (31, 32).

In addition, raloxifene reduces the risk of vertebral fractures in postmenopausal osteoporotic women with or without preexisting fractures by about 40% vs. a placebo (33-36), thereby improving quality of life (37).

In women treated with GnRH-a, the positive effect of raloxifene on bone metabolism was also confirmed by the lack of significant change in biochemical parameters of bone formation and reabsorption (38). Goldstein et al (27) confirmed that raloxifene did not induce endometrial proliferation in

post-menopausal women, unlike estrogen.

Besides, a variety of anti-reabsorptive drugs has been used to preserve the bone tissue during GnRH-a treatment. During our study period, few side- effects were detected and raloxifene treatment was tolerated.

In the case of severe endometriosis, patients were administered GnRH-a for 6 months. However, sometimes the pain recurred after normal menstruation restarted. Therefore, a method of treating patients has not been fully established.

If necessary, the treatment could be administered in the oral pill, progestin but GnRH-a is known to suppress endometrial lesions and symptoms. Therefore, GnRH-a was administered with raloxifene to inhibit bone loss that was the greatest side effect of GnRH-a administration.

In a previous report, there was no change in BMD when a combination of GnRH-a and raloxifene was administered for six months, thereby the present study administered a combination of GnRH-a and raloxifene for 1 year in patients who suffered from pain.

Our findings suggest that BMD is reduced slightly over 1 year of treatment with GnRH-a and raloxifene, but was not statistically significantly different from the start of the study. Therefore, this treatment does not seem to affect bone loss significantly.

In conclusion, our study shows that the administration of GnRH-a plus raloxifene in pre-menopausal women with severe endometriosis is effective to prevent bone loss for long- term treatment. It is possible that raloxifene could be used as an ‘add-back therapy’ in women treated with GnRH-a.

REFERENCES

1. Haney AF. The pathogenesis and etiology of endometriosis. In: Thomas E, Rock J, eds. Modern approaches to endometriosis. The Netherlands: Kluwer Academic Publishers, 1991:3-19.

2. Howell R, Edmonds DK, Dowsett M, Crook D, Lees B, Stevenson JC. Gonadotropin-releasing hormone analogue(goserelin) plus hormone replacement therapy for the treatment of endometriosis: a randomized controlled trial. Fertil Steril 1995;64:474-81.

3. McLachlan RI, Healy DL, Berger HG. Clinical aspects of LHRH analogues in gynecology: a review. Br J Obstet Gynecol 1986;93:431-54.

4. Erickson LD, Ory SJ. GnRH analogues in the treatment of endometriosis. Obstet Gynecol Clin North Am 1989;16:123-45.

5. Meldurm DR,Chang RJ, Lu J, Vale W, Rivier J, Judd HL. Medical oophorectomy: using a long acting GnRH agonist-a possible new approach to the treatment of endometriosis. J Clin Endocrinol Metab 1982;54:1081-3.

6. Lemay A, Maheux R, Faure N, Jean C, Fazekas ATA. Reversible hypogonadism induced by a luteinizing hormone releasing hormone(LH-RH) agonist(buserelin) as a new therapeutic approach for endometriosis. Fertil Steril 1984;41:663-71.

7. Fogelman I. Gonadotropin-releasing hormone agonists and the skeleton. Fertil Steril 1992;57:715-24.

8. Lemay A, Surret Es, Friedman AJ. Extending the use of gonadotropin-releasing hormone agonists: the emerging role of steroidal and non-steroidal agents. Fertil Steril 1994;61:21-34.

9. Orwoll ES, Yuzpe AA, Burry KA, Heinrichs L, Buttram VC Jr, Hornstein MD. Nafarelin therapy in endometriosis: Long-term effects on bone mineral density. Am J Obstet Gynecol 1994;171:1221-5.

10. Crosignani PG, Olive D, Bergqvist A, Lucianl A. Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update 2006;12:179-89.

11. Surrey Es. Steroidal and nonsteroidal "add-back" therapy: extending sagety and efficacy of gonadotropin-releasing hormone agonist in the gynecologic patient. Fertil Steril 1995;64:673-85.

12. Pickergill A. GnRH agonists and add-back therapy: is there a perfect combination? Br J Obstet Gynecol 1998;105:475-85.

13. Palomba S, Affinito P, Tommaselli GA, Nappi C. A clinical trial on the effects of tibolone association with gonadotropin-releasing hormone analogues for the treatment of uterine leiomyomata. Fertil Steril 1998;70:111-8.

14. Palomba S, Affinito P, Di Carlo C, Bifulco G, Nappi C. Effects of long-term administration of tibolone plus GnRH-a in the treatment of uterine leiomoymata on effectiveness, vasomotor symptoms, bone mass and lipid profile. Fertil Steril 1999;72:889-95.

15. Di Carlo C, Palomba S, Tommaselli GA, Guida M, Di Spiezio Sardo A, Nappi C. Use of leurpolide acetate plus tibolone in the treatment of the severe premenstrual syndrome. Fertile Steril 2000;75:380-4.

16. Palomba S, Pellicano M, Affinito P, Di Carlo C, Zullo F, Nappi C. Effectiveness of short-term administration of tibolone plus gonadotropin-releasing hormone analogue on the surgical outcome of laparoscopic myomectomy. Fertil Steril 2001;75:429-33.

17. Taskin O, Yalcinoglu AI, Kucuk S, Uryan I, Buhur A, Burak F. Effectiveness of tibolone on hypoestrogenic symptoms 21. Walsh BW, KullerLH, Wild RA,

Paul S, Farmer M, Lawrence JB, Shah AS, Anderson PW. Effect of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. J Am Med Assoc 1998;279:1445-51.

22. Ettinger B, Black DM, Mitlak BH, Knickerbocker RH, Nickelsen T, Genant NK. Reduction of vertebral fracture risk in postmenopausal women with osterporosis treated with raloxifene. J Am Med Assoc 1999;282:637-45.

23. Mosca L. Rationale and overview of the raloxifene use for the heart(RUTH) trial. Ann Ny Acad Sci 2001;949,181-5.

24. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, RAutaharju P, Harper KD and The MORE Investigators(Multiple Outcome of Raloxifene Evaluation). Raloxifene and cardiovascular enents in osteoporotic postmenopausal women: four-year results from the MORE(Multiple Outcomes of Raloxifene Evaluation) randomized trial. J Am Med Assoc 2002;287:847-57.

25. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized

trial. Multiple Outcomes of Raloxifene Evaluation. J Am Med Assoc 1999;281:2189-97.

26. Cohen FJ, Watts S, Shah A, Akers R, Plouffe L. Uterine effects of 3-years raloxifene therapy in postmenopausal women younger than age 60. Obstet Gynecol 2000;95:104-10.

27. Goldstein SR, Scheele WH, Rajagopalas SK, Wilkie JL, Walsh BW, Parsons AK. A 12-month comparative study of raloxifene, estrogen and placebo on the postmenopausal endometrium. Obstet Gynecol 2000;95:95-103.

28. Dawood MY, Lewis V, Ramos J. Cortical and trabecular bone mineral content in women with endometriosis: effect of gonadotropin-releasing hormone agonist and danazol. Fertil Steril 1989;52:21-6.

29. White house RW, Adams JE, Bancroft K, Vaughan-Williams CA, Elstein M. The effects of nafarelin and danazol on vertebral trabecular bone mass in patients with endometriosis. Clin Endocrinol 1990;33:365-73.

30. Stevenson JC, Lees B, Gardner R, Shaw RW. A comparison of the skeletal effects of goserelin and danazol in premenopausal women with endometriosis. Horm Res 1989;32 Suppl:161-4.

31. Clemett D, Spencer CM. Raloxifene: a review of its use in postmenopausal osteoporosis. Drugs 2000;60:379-411.

32. Diez JL. Skeletal effects of selective oestrogen receptor modulators(SERMs). Hum Reprod Update 2000;6:255-8.

33. Prestwood KM, Gunness M, Muchmore DB, Lu Y, Wong M, Raisz LG. A comparison of the effects of raloxifene and estrogen on bone in postmenopausal women. J Clin Endocrinol Metab 2000;85:2197-2202.

34. Lufkin EG, Whitaker MD, Nickelsen T, Argueta R, Caplan RH, Knicker-bocker RK, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res 1998;13:174754.

35. Meunier PJ, Vignot E, Garnero P, Confavreux E, Paris E, Liu-Leage S, et al. Treatment of postmenopausal women with osteoporosis or low bone density with raloxifene. Raloxifene study Group. Osteoporosis or low bone density with raloxipene. Raloxifene Study Group. Osteoporos Int 1999;10:330-6.

36. Ettinger B, Black DM, Mitlak BH, Knicker bocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outxomes of Raloxifene Evaluation(MORE) Investigators. JAMA

1999;282:637-45.

37. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outxomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611-9.

38. Palomba S, Orio F, Morelli M, Susso T, Pellicano M, Nappi C, et al.Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. J Clin Endocrinol 2002;87:4476-81.

Table 1

Demographic characteristic of subjects

Characteristic		
Treatment regimen	LAD 3.75 mg/4 weeks + raloxifene 60 mg/day	
No. of patients		22
Age (years)	Mean ± SD	40.4 ± 7.4
	Range (min-max)	25-51
Weight(kg)	Mean ± SD	62.2 ± 10.2
	Range (min-max)	48-80
Height(cm)	Mean ± SD	159 ± 5.1
	Range (min-max)	148-166
Body Mass Index (kg/m^2)	Mean ± SD	24.7 ± 4.3
	Range (min-max)	18.7-32.5
Previous pregnancy	Mean ± SD	1.4 ± 0.8
	Range (min-max)	0-3

Data are expressed as mean ± SD.

LAD = leuprolide acetate depot.

Table 2

Comparison of BMD in women before and 1 year after treated with GnRH agonist plus raloxifene

BMD	Before (mean ± SD) N=22	1 year after (mean ± SD) N=22	P
T-score			
Lumbar spine	-.732 ± 1.22	-.897 ± 1.22	.065
Trochanter	.645 ± 1.67	.335 ± 1.65	.057
Femoral neck	.382 ± 1.47	.432 ± 1.47	.866
Wards	.24 ± 1.5	-.041 ± 1.63	.099
Z-score			
Lumbar spine	-.991 ± 1.11	-.959 ± 1.4	.072
Trochanter	.259 ± 1.45	.068 ± 1.56	.055
Femoral neck	.432 ± 1.47	.509 ± 1.41	.162
Wards	-1.068 ± 1.22	.177 ± 1.65	.108

Values are reported as mean ± SD.

P < .05 versus baseline.