A Canadian Observational Study of the Optimal Method of Transition From Postmenopausal Hormone Therapy to Raloxifene

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Abstract

Objective: To determine the optimal method of transition from postmenopausal hormone therapy (HT) to raloxifene (RLX) therapy in order to minimize hot flashes and night sweats.

Methods: Postmenopausal women in Canada who had discontinued HT (estrogen with or without progestogen) in the preceding nine months and who were starting RLX were followed for approximately nine months in this observational study. The method of transition from HT to RLX therapy (method and duration of tapering HT, duration of washout) and the frequency and severity of hot flashes during the transition and RLX treatment periods were recorded.

Results: There were 373 women who participated in this study. Most women (86.3%) had a washout period between HT and RLX, and 55.2% had tapered their HT in some fashion. After beginning RLX, women who had had a washout duration of more than one week were found to be more likely to have an improvement in the severity of hot flashes (odds ratio [OR] = 6.3), and in the frequency of hot flashes (OR = 4.6), than women with a shorter washout or no washout period at all. The method of tapering of HT did not seem to affect either the severity or the frequency of hot flashes once on RLX. Women who had undergone a tapering period of more than one week's duration were more likely (OR = 2.6) to experience an improvement in the frequency (but not the severity) of hot flashes on RLX.

Conclusion: Women who had a washout period following HT had better amelioration of hot flashes on RLX therapy.

Résumé

Objectif : Déterminer la méthode optimale de transition entre l'hormonothérapie (HT) et le traitement au raloxifène (RLX) chez les femmes postménopausées afin de minimiser les bouffées de chaleur et les sueurs nocturnes.

Méthodes : Dans le cadre de cette étude observationnelle, des Canadiennes postménopausées qui avaient abandonné l'HT (œstrogènes avec ou sans progestatif) au cours des neuf mois précédents et qui entamaient un traitement au RLX ont fait l'objet d'un suivi d'environ neuf mois. La méthode de transition entre l'HT et le traitement au RLX (méthode et durée de la réduction progressive de l'HT, durée de la période sans traitement), la fréquence et la gravité des bouffées de chaleur au cours de la transition, et les périodes de traitement au RLX ont été consignées.

Résultats : Cette étude comptait 373 participantes. La plupart des femmes (86,3 %) ont vécu une période sans traitement entre l'HT et le traitement au RLX, et 55,2 % des femmes avaient, d'une façon ou d'une autre, réduit progressivement la posologie de leur HT. Après le début du traitement au RLX, on a constaté qu'il était plus probable que les femmes qui avaient vécu une période sans traitement de plus d'une semaine connaissent une atténuation de la gravité des bouffées de chaleur (rapport de cotes [RC] = 6,3) et une diminution de la fréquence de celles-ci (RC = 4,6), par comparaison avec les femmes qui avaient vécu une période sans traitement plus courte ou qui n'en avaient vécu aucune. La méthode choisie pour la diminution progressive de l'HT n'a pas semblé affecter la gravité ou la fréquence des bouffées de chaleur, une fois le traitement au RLX entamé. On a constaté qu'il était plus probable que les femmes qui avaient vécu une période de diminution progressive de plus d'une semaine connaissent (RC = 2,6) une diminution de la fréquence (sans atténuation de la gravité) des bouffées de chaleur, une fois le traitement au RLX entamé.

Conclusion : Les femmes qui avaient vécu une période sans traitement à la suite de l'HT ont connu une atténuation des bouffées de chaleur, une fois le traitement au RLX entamé.

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INTRODUCTION

For many years, postmenopausal hormone therapy (HT) has been used with excellent results for the amelioration of postmenopausal symptoms such as hot flashes,[1] night sweats,[1] mood lability,[2] vaginal dryness,[3] and insomnia.[4] Other benefits attributed to HT have included maintenance of bone mineral density in postmenopausal women,[5,6] reduction of cardiovascular events in observational studies,[7] and improvements in cognition in older women.[8,9]

Along with the advantages of HT, it has long been known that estrogen may cause the side effects of endometrial proliferation (when given without progesterone), vaginal bleeding or spotting, and breast tenderness.[1,10] Randomized trials

published over the past seven years have found no benefit for HT compared with placebo with respect to cardiovascular or cerebrovascular events.[11–16] The widespread publicity surrounding the publication of results from one arm of the Women's Health Initiative (WHI) has created further confusion among prescribers and users of HT.[17–21] In this study, more than 16 000 women were randomized to treatment with either conjugated equine estrogen (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg or placebo. The absolute excess risks attributable to the CEE-MPA combination were seven more coronary heart disease events, eight more strokes, and eight more invasive breast cancers per 10 000 woman-years. Although there was also a reduction in rates of colon cancer and hip fracture in the CEE-MPA group relative to placebo, the overall harm of treatment with CEE-MPA was felt to outweigh the benefits, and the study was terminated early at 5.2 years.[17]

After release of these results, many women became concerned about continuing postmenopausal HT and decided to discontinue treatment with or without the guidance of their physicians.[19,22–24] Some of these women began using other treatments because of concerns related to loss of bone mineral density.[23,24] Raloxifene (Evista) is a selective estrogen receptor modulator (SERM) that is approved for use in Canada for the prevention and treatment of osteoporosis. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a randomized prospective trial enrolling 7705 postmenopausal women with osteoporosis, raloxifene (RLX) was shown to be effective in increasing bone mass and preventing both first and subsequent vertebral fractures.[25] Analyses of the four-year data from this trial showed that women receiving RLX experienced a sustained reduction in rates of vertebral fracture,[26] a 72% reduction in rates of invasive breast cancer,[27] and no increased risk of coronary or cerebrovascular events.[28] In both osteoporosis prevention and treatment trials, RLX treatment has been associated with an increased incidence of hot flashes compared with placebo.[25,26,29,30]

The optimal method for transitioning women from HT to RLX therapy to minimize hot flashes or night sweats has not been established. Given that hot flashes may occur for many months after the cessation of estrogen therapy, it may be unclear whether the hot flashes and night sweats occurring after the initiation of RLX therapy are related to the withdrawal of estrogen, to the initiation of RLX, or to both.

The primary objective of this observational study was to determine the optimal method of transitioning women from HT to RLX in order to minimize vasomotor symptoms. We chose to conduct an observational study in order to allow patients to discontinue their HT according to their symptoms and according to usual clinical practice patterns.

METHODS

The primary objective of this study was to determine the optimal method of transition from HT to RLX to minimize the hot flashes and night sweats experienced during RLX treatment. Secondary objectives included determining the reasons for discontinuation of HT; documenting the methods currently in use for HT tapering and washout; comparing the frequency and severity of hot flashes and night sweats in the HT tapering/washout period and the RLX therapy period; documenting the use and perceived efficacy of concomitant medications for vasomotor symptoms; and assessing compliance with RLX treatment.

The study was conducted at 44 study centres in Canada. Postmenopausal women who had discontinued HT (either spontaneously or on the advice of their physicians) within the preceding nine months and who were initiating RLX treatment in accordance with Canadian prescribing information were eligible to enter the study. They were required to provide adequate information about the manner of tapering and washout from HT (time after HT discontinuation and before initiation of RLX) and about vasomotor symptoms during these tapering and washout periods. Other than the requirement for postmenopausal status, no age restrictions were imposed. Women were excluded if they had any contraindication to the prescription of RLX (i.e., known or suspected breast cancer, abnormal vaginal bleeding of unknown cause, any history of venous thromboembolic event, or severe hot flashes or night sweats). Ethics approval was obtained for the study (Institutional Review Board Services, Aurora, ON) and all subjects signed informed consent documents. Study subjects were followed for approximately nine months after the initiation of RLX therapy.

At baseline, clinicians recorded the method and duration of tapering HT, and the duration of any HT washout period (Figure 1), together with the reasons for the discontinuation of HT and initiation of RLX treatment. The frequency and severity of hot flashes or night sweats during tapering and washout periods were recorded from each woman's recollection. Women were prescribed commercial RLX (60 mg orally once daily) according to their clinician's usual practice at the baseline visit. Visit two was scheduled to take place approximately three months (10–14 weeks) after the initiation of RLX, and visit three approximately nine months (37–41 weeks) after initiation of RLX. At visit two and visit three, the frequency and severity of hot flashes or night sweats experienced by women during RLX therapy was recorded, along with compliance or discontinuation information. The actual date range of the visits was very wide: about a quarter of the actual visit two dates and more than a third of the actual visit three dates fell outside the suggested