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ORIGINAL ARTICLE

Intermittent progestin administration as part of hormone replacement therapy: long-term comparison between estradiol 1 mg combined with intermittent norgestimate and estradiol 2 mg combined with constant norethisterone acetate

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Background. To decrease exposure to progestin during hormone replacement therapy (HRT), a novel oral regimen consisting of constant 17β-estradiol (E_2) daily plus intermittent norgestimate (NGM) has been developed.
Methods. A multicenter study compared the safety and efficacy of E_2 1 mg daily plus intermittent NGM 90 µg (3 days off, 3 days on) ($n = 150$) vs. a continuous oral dose of E_2 2 mg plus norethisterone acetate (NETA) 1 mg ($n = 172$) daily, for a period of 2 years. Endometrial biopsies were performed at 1 and 2 years. Subjects recorded the occurrence of vasomotor symptoms, uterine bleeding, and adverse events on diary cards.
Results. At 2 years' follow-up, no subject had developed endometrial hyperplasia or cancer. Endometrial atrophy was seen in 75% of subjects using the intermittent NGM regimen and in 78% of women using the constant NETA regimen. Both groups maintained a 96% reduction in vasomotor symptoms up to 2 years. The rates of bleeding and/or spotting showed no difference between the groups, and at 2 years' follow-up, 73% of women in the intermittent NGM group and 83% of subjects in the constant NETA group were amenorrheic. There was a lower incidence of progestin-associated side-effects, such as abdominal discomfort, edema, painful bleeding episodes, and breast symptoms, with the intermittent progestin regimen vs. the constant progestin regimen. Intermittent NGM use was associated with an elevation in HDL- and HDL_2-cholesterol, whereas constant NETA reduced these lipoproteins.
Conclusions. The intermittent administration of a progestin, such as NGM, provides a new, well-tolerated regimen to achieve endometrial safety, an adequate rate of amenorrhea, and effective reduction of vasomotor symptoms in postmenopausal women.

Key words: hormone replacement therapy; 17β-estradiol; norgestimate; norethisterone acetate; intermittent progestin

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Estrogen replacement therapy (ERT) relieves the vasomotor and urogenital symptoms associated with menopause (1) and reduces the risk of cardiovascular disease (2) and osteoporosis (3,4). In addition, based on prospective studies, ERT may reduce the risk of colon cancer (5) and Alzheimer's

Abbreviations:
ERT: estrogen replacement therapy; HRT: hormone replacement therapy; E_2: 17β-estradiol; NGM: norgestimate; NETA: norethisterone acetate; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

disease (6), and preserve cognitive function (7). However, estrogen stimulates endometrial proliferation and can lead to endometrial hyperplasia and endometrial cancer (1). Therefore, estrogen should be combined with progestin, which inhibits endometrial proliferation, significantly decreasing the risk of endometrial cancer (1, 8–10). In addition, 19 nortestosterone-derived progestins have been associated with a lower relative risk for endometrial cancer when used in hormone replacement therapy (HRT) regimens than progesterone-derived progestins (11).

Progestins can cause side-effects such as breakthrough bleeding, breast tenderness, edema, and nausea, all of which can decrease compliance (12). Long-term progestin use may negate the beneficial cardiovascular effects of ERT, partially through effects on lipid metabolism (13). Thus, the consensus is that women with an intact uterus should be given progestins at the smallest doses that provide endometrial protection. Therefore, the R. W. Johnson Pharmaceutical Research Institute (RWJPRI) has designed a novel oral regimen consisting of a constant estrogen and intermittent progestin that decreases both the time a woman is exposed to progestin and the total amount of progestin administered during the course of HRT.

The administration of estrogen induces both estrogen and progestin receptors in human endometrial cells, with maximal stimulation achieved in approximately 3 days (14, 15). Progestins exert an antiestrogenic effect by down regulating estrogen and progestin receptors, which inhibits estrogen-induced proliferation (14, 16). When postmenopausal women are treated with progestin after estrogen priming, endometrial estrogen receptors show reduced expression after 3 days of treatment (17). This innovative HRT regimen, which consists of a continuous administration of 17β-estradiol (E_2) 1 mg alone for 3 days, followed by E_2 1 mg plus norgestimate (NGM) 90 μg for 3 days, takes advantage of estrogen and progesterone receptor dynamics, thereby producing the desired effects on the endometrium with lower doses of both hormones (18). E_2 is the most commonly used estrogen in HRT (19), while NGM, which possesses minimal androgenic activity (20, 21), has been used primarily in oral contraceptives.

A randomized, parallel-group study was conducted to evaluate the safety and efficacy of constant E_2 1 mg, intermittent NGM 90 μg [Prefest™ (Ortho-Prefest™ in the USA) RWJPRI, Raritan, NJ, USA] compared with a continuous combined HRT regimen containing E_2 2 mg and norethisterone acetate (NETA) 1 mg (Kliogest®, Novo Nordisk, Copenhagen, Denmark) in postmenopausal women. The results of this 1-year study indicated that a continuous E_2 1-mg/intermittent NGM 90-μg regimen was well tolerated and effectively reduced the incidence of vasomotor symptoms, while providing endometrial protection, an acceptable bleeding profile, and beneficial effects on lipid metabolism (22–24).

Because NGM is a novel progestin for HRT, and a low dose of NGM was used in the intermittent progestin regimen, the decision was made to continue follow-up on these subjects for a total of 2 years to assess the long-term endometrial safety of this regimen. Therefore, participants were offered the option of continuing study medication for another year. This article reports the endometrial safety, efficacy, and tolerability data for the extension study.

Materials and methods

This extension study, which began at Month 12 and ended at Month 24, was an open-label, parallel-group, multicenter study designed to evaluate the long-term (up to 24 months) safety and efficacy of an oral constant estrogen/intermittent progestin HRT regimen consisting of 1 E_2 1-mg tablet daily for 3 days followed by 1 E_2 1-mg/NGM 90-μg tablet daily (Prefest™) for 3 days ($n = 150$) compared with a reference continuous, combined HRT regimen consisting of 1 E_2 2-mg/NETA 1-mg tablet (Kliogest®) daily ($n = 172$). For the constant estrogen/intermittent progestin regimen, the 6-day sequences were repeated for 360 days, and the continuous combined HRT regimen was continued for 364 days. An E_2 2-mg/NGM 180-μg regimen was included in the study, but is omitted from this paper because it is no longer in clinical development.

Postmenopausal women who had participated in the 1-year study comparing the safety and efficacy of E_2/NGM and E_2/NETA were offered the opportunity to continue the same treatment for a second year. Exclusion criteria included evidence of malignancy on mammogram, pathology on cervical smear, hyperplasia or malignancy on endometrial biopsy or smear sample, or clinically relevant changes in laboratory tests at the final 1-year study visit. Women who smoked more that 10 cigarettes per day were also excluded. All participants gave informed consent to continue in the extension of the 1-year study.

The primary endpoint was the yearly incidence of endometrial hyperplasia and other histologic endometrial findings. Efficacy evaluations also included the effect on vasomotor symptoms (based on the reduction in the number of hot flushes) and changes in the incidence and severity of uterine bleeding.

Study participants recorded daily tablet intake, hot flushes, bleeding, and adverse events on diary cards that were reviewed by study investigators at 3-month intervals. Bleeding was rated on a 5-point scale with 0 indicating no bleeding or spotting and 4 representing severe bleeding. A statistical analysis was performed to examine the relationship between the occurrence of bleeding or spotting and endometrial histology (atrophic or not atrophic) at the end of treatment. Endometrial biopsies were to be performed at study entry (Month 12) and at Month 24 for all subjects. In addition, a biopsy could be performed at the discretion of the investigator at any time between Month 12 and Month 24 if endometrial thickness exceeded 5 mm at vaginal ultrasound examination, or if the investigator deemed it necessary. Biopsy specimens were evaluated on an ongoing basis by one pathologist who was blinded to treatment and at the end of the study by a second pathologist, who was also blinded to treatment. If the two pathologists differed in their evaluations, the specimen was sent to a third pathologist for adjudication.

Histologic examination of the endometria was performed with the results recorded as menopausal atrophy (no mitosis; glands occupy $<50\%$ of the area; glandular epithelium flattened; uterine lumen narrowed; stroma dense); progestogenic atrophy (endometrial thickness reduced; some glands present in $<50\%$ of the area; glandular epithelium flattened; intercellular matrix homogeneous; predecidual cells absent; luminal diameter narrowed; endometrial epithelial surface slightly irregular), estrogen effect (proliferative, with mitosis present in glandular epithelium and stroma; glands with pseudostratified, high epithelium, and irregular outline; glands predominate over stroma), progestin effect, secretory endometrium, simple hyperplasia (hypertrophy without malignancy), complex hyperplasia with or without cellular atypia, adenocarcinoma, and polyps. Cervical smears were taken at 18 and 24 months and analyzed by a central laboratory. Safety was evaluated based on adverse events (each visit), changes in serum lipids and other laboratory values (Months 12 and 24), vital signs (every 3

Table I. Demographic and baseline characteristics

	E_2 1 mg/NGM 90 μg ($n = 150$)	E_2 2 mg/NETA 1 mg ($n = 172$)
Age (years)		
Mean (SD)	54.1 (4.32)	53.8 (4.07)
Range	41–65	43–64
Weight (kg)		
Mean (SD)	66.0 (8.59)	66.8 (10.09)
Range	45–90	47–103
BMI (kg/m^2)*		
Mean (SD)	24.4 (2.83)	24.8 (3.04)
Range	17.6–31.5	17.0–36.1
Prior HRT		
No	36 (24%)	51 (30%)
Yes	113 (75%)	121 (70%)
Unknown	1 (0.7%)	0 (0%)
Time since last menses (months)†		
N	93	107
Mean (SD)	51.9 (34.51)	53.6 (40.38)
Range	13–148	12–182

*$>30\,kg/m^2$, six women in the E_2 1 mg/NGM 90 μg group; five women in the E_2 2 mg/NETA 1 mg group.
†Includes only subjects who provided month and year for last menstrual period.

Table II. Endometrial histology at 24 months of treatment

	E_2 1 mg/NGM 90 μg ($n = 125$*)	E_2 2 mg/NETA 1 mg ($n = 157$*)
Hyperplasia or cancer	(0%)	0 (0%)
Atrophic	94 (75%)	122 (78%)
Menstrual/progestational effect	20 (16%)	19 (12%)
Estrogen effect only	3 (2%)	5 (3%)
Insufficient tissue	8 (6%)	11 (7%)

*Subjects from whom an endometrial biopsy was obtained at end of treatment.

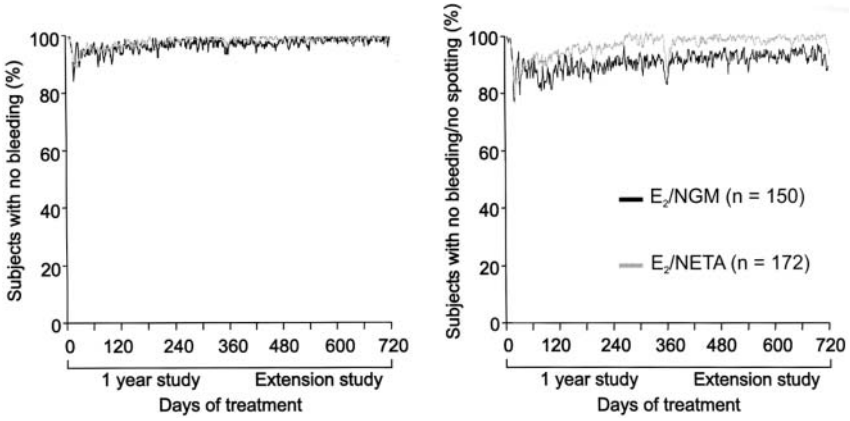

Fig. 1. Proportion of subjects with no bleeding and no bleeding/no spotting.

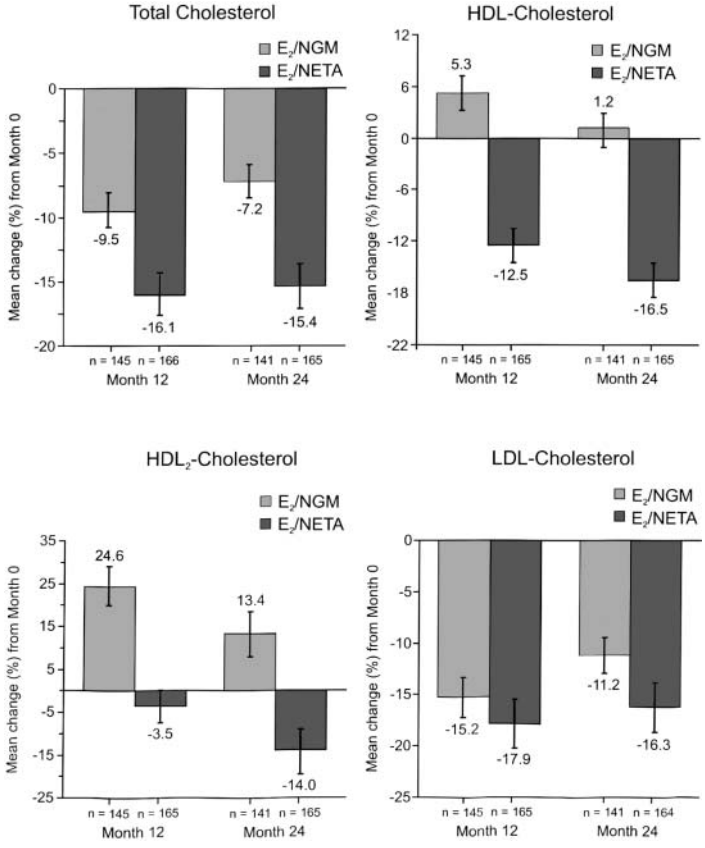

Fig. 2. Mean changes in lipids from Month 0.

months), and physical and gynecologic examinations (Months 12, 18 and 24).

Results

Efficacy and endometrial safety

The two groups were similar with respect to clinical characteristics (Table I). No endometrial hyperplasia was detected in any subject at 24 plus months' exposure to treatment (Table II). Atrophic endometria were observed in 75% of the subjects in the E_2/NGM group and 78% of the subjects in the E_2/NETA group. The average reduction in mean number of hot flushes (including night sweats) during the first study was 96% for both treatment groups (23), and this efficacy was fully maintained and preserved during the extension study.

Table III. Relationship between occurrence of bleeding/spotting and state of the endometrium

.	*n**	Bleeding/spotting number of subjects (%)	Common odds ratio† (95% confidence limit)
E_2 1 mg/NGM 90 μg			
Atrophic	92	36 (39)	
Not atrophic	20	13 (65)	0.322‡
E_2 2 mg/NETA 1 mg			(0.166, 0.624)
Atrophic	117	33 (28)	
Not atrophic	23	13 (57)	

Atrophic, menstrual/progestogenic; not atrophic, all tissue samples not atrophic.
*Number of subjects who completed 2 years of treatment, with data available.
†Mantel–Haenszel odds ratio.
‡$p = 0.001$.

Tolerability

Bleeding episodes. Ninety-one women in the intermittent NGM group as compared with 103 women in the constant NETA group reported bleeding during the 2 years of treatment. The proportion of subjects with no bleeding and no spotting are presented by day in Fig. 1. There was no difference in the rate of mild, moderate, or serious bleeding between the groups and, at the end of the study, 73% of subjects in the E_2/NGM group and 83% of subjects in the E_2/NETA group were amenorrheic. The number of days of bleeding per 1000 days of exposure was 29 (2.9%) for the E_2/NGM group and 16 (1.6%) for the E_2/NETA group. Uterine bleeding resulted in the discontinuation of three subjects in the E_2/NGM group and no subject in the E_2/NETA group. Subjects with an atrophic endometrium were significantly ($p = 0.001$) less likely to have bleeding or spotting during the final 6 months of treatment than were subjects without an atrophic endometrium, regardless of the treatment received (Table III).

Adverse events. A number of adverse events were reported during the 2-year trial (Table IV). Breast symptoms (discomfort and enlargement) were reported by 14% vs. 27% in the E_2/NGM and E_2/NETA treatment groups, respectively, and painful bleeding episodes by 3% vs. 8%. Seventeen subjects (11%) discontinued in the constant estrogen/intermittent progestin group and 11 (6%) discontinued in the continuous combined HRT group. Adverse events were the reason for discontinuation in seven subjects (5%) in the E_2/NGM group and one subject (1%) in the E_2/NETA group, and subject choice was the reason in three subjects (2%) from the E_2/NGM group.

Table IV. Selected adverse events during 2 years of treatment

Adverse event	E_2 1 mg/NGM 90 μg ($n = 150$) N (%)	E_2 2 mg/NETA 1 mg ($n = 172$) N (%)
Abdominal discomfort	21 (14)	38 (22)
Breast symptoms	21 (14)	46 (27)
Headache	43 (29)	55 (32)
Edema	7 (5)	14 (8)
Depression	7 (5)	10 (6)
Painful bleeding episodes	5 (3)	14 (8)
Weight increase	1 (1)	3 (2)

Other safety evaluations. Reductions in total cholesterol and low-density lipoprotein (LDL) cholesterol were observed in both groups from the start of the study to Month 12 (22), and these reductions were maintained for up to 24 months of treatment (Fig. 2). In addition, the changes in high-density lipoprotein (HDL) and HDL-2 cholesterol levels (a rise in the E_2/NGM treatment group and a fall in the E_2/NETA group) were maintained during this extension study. No changes were observed in other laboratory tests (liver and renal function tests, hemoglobin, hematocrit, and blood cell and platelet counts). There were no clinically meaningful changes in physical or gynecologic examination findings or vital signs.

Discussion

The optimum dose of progestin in an HRT regimen is one that protects the endometrium against estrogen-induced hyperplasia and provides adequate cycle control or amenorrhea. The constant E_2 1 mg, intermittent NGM 90-μg regimen has been developed to meet these criteria (14, 25), including the goal of achieving amenorrhea. While the first-year data were encouraging (22–24), the decision was made to continue the follow-up on these subjects for a total of 2 years to assess the long-term endometrial safety of using low-dose NGM in this novel regimen. No subject developed endometrial hyperplasia at 2 years' follow-up, and the rate of endometrial atrophy was similar in the group using the intermittent progestin regimen (75%) as it was in the group using the reference

regimen (78%). Endometrial atrophy rates at the end of the initial 1-year study were 65% and 83%, respectively (24). This suggests that it may take a longer time to achieve atrophy with the E_2/NGM regimen. Thus, our present data confirm that an intermittent 90-μg dose of NGM protects the endometrium against the effects of 1 mg of E_2, as evidenced by the lack of hyperplasia, and maintains a more physiologically balanced endometrium (lower rate of atrophy).

It is equally clear from our data that even though the estrogen dose in the constant estrogen, intermittent progestin regimen was only half that used in the reference regimen, vasomotor symptoms were controlled adequately when given in combination with intermittent NGM. Moreover, the incidence and severity of bleeding or spotting were similar with the E_2 1-mg/NGM 90-μg regimen and the E_2 2-mg/NETA 1-mg reference regimen, and the majority of subjects were amenorrheic at the end of the study. The rate of amenorrhea was 60% in the E_2/NGM group and 69% in the E_2/NETA group at the end of the initial 1-year study (23) compared with 73% and 83%, respectively, at the end of 24 months of treatment. Of course, it is possible that only those women with amenorrhea and/or mildest bleeding decided to continue the trial for the full 24 months, and this possible selection bias may partly explain the higher amenorrhea rate at 24 vs. 12 months of treatment.

The E_2/NGM regimen was associated with a lower incidence of side-effects, such as breast discomfort and enlargement, abdominal symptoms, painful bleeding episodes, and edema. The difference in the rates of these side-effects may be a consequence of a shorter exposure time to progestin as these side-effects are caused by the progestin component in HRT (13, 26). As a result of this difference, a novel intermittent administration of progestin appeared to make this HRT regimen better tolerated, although the discontinuation rates did not show any difference between the regimens.

It has previously been reported that more beneficial changes in blood lipids and lipoproteins were observed with the E_2 1-mg/intermittent NGM 90-μg regimen than with the reference regimen (22). The present data demonstrate that a positive lipid effect is well maintained for up to 2 years of treatment. It appears that 1 mg of E_2 can exert stronger effects on lipids if combined with intermittent NGM than 2 mg of E_2 if combined with continuous NETA. There are no data to show whether NGM 90 μg is equivalent to NETA 1 mg, but we believe that this progestin type and a shorter exposure time to it may account for the greater beneficial effect on lipids.

In conclusion, the constant E_2 1-mg/intermittent NGM 90-μg HRT regimen provides endometrial protection during 2 plus years of use. In addition, it is well tolerated, effectively controls vasomotor symptoms, causes amenorrhea in a majority of subjects, and results in beneficial lipid changes. Thus, this novel HRT regimen should be considered whenever HRT without withdrawal bleeding is desired.

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