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TRIMEGESTONE AND MENOPAUSE

A comparative 2-year study of the effects of sequential regimens of 1 mg 17β-estradiol and trimegestone with a regimen containing estradiol valerate and norethisterone on the bleeding profile and endometrial safety in postmenopausal women

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Abstract

Objective. To compare the bleeding profiles and endometrial protection of two sequential regimens of 17β-estradiol (17β-E_2) and trimegestone (TMG) with a sequential estradiol valerate (E_2V)/norethisterone (NET) regimen.

Study design. This was a randomized, double-blind, multicenter study conducted in eight countries in healthy, postmenopausal women with an intact uterus. A total of 1218 women were enrolled into the initial 1-year study (13 cycles), and subsequently 531 of these received treatment for a further year (26 cycles). Treatment regimens were 1 mg 17β-E_2 on days 1–14 and 1 mg 17β-E_2/0.125 mg TMG or 1 mg 17β-E_2/0.25 mg TMG on days 15–28, and 1 mg E_2V on days 1–16 and 1 mg E_2V/1 mg NET on days 17–28.

Results. Mean percentage of women reporting onset of withdrawal bleeding episodes during the week following discontinuation of progestogen was higher in the 1 mg 17β-E_2/0.25 mg TMG group than in the other two treatments, showing a more efficient progestogen effect on the endometrium and good predictability of bleeding onset with this treatment. The mean numbers and average lengths of bleeding episodes were similar in the three treatment groups. Overall, the bleeding profile was more favorable with 1 mg 17β-E2/0.25 mg TMG than with the lower-dose TMG preparation. Both of the TMG regimens demonstrated a good protective effect on endometrial proliferation, with the 0.25 mg TMG dose showing a lower incidence of proliferative endometrium.

Conclusion. The 1 mg 17β-E_2/0.25 mg TMG regimen showed an adequate protection of the endometrium, with an overall favorable bleeding profile.

Keywords: *Trimegestone, estradiol, norethisterone, sequential combined hormone replacement therapy, menopause, bleeding profile, endometrial safety*

Introduction

The most effective treatment for menopausal symptoms, which are caused by depletion in estrogen levels, is hormone replacement therapy (HRT). The main goal of HRT is the relief of vasomotor symptoms, although there is evidence for other benefits, such as protection against bone loss and alleviating other typical menopausal symptoms (e.g., sleep and psychological disturbances). For women with an intact uterus, current HRT regimens combine an estrogen with a progestogen to oppose the proliferative effect of estrogen on the endometrium [1,2].

Trimegestone (TMG) is a novel 19-norpregnane derivative with a high relative binding affinity for the progesterone receptor and high selectivity for the endometrium. At clinically relevant doses, it is strongly progestogenic but also very specific: it is devoid of androgenic, glucocorticoid, antiglucocorticoid, mineralocorticoid and estrogenic activity. In pre-clinical studies it has been shown to possess some antiandrogenic and antimineralocorticoid activity, but at doses higher than used in humans [3]. Thus, a hormone therapy that combines 17β-estradiol (17β-E_2) with TMG should prevent endometrial hyperplasia and cause minimal interference with the beneficial effects of estradiol.

Sequential estrogen/progestogen regimens mimic the natural menstrual cycle by inducing withdrawal bleeding, which is more predictable than the irregular bleeding/spotting often induced by continuous combined regimens. For sequential regimens, the duration of progestogen administration must be carefully defined to minimize the likelihood of developing endometrial cancer. An increased risk of endometrial cancer has been found among women who received progestogen for less than 10 days per

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28-day cycle over 5 or more years, compared with those who were not on HRT. This increase was, however, much less pronounced than for estrogens alone [4–7]. Currently, the recommended minimal length for cyclic progestogen administration to protect the endometrium is 10 days, with adequate protective effects obtained with 12–14 days' administration [8–11].

In previous clinical studies, a sequential regimen of 2 mg 17β-E_2/0.5 mg TMG was shown to have a better bleeding pattern than other doses of TMG and norethisterone acetate (NETA), and to be at least as effective as the comparators in relieving menopausal symptoms [12]. In addition, the overall safety profile was similar to that of the comparator groups, and the incidence of endometrial hyperplasia or carcinoma was acceptably low. The present paper is the second of a comparative study investigating the efficacy, bleeding profile and safety of a lower-dose sequential regimen of 1 mg 17β-E_2/0.25 mg TMG. It describes the bleeding and safety findings, with the efficacy results reported in the accompanying paper [13].

Methods

Study design and population

This was a randomized, double-blind, multicenter study. The study design, study population, and a description of the clinical examination are presented in the accompanying paper [13].

Bleeding profile

Women were requested to complete a daily menstrual diary card by recording bleeding data subjectively as 0 (none), 1 (spotting), 2 (light bleeding), 3 (moderate bleeding), or 4 (heavy bleeding). A bleeding episode was defined as one or more bleeding days, preceded or followed by two or more bleed-free days. A withdrawal bleeding episode for a cycle was defined as an episode beginning between day 22 of that cycle and day 7 of the subsequent cycle, and could only be a maximum of 8 days in length. An irregular bleeding episode for a cycle was defined as an episode beginning between day 8 and day 21 of that cycle, and could only be a maximum of 8 days in length. A prolonged bleeding episode was defined as any bleeding episode lasting at least 9 days. The predictability of a withdrawal bleeding episode was defined as the difference between the day of onset of the first withdrawal bleeding episode in cycle 3 and the day of onset of the first withdrawal bleeding episode of subsequent cycles.

Endometrial histology

Endometrial biopsies were collected at screening and in cycles 13 and 26 using a Vabra suction curette or a Pipelle endometrial sampling device. If the histological result for the last endometrial biopsy assessment was 'no endometrium identified' or 'endometrial tissue insufficient for diagnosis', transvaginal ultrasonography was performed during treatment to confirm the endometrial atrophy [12,14]. The above-mentioned histological categories were then re-categorized as 'endometrium tissue–other' (i.e., atrophic or inactive endometrium). If the atrophy was not confirmed, no re-categorization was performed. Two independent pathologists, blinded to study treatment, evaluated each biopsy. If there was disagreement between the two pathologists on a diagnosis of hyperplasia (carcinoma), a third pathologist reviewed the slides, and the majority diagnosis was taken.

Safety

Adverse events observed by the investigator or reported by the woman spontaneously were recorded and evaluated by the investigator in terms of severity and relationship to treatment. Any adverse event not present at baseline or events present at baseline that worsened during treatment was considered as possibly treatment-related. Concomitant medications were also documented.

Treatment compliance was evaluated by a tablet count at each cycle.

Statistical analyses

All women randomly assigned to treatment were included in the safety population. Primary analyses of bleeding profile data were performed on the intent-to-treat (ITT) population. A secondary efficacy evaluable (EE) population was used only for the analysis of bleeding data. Women were included in the efficacy population if they met stricter criteria than the ITT population at the woman and cycle level. Both ITT and EE populations are described in the accompanying paper [13]. Descriptive statistics were produced up to and including cycle 13 for the number of bleeding days and the total severity score. Analyses of covariance (ANCOVA) were performed up to cycle 13 on the number of bleeding days. Analyses using the Kruskal–Wallis test for overall treatment effect, the Wilcoxon rank sum test for pair-wise comparisons and the χ^2 test were made where appropriate. Fisher's exact test was used to determine any differences between treatment groups for non-serious adverse events when the incidence was $\geqslant 10\%$ in any treatment group. For the primary safety assessment, endometrial hyperplasia, 95% confidence intervals were calculated by using an exact two-sided binomial test, and an exact one-sided binomial test vs. a 1% theoretical incidence.

Results

The demographic characteristics, including menopausal history, for the three treatment groups (safety population) are shown in Table I. No significant differences were observed among treatment groups nor between this population and the EE population reported in the accompanying paper [13].

Bleeding profile

The mean number of bleeding/spotting days decreased from cycle 2 to 13 in all three groups (Figure 1). The results of the ANCOVA revealed that there was no significant difference in the number of bleeding/spotting days at cycles 2, 8 and 13 between the 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET groups when only women who bled were considered. In addition, both 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET induced significantly less bleeding than 1 mg 17β-E_2/0.125 mg TMG. The total severity score for cycles 2–12 inclusive was decreased in all treatment groups, with a slightly lower severity score observed for the E_2V/NET group, possibly because of its higher progestogen dose relative to estrogen.

The mean number of bleeding episodes ranged from 1.16 to 1.32 at cycles 2, 8 and 12, and was similar in the three treatment groups. The average length of bleeding episodes decreased with the duration of treatment in all three groups. The results for the number of withdrawal, irregular and prolonged bleeding episodes are shown in Figure 2. There was a reduction in the number of days of withdrawal bleeding in each group (from 5 days in early cycles to 4 days on average in later cycles), with no significant difference between groups. The mean numbers of irregular bleeding episodes were similar from cycles 2–12 in all three groups, and showed no significant difference between treatment groups. Logistic regression analysis showed that, for cycles 2–13, fewer women reported episodes of irregular bleeding with E_2V/NET than with 1 mg 17β-E_2/0.25 mg TMG ($p = 0.019$). This could be explained by a higher number of episodes reported per woman in the E_2V/NET group. The mean number of prolonged bleeding episodes was approximately 1 in each treatment group. Logistic regression showed that, over cycles 2–13, fewer women reported prolonged bleeding episodes with 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET than with 1 mg 17β-E_2/0.125 mg TMG. No significant difference in the number of prolonged bleeding days was observed between the 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET groups, except at cycle 12 ($p = 0.05$). No difference was seen between the two TMG groups.

A sequential HRT regimen should induce withdrawal bleeding episodes shortly after discontinuation of the progestogen, to prove an efficient progestogen effect on the endometrium. Thus, onset of withdrawal bleeding between days 1 and 7 was evaluated. The mean percentage of women reporting onset of withdrawal bleeding during the week following discontinuation of the progestogen at cycle 12 was 37% for 1 mg 17β-E_2/0.125 mg TMG, 69% for 1 mg 17β-E_2/0.25 mg TMG and 50% for E_2V/NET (Figure 3). Within these groups, amenorrhea was detected in 29%, 20% and 49% of the women, respectively. The percentages of withdrawal bleeding observed at cycles 2 and 8 and until the end of the 2-year treatment period were similar to those of cycle 12. The mean percentages were significantly higher in the 1 mg 17β-E_2/0.25 mg TMG group than in the

Table I. Baseline demographic characteristics of postmenopausal women in the safety population.

Variable	1 mg 17β-E_2/0.125 mg TMG ($n = 405$)	1 mg 17β-E_2/0.25 mg TMG ($n = 409$)	E_2V/NET ($n = 404$)
Ethnic origin (*n*)			
White	403	407	400
Black	1	2	
Other	1		4
Age (years)	52.5 ± 4.4	52.7 ± 4.5	52.6 ± 4.6
Height (cm)	163.8 ± 6.3	163.4 ± 6.2	163.6 ± 6.5
Weight (kg)	67.2 ± 11.1	66.9 ± 9.8	67.6 ± 10.5
Body mass index (kg/m^2)	25.0 ± 3.6	25.0 ± 3.3	25.2 ± 3.7
Years since last natural menstrual period	4.1 ± 3.9	4.4 ± 4.1	4.4 ± 3.9
Cigarettes per day	2.0 ± 4.2	2.1 ± 4.3	2.3 ± 4.4
Smoking status (*n*)			
Smoker	88	87	105
Non-smoker	317	322	299
Current alcohol usage (*n*)			
None	120	115	127
Occasionally	206	221	192
Weekly	38	40	41
Daily	41	33	44

17β-E_2, 17β-estradiol; TMG, trimegestone; E_2V, estradiol valerate; NET, norethisterone; data are expressed as mean ± standard deviation (or *n*, when indicated).

other two groups at cycles 2, 8 and 12, supporting an appropriately timed withdrawal bleeding. Cycle 3 was used as the reference cycle to assess predictability of onset of withdrawal bleeding episodes. Mean predictability of onset of withdrawal bleeding episode showed a consistent onset throughout the treatment period in all groups (Table II). The mean differences between the day of onset of a withdrawal bleeding episode at cycle 3 and in the subsequent cycles were less than 1 day for each cycle.

Although amenorrhea is not an aim of treatment with sequential hormone therapy, the percentage of amenorrheic women throughout the study ranged from 13% at cycle 2 to 21% at cycle 24 in the 1 mg 17β-E_2/0.125 mg TMG group, from 15% to 20% in the 1 mg 17β-E_2/0.25 mg TMG group, and from 28% to 42% in the E_2V/NET group. The logistic regression overall for cycles 2–13 showed that the

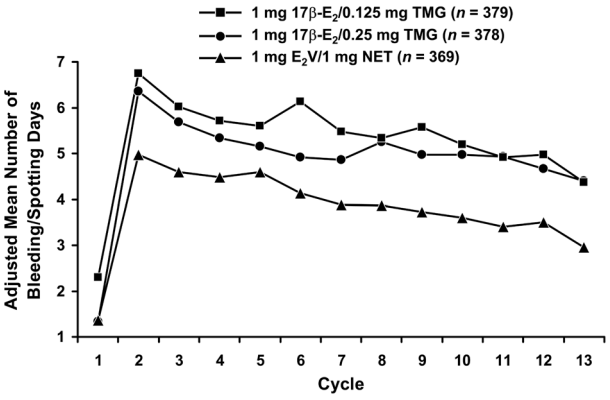

Figure 1. Number of bleeding days in postmenopausal women treated with 1 mg 17β-estradiol (17β-E_2) and either 0.125 mg or 0.25 mg trimegestone (TMG), or 1 mg estradiol valerate/1 mg norethisterone (E_2V/NET).

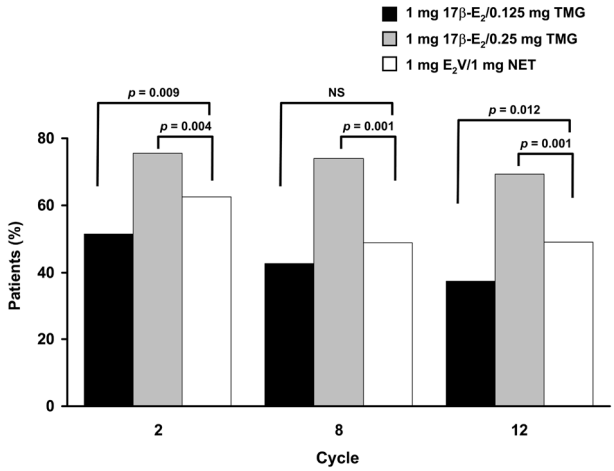

Figure 3. Percentage of women in the efficacy evaluable population with withdrawal bleeding onset from days 1 to 7. The postmenopausal women were treated with 1 mg 17β-estradiol (17β-E_2) and either 0.125 mg or 0.25 mg trimegestone (TMG), or 1 mg estradiol valerate/1 mg norethisterone (E_2V/NET). Statistical significance of the difference between treatments is shown by the p value (from the Pearson χ^2 test) positioned above the lines connecting the relevant bars. NS, not significant.

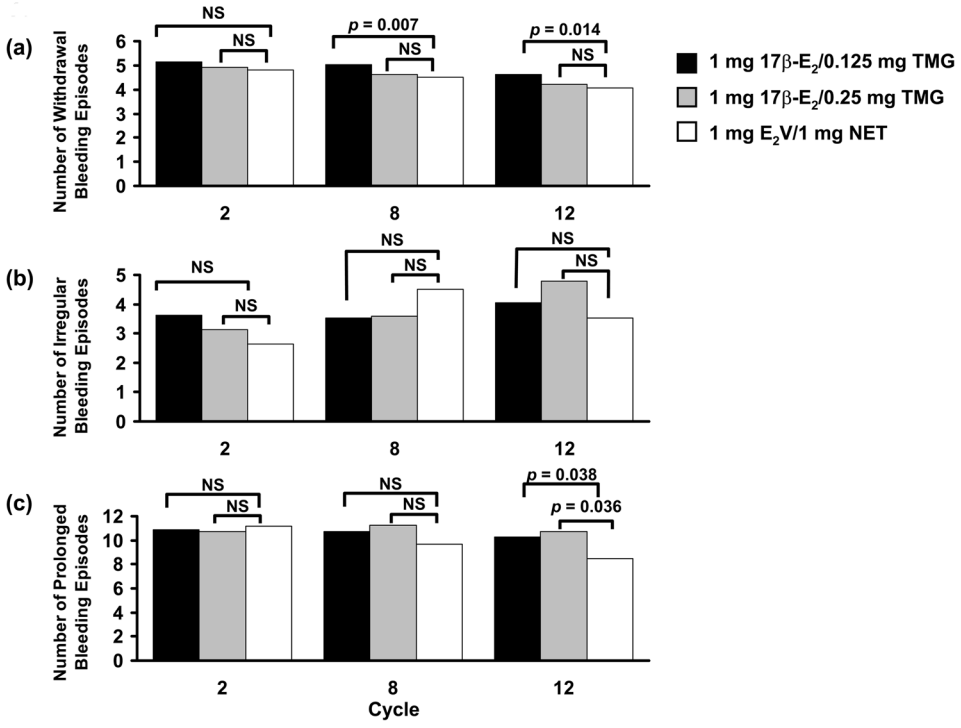

Figure 2. Bleeding episodes in postmenopausal women in the efficacy evaluable population, treated with 1 mg 17β-estradiol (17β-E_2) and either 0.125 mg or 0.25 mg trimegestone (TMG), or 1 mg estradiol valerate/1 mg norethisterone (E_2V/NET). (a) Withdrawal bleeding episodes; (b) irregular bleeding episodes; (c) prolonged bleeding episodes. Statistical significance of the difference between treatments is shown by the lines connecting the relevant bars ($p < 0.05$ by analysis of covariance; NS, not significant).

Table II. Predictability of onset of withdrawal bleeding/spotting episodes.

	1 mg 17β-E_2/0.125 mg TMG	1 mg 17β- E_2/0.25 mg TMG	E_2V/NET
Cycle 8			
n	126	163	123
Mean	–0.46	0.1	–0.07
SD	3.08	2.55	2.29
Cycle 12			
n	98	90	82
Mean	–1.03	–0.28	–0.38
SD	2.63	3.08	2.8

Table III. Bleeding classification with 1 mg 17β-E_2 plus 0.25 mg TMG as reference dose.

	1 mg 17β-E_2/0.25 mg TMG		1 mg 17β-E_2/0.125 mg TMG					1 mg E_2V/1 mg NET				
	n	%	*n*	%	OR	95% CI	*p* Value*	*n*	%	OR	95% CI	*p* Value†
$\geqslant$ 1 cycle amenorrheic	167	56	138	48	1.47	(1.05, 2.07)	0.026	190	67	0.61	(0.43, 0.86)	0.005
Not amenorrheic	132	44	150	52				93	33			

17β-E_2, 17β-estradiol; TMG, trimegestone; E_2V, estradiol valerate; NET, norethisterone; OR, odds ratio; CI, confidence interval; logistical regression was carried out overall on cycles 2–13 (at least eight evaluable cycles) on the efficacy evaluable population; †the variables body mass index and years since last menstrual period were adjusted for in the model.

incidence of amenorrheic women was statistically higher in the 1 mg 17β-E_2/0.25 mg TMG group than in the 1 mg 17β-E_2/0.125 mg TMG group (Table III). It was also significantly higher in the E_2V/NET group than in both TMG groups, which is consistent with the higher relative dose of progestogen to estrogen in this HRT preparation.

Endometrial status

After at least 12 cycles, a total of 266, 278 and 257 evaluable endometrial biopsies were obtained from women in the 1 mg 17β-E_2/0.125 mg TMG group, 1 mg 17β-E_2/0.25 mg TMG group and E_2V/NET group, respectively. These figures are close to those recommended in the European Agency for the Evaluation of Medicinal Products (EMEA) guidelines (300 evaluable biopsies after 1 year of treatment [15]). In addition, since the lowest progestogen dose was expected to provide less protection of the endometrium, the pooling of the biopsies obtained in both TMG groups (i.e., 544 evaluable biopsies) provides more than adequate information on the endometrial protection induced by the highest dose of TMG. Endometrial hyperplasia was observed in two women (one simple without atypia, and one complex without atypia) in the 1 mg 17β-E_2/0.125 mg TMG group, and in three women (one simple without atypia, and two complex without atypia) in the 1 mg 17β-E_2/0.25 mg TMG group. Endometrial malignancy was observed in one woman in the E_2V/NET group. The observed rate of endometrial hyperplasia in the 1 mg 17β-E_2/0.25 mg TMG group was 1.08% (exact two-sided 95% confidence interval of 0.22%–3.12%) (Table IV). The theoretical exact two-sided 95% confidence interval corresponding to the EMEA-recommended 1% incidence was 0.21%–2.89% [15]. The exact binomial one-sided test showed no significant difference between the rate in the 1 mg 17β-E_2/0.25 mg TMG group (1.08%) and the theoretical rate of 1.0% ($p = 0.527$), thus demonstrating an acceptable protective effect of the 1 mg 17β-E_2/0.25 mg TMG treatment on endometrial proliferation. Similarly, no difference was seen between the EMEA-recommended incidence of endometrial hyperplasia and that for 1 mg 17β-E_2/0.125 mg TMG or E_2V/NET ($p = 0.503$ and $p = 0.272$, respectively) (Table IV).

The percentages of proliferative endometrium in the 1 mg 17β-E_2/0.25 mg TMG group were similar to those in the E_2V/NET group (10.4% vs. 10.9% after 1 year, and 10.8% vs. 11.3% after 2 years, respectively). The overall on-treatment incidence of proliferative endometrium was higher in the 1 mg 17β-E_2/0.125 mg TMG group (12.4% and 16.3% after 1 and 2 years, respectively) than in the 1 mg 17β-E_2/0.25 mg TMG group, suggesting the 0.25 mg TMG dose provided better prevention of the development of endometrial hyperplasia than the lower 0.125 mg TMG dose (Table V).

Body weight

Mean body weight decreased from cycle 6 onwards in the 1 mg 17β-E_2/0.25 mg TMG group (maximum mean decrease of -0.9 kg), while a slight gain was observed in the 1 mg E_2V/NET group from cycle 9 onwards. This favorable effect was significantly different from that of 1 mg E_2V/1 mg NET at cycle 19 ($p = 0.026$) and cycle 22 ($p = 0.041$).

Table IV. Numbers and rates of endometrial hyperplasia.

Treatment	Number of cases diagnosed/evaluable biopsies	Observed rate (%)	Exact two-sided 95% CI*	*p* Value†
Pooled TMG regimens	5/544	0.92	0.3%–2.13%	0.539
1 mg 17β-E_2/0.125 mg TMG	2/266	0.75	0.09%–2.69%	0.503
1 mg 17β-E_2/0.25 mg TMG	3/278	1.08	0.22%–3.12%	0.527
1 mg E_2V/1 mg NET	1/257	0.39	0.01%–2.15%	0.272

CI, confidence interval; TMG, trimegestone; 17β-E_2, 17β-estradiol; E_2V, estradiol valerate; NET, norethisterone; *CI was calculated using a binomial test with the observed incidence; †*p* value from an exact one-sided binomial test vs. a 1% theoretical incidence.

Table V. Endometrial pattern: Proliferative endometrium.

	Screening	1-year treatment (cycle 13)	2-year treatment (cycle 26)
1 mg 17β-E_2/0.125 mg TMG	35/334 (10.5)	33/266 (12.4)	15/92 (16.3)
1 mg 17β-E_2/0.25 mg TMG	40/339 (11.8)	29/278 (10.4)	11/102 (10.8)
1 mg E_2V/1 mg NET	41/333 (12.3)	28/257 (10.9)	12/106 (11.3)

17β-E_2, 17β-estradiol; TMG, trimegestone; E_2V, estradiol valerate; NET, norethisterone; data are expressed as number of women/? (%).

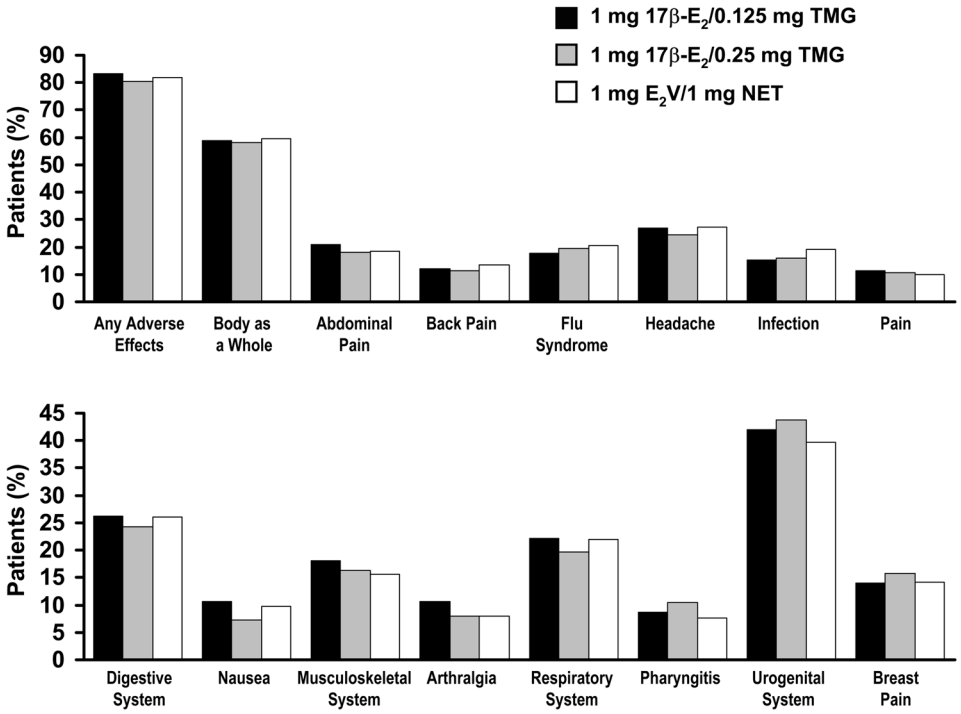

Figure 4. Non-serious adverse events reported in postmenopausal women treated with 1 mg 17β-estradiol (17β-E_2) plus either 0.125 mg or 0.25 mg trimegestone (TMG), or 1 mg estradiol valerate/1 mg norethisterone (E_2V/NET).

Safety evaluation

Safety analyses were performed on all women enrolled in the study. One or more drug-related adverse events were reported by 52.3%, 56.5% and 48.3% of women in the 1 mg 17β-E_2/0.125 mg TMG, 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET groups, respectively. There was no overall significant difference between groups for any study period.

The most common non-serious adverse events, organized by body system, and reported by at least 10% of women in one group, are shown in Figure 4. These include headache (26% of women), abdominal pain (19%), flu syndrome (16%) and breast pain (15%). No significant difference was seen between groups for any of the common non-serious adverse events. The incidence of non-serious adverse events reported in the first year of treatment was similar to that seen overall, indicating no accumulative toxicity.

Thirteen women had serious adverse events considered as possibly related to the study drug treatment. They included four women in the 1 mg 17β-E_2/0.125 mg TMG group, five women in the

1 mg 17β-E_2/0.25 mg TMG group and four women in the E_2V/NET group. The most serious cases involved breast carcinoma in seven women (three in the 1 mg 17β-E_2/0.125 mg TMG group, two in the 1 mg 17β-E_2/0.25 mg TMG group and two in the E_2V/NET group), endometrial adenocarcinoma in one woman (E_2V/NET), and papillary adenocarcinoma of the ovary in one woman (E_2V/NET).

Discussion

The results of this study indicate that the 1 mg 17β-E_2/0.25 mg TMG sequential regimen provides adequate protection on the endometrium according to EMEA recommendations, with an overall more favorable bleeding profile and a significantly lower number of bleeding days than the 1 mg 17β-E_2/0.125 mg TMG regimen. It is also well tolerated and generally as safe as the 1 mg E_2V/1 mg NET comparator. The mean percentage of women reporting onset of withdrawal bleeding episodes during the week following discontinuation of the progestogen was 69% with 1 mg 17β-E_2/0.25 mg, significantly higher than that observed with the 1 mg 17β-E_2/0.125 mg TMG (37%) or the E_2V/NET regimen (50%). This is indicative of a more efficient progestogen effect on the endometrium of the 0.25 mg TMG group compared with the 0.125 mg TMG and E_2V/NET groups and a predictable onset of withdrawal bleeding throughout the treatment period.

In all treatment groups the incidence of bleeding was reduced from cycle 2 onwards. This finding is consistent with that of a previous study examining bleeding profiles in postmenopausal women taking sequential regimens of 0.625 mg of conjugated equine estrogens and either 5 or 10 mg of medroxyprogesterone acetate [16]. Among the women who bled, there were no significant differences between the 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET groups after cycle 2, although the number of bleeding days was smaller with E_2V/NET. Although amenorrhea is not an aim of treatment with sequential hormone therapy, the incidence of amenorrheic women was significantly higher in the E_2V/NET group than in both TMG groups, reflecting the higher relative dose of progestogen to estrogen in E_2V/NET.

An incidence rate of endometrial hyperplasia of 1.08% was observed in the 1 mg 17β-E_2/0.25 mg TMG group, which was not significantly different from the theoretical 1% incidence, demonstrating an acceptable protective effect of the 1 mg 17β-E_2/0.25 mg TMG treatment on endometrial proliferation. This higher TMG dose showed a better proliferative pattern than that observed with the lower 0.125 mg TMG dose. Published data on the incidence of endometrial cancer in long-term users of sequential combined hormone therapy is limited. While two studies suggest that using progestogens for more than 10 days in therapies of 5 years or longer may not completely eliminate the risk [4,7], others indicate that this risk is not higher than that found in non-users of HRT [5,17,18]. This latter statement is supported by the present study showing that both 1 mg 17β-E_2/0.25 mg TMG and E_2V/NET treatment groups had lower rates of proliferative endometrium at cycles 13 and 26 than at screening. Both TMG-containing treatments were well tolerated and were generally as safe as E_2V/NET for up to 2 years of treatment. Non-serious adverse events were reported by similar percentages of women in each treatment group. No significant differences were seen between the three groups for any of the common non-serious adverse events.

Acknowledgement

The list of investigators who participated in this study is reported in the accompanying paper [13].

References

1. Schiff I, Sela HK, Cramer D, Tulchinsky D, Ryan KJ. Endometrial hyperplasia in women on cyclic or continuous estrogen regimens. Fertil Steril 1982;37:79–82.
2. Harlap S. The benefits and risks of hormone replacement therapy: an epidemiologic overview. Am J Obstet Gynecol 1992;166:1986–1992.
3. Philibert D, Bouchoux F, Degryse M, Lecaque D, Petit F, Gaillard M. The pharmacological profile of a novel norpregnane progestin (trimegestone). Gynecol Endocrinol 1999;13:316–326.
4. Weiderpass E, Adami H-O, Baron JA, Magnusson C, Bergström R, Lindgren A, Correia N, Persson I. Risk of endometrial cancer following estrogen replacement with and without progestins. J Natl Cancer Inst 1999;91:1131–1137.
5. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, Wan PC, Mack TM. Estrogen–progestin replacement therapy and endometrial cancer. J Natl Cancer Inst 1997;89:1110–1116.
6. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJB. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. N Engl J Med 1981;305:1599–1605.
7. Beresford SAA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. Lancet 1997;349:458–461.
8. Whitehead MI. Prevention of endometrial abnormalities. Acta Obstet Gynecol Scand Suppl 1986;134:81–91.
9. Woodruff JD, Pickar JH. Incidence of endometrial hyperplasia in postmenopausal women taking conjugated estrogens (Premarin) with medroxyprogesterone acetate or conjugated estrogens alone. Am J Obstet Gynecol 1994;170:1213–1223.
10. Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1996;275:370–375.
11. Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding. Cochrane Database Syst Rev 2000;CD000402.
12. Granberg S, Wikland M, Karlsson B, Norstrom A, Friberg L-G. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am J Obstet Gynecol 1991;164:47–52.

13. Pornel B, Spielmann D, Trimegestone 302 Study Group. A study of the control of climacteric symptoms in postmenopausal women following sequential regimens of 1 mg 17β-estradiol and trimegestone compared with a regimen containing 1 mg estraiol valerate and norethisterone over a 2-year period. Gynecol Endocrinol 2005;21(2):74–81.
14. Nasri MN CGJ. Correlation of ultrasound findings and endometrial histopathology in postmenopausal women. Br J Obstet Gynaecol 1989;96:1333–1338.
15. Committee for Proprietary Medicinal Products. Points to consider on hormone replacement therapy. London: European Agency for the Evaluation of Medicinal Products; 1997.
16. Archer DF, Pickar JH, Bottiglioni F, for the Menopause Study Group. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Obstet Gynecol 1994;83:686–692.
17. Archer DF. The effect of the duration of progestin use on the occurrence of endometrial cancer in postmenopausal women. Menopause 2001;8:245–251.
18. Erkkola R, Kumento U, Lehmuskoski S, Mattila L, Mustonen M. No increased risk of endometrial hyperplasia with fixed long-cycle oestrogen–progestogen therapy after five years. J Br Menopause Soc 2004;10:9–13.