Comparison of efficacy and local tolerability of estradiol metered-dose transdermal spray to estradiol patch in a network meta-analysis

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ABSTRACT

Objectives: Transdermal hormone replacement therapy is preferred for menopausal vasomotor symptoms. Our purpose was to compare the efficacy and local tolerability of a patch and a metered-dose transdermal spray that have never been directly compared.

Method: The relative change in the number of hot flushes between baseline and week 12 was selected as an efficacy indicator and the frequency of local skin reactions as a tolerability indicator. A network meta-analysis was performed to compare efficacy. Application site tolerability was compared descriptively.

Results: Overall 46 studies were identified. In the efficacy analysis, eight active treatment arms and a placebo arm were determined based on the estradiol daily dose (from 14 μg to 50 μg). All but one had a significantly higher effect on relative change in the number of hot flushes than did the placebo. We found no evidence for different efficacy of the patch and the metered-dose transdermal spray. The latter performed better in terms of local skin reactions.

Conclusion: The patch and the metered-dose transdermal spray seem to have the same efficacy on vasomotor symptoms in estradiol hormone replacement. The local tolerability of the metered-dose transdermal spray is favorable.

Introduction

The median age of menopause in women living in industrialized countries ranges between ages 50 and 52 years. The hormonal changes affect the function of several organ systems and result in well-known signs and symptoms including vasomotor, vaginal, musculoskeletal, psychological and sexual symptoms. Especially vasomotor symptoms (VMS) can cause a significant burden for women with menopause since 10–20% report severe symptoms. VMS of any severity are associated with significantly worse quality of life, making VMS one of the primary short-term targets of treatments. The treatment requires a complex approach in which replacement of depleted hormones (mainly estradiol, E2) plays a central role. Hormone replacement therapy (HRT) is widely accepted and has effects, among others, on VMS. Risk for venous thromboembolism seems unequivocally to depend on the route of administration: increased risk is associated with oral rather than transdermal HRT. Transdermal routes include gel or patch application or spraying small amounts of E2 solution onto skin by a metered-dose transdermal spray (MDTS) device.

Two types of patches have been developed: the older reservoir and the newer matrix type. The former consists of a reservoir with E2 and an alcohol-containing layer. E2 diffuses through this rate-limiting membrane. Local skin reactions at the application site and cutaneous reactions to ethanol, a solvent in E2 patches, were frequently reported. The matrix-type patch was the next generation. The diffusion of E2 from the patch matrix into the skin is facilitated by the so-called penetration enhancers. Matrix patches have a significantly better skin tolerability profile compared to reservoir patches.

MDTS is a clear spray that dries within 60 s. Washing or exposing the application site to sunscreen before spraying it did not affect E2 absorption significantly. The efficacy and safety of E2 MDTS were evaluated in one randomized, double-blind, placebo-controlled, phase-III clinical trial that compared one or two or three E2 sprays per day (equivalent to 21, 29 and 40 μg/day). All three doses showed a significant decrease in hot flushes, as the efficacy endpoint, at weeks 4 and 12 compared to placebo. Common skin reactions were similar to those previously reported with other transdermal products. The results supported the conclusion that E2 MDTS is an effective and well-tolerated method of delivering low-dose E2 transdermally. Taking into account its unique features, and its efficacy and safety outcomes profile, it was suggested that MDTS may have application advantages while its efficacy and safety are similar to other transdermal methods. If considering transdermal E2 applications in Europe, patches are used more often, so comparison of MDTS to patches seemed to be reasonable.
Therefore, our objectives were to study the efficacy and tolerability of E2 MDTS compared to E2 patches in women with postmenopausal hot flushes. Seeing that the two E2 delivery modes have never been compared directly before, an indirect statistical comparison was applied to compare their efficacy outcomes quantitatively. Comparison of tolerability was performed in a descriptive manner and limited to local skin reactions since it could reasonably be supposed that any differences in types and rates of adverse events between these two E2 delivery methods could probably stem from their application mode.

Methods

Outcomes selected to be analyzed

For the comparison of the efficacy of E2 MDTS with patches, the selected endpoint was the mean between-arm difference of the relative changes (%) in the number of hot flushes from baseline (week 0) to week 12. The daily dose involved in the analysis was limited to 14–50 µg. The analysis of the relative change accounts for the heterogeneity in the baseline number of hot flushes. Inclusion of those studies into the analysis that presented hot flush frequency data for the week 12 of treatment made it possible to compare their results to that of the E2 MDTS study in which the daily doses (with one, two or three sprays/day) were calculated for a 12-week usage period. In addition, it was assumed that, by the end of 12 weeks, the treatment effects on hot flushes would be stabilized, and the patients become skilled in using their own delivery methods appropriately. The daily dose patch treatments involved in the analysis were limited to 14–50 µg because this range best covers the range of doses delivered by MDTS. In order to compare the local tolerability of E2 MDTS with patches, all local sign and symptom outcomes (skin reactions) that were regularly presented in studies of E2 patches and MDTS were considered.

Systematic literature review

The aim of the systematic literature review was to identify: (1) placebo- or active-controlled clinical studies of E2 HRT with patches or MDTS that had efficacy endpoints of interest, or (2) other observational and patch versus placebo-controlled studies that had outcomes for local tolerability of patches. The search algorithm and the number of studies included into this analysis are detailed in Appendix S1 (see Supplementary Appendix S1 at http://dx.doi.org/10.1080/113697137.2016.1221919). In addition, some efficacy and safety outcomes were used from the Clinical Study Report of the only phase-III, double-blind, multicenter, placebo-controlled clinical trial (ClinicalTrials.gov Identifier: NCT01389102)(CSR) whose design and results were presented elsewhere17.

Network meta-analysis of the efficacy outcome

Since the outcomes of interest from the E2 MDTS and the E2 patch were never compared directly, an indirect comparison statistical method, a network meta-analysis (NMA), was performed18,19. A standard meta-analysis uses evidence from direct comparison only, say clinical trials that compare drug A to drug B. With the appropriate statistical methodology, a pooled-effect measure can be estimated based on the results of the individual trials that compared these two drugs. A network meta-analysis can combine the evidence from direct and indirect comparisons. For example, if there are trials in which drug A were compared to drug C, and others in which drug B were compared to drug C, then indirectly they also convey information on the relative effect of drug A versus drug B. This information can be combined with the direct evidence. Furthermore, with this technique, the relative effects of two treatments that have never been compared to each other, but share comparators in different studies, can be assessed. In this NMA, the relative effect of MDTS versus patch could only be estimated through the treatment of placebo, as no direct comparison was available. When weekly hot flush frequencies were published, they were converted to daily frequencies. Standard errors of relative changes were calculated from the variances of the measurements20. When the outcomes of interest were presented only in figures, a widely applied, easy-to-use plot digitalizing software (WebPlotDigitizer) was utilized to capture the required data.

The “mvmeta” module of the statistical package of STATA SE 12.0 was used for the network meta-analysis. The results are presented in (1) a network graph in which the size of a node is proportional to the number of patients receiving a specific treatment, and the width of a line between two treatments is proportional to the number of comparisons for this specific treatment contrast; (2) the mean difference of the relative changes for each active treatment versus placebo presented in a forest plot diagram; (3) the mean differences in the relative change for each pair of treatments involved presented in a league table; and (4) the probability for each treatment being the best treatment. The probability was estimated under a Bayesian model with flat priors, assuming that the posterior distribution of the parameter estimates (in cases of odds ratios, their logarithm) were approximated by a normal distribution. Rankings were constructed by drawing the coefficients 10,000 times from their approximate posterior density21.

Descriptive presentation of local tolerability outcomes

The systematic search identified large-scale patch studies that contained data on local skin reactions. These outcomes were summarized and comparatively presented together with the same local skin reactions detected with the use of E2 MDTS. No statistical analysis was performed due to the heterogeneity of the reported outcomes.

Matrix- and reservoir-type patches were distinguished. Placebo-controlled trials were handled separately as the placebo patch arms can carry additional information in contrast to MDTS placebo arms, where the differences can probably only stem from the delivery form. MedDRA coding was used in the clinical study report of E2 MDTS trial (CSR) that was slightly different from the patch studies, so the final
terminology we used was: application site reaction, including skin irritation, rash/erythema, rash pruritic/itching, and blisters/vesicle. In a few patch studies, further local skin reactions, such as edema or local burning sensation, also appeared, and these data were also collected. In addition, the discontinuation rates due to local skin reactions related to patch and MDTS application are also presented.

Results

Network meta-analysis results

Overall, eight randomized controlled studies could be included in the network meta-analysis (see Appendix S1, at http://dx.doi.org/10.1080/113697137.2016.1221919): one investigated E2 MDTS versus placebo17,22, five investigated E2 matrix patch versus placebo13,23–26, and one compared matrix and reservoir patches27. The basic information of the included studies is summarized in Table S1 (see Supplemental Table S1 at http://dx.doi.org/10.1080/113697137.2016.1221919). The daily E2 doses ranged from 14 μg to 50 μg in patch studies and from 21 μg to 29 μg in the E2 MDTS study. In all placebo-controlled studies, the active treatment E2 arms proved to be superior to placebo in relieving vasomotor symptoms13,17,22–26,28.

For the NMA, nine treatments including placebo were generated from the treatment arms in the studies included. Their network is presented in Figure 1. Figure 2 shows that all treatments but one (14 μg/day patch) resulted in a significantly greater relative reduction in the number of hot flushes than placebo. In a pairwise comparison of the treatments, a clear dose–response pattern could be shown: the 50 μg/day matrix and 50 μg/day reservoir patches proved to be the most effective treatment with essentially the same effect size (Table 1). MDTS with 40 μg/day spray were somewhat less effective (by 6–7%), although the difference was not statistically significant. The 21 and 29 μg/day MDTS and the 25 μg/day patch had a similar effect size. In a pairwise comparison of active treatments, only the 50 μg/day matrix and reservoir patch treatments were shown to be significantly superior over 14 and 25 μg/day patch treatments. Table 1 shows that the 50 μg/day matrix patch had the highest probability (52.1%) to be the most effective treatment followed by the 50 μg/day reservoir patch with 32% and the 40 μg/day MDTS with 10.2%. None of the pairwise comparisons between MDTS versus patch treatment in contrast showed significant differences.

Local skin reactions

The following section summarizes the findings on local skin reactions. The results are presented in a descending order of number of studies related to various reactions. The duration of observation varied across different studies.

Application site reactions

An application site reaction is considered to be any reaction occurring on the surface that contacts the topical medication (patch or MDTS)29. In the literature search, we found numerous studies that published data on local skin reactions related to patches. The following analysis included those studies that used the term ‘application site reaction’. Ten placebo-controlled24,30–38 and 17 additional observational studies11,13,14,25,27,37,39–49 were identified. The summarized results of the placebo-controlled studies are presented in Figure 3. The ranges of the cumulative incidence of skin reactions during the study period varied from 1.3% to 54.9%. The figures for the placebo arms were roughly comparable to those for the active arms within each study. The E2 MDTS performed well compared to patches; the proportion of users with skin reactions was low, both on the active (1.3%) and on the placebo (1.8%) arms.
The detailed data of all study arms according to descending daily E2 doses are presented in Figure 4. No clear dose–response pattern could be observed. Outlier results could also be seen (e.g. Notelovitz, 2002; Shulman, 2002; Akhila, 2006). Within-study correlations could be observed between active and placebo arms. In the E2 MDTS study, two cases were reported in the ’one E2 spray’ and one case in the ’three E2 sprays’ arms, representing 2.6% and 1.3%, respectively. Four application site reactions were reported in the three placebo arms together. There were variations between the studies. With the use of 50-µg reservoir-type patches, a higher frequency of application site reactions was reported than with similar matrix-type patches.

Erythema

Erythema is a common complaint in the case of patch delivery systems. Five placebo controlled trials and nine other observational studies were found that published data on the incidence of erythema. In cases of placebo-controlled trials, the variability of the results was large within a range of 0–47% (see Supplemental Figure S1 at http://dx.doi.org/10.1080/113697137.2016.1221919). Erythema was more prevalent in the active arms than in the placebo arms; only Holst and colleagues reported more erythema in the placebo arms. The E2 MDTS had an advantageous local tolerability profile in terms of erythema, since only a small number of patients experienced this sign: one case was reported in the ’one E2 spray’ and two cases in the placebo arms (0.4% and 0.9%, respectively). The detailed results of all observational studies can be seen in Figure S2 (see Supplemental Figure S2 at http://dx.doi.org/10.1080/113697137.2016.1221919).

Skin irritation

Skin irritation is also a frequent complaint in the case of patches. Five placebo-controlled trials and three
additional observational studies were identified that published data on the incidence of skin irritation. Figure S3 (see Supplemental Figure S3 at http://dx.doi.org/10.1080/113697137.2016.1221919) shows the summarized results of the placebo-controlled trials. Incidences in active and placebo arms were in a relatively narrow range within one study, although Vrijer and colleagues reported a higher frequency of skin irritation in the placebo arm. The variability of the results with patches ranged from 2.9% to 91.3% (see Supplemental Figure S4 at http://dx.doi.org/10.1080/113697137.2016.1221919). Toole and colleagues reported very high frequencies of skin irritation. In cases using the E2 spray, only one patient experienced skin irritation in the 'three E2 sprays arm' (1.3%) (see Supplemental Figure S4 at http://dx.doi.org/10.1080/113697137.2016.1221919).

Itching, vesicles, edema and burning sensation
A small number of patch studies reported data on the incidence of itching with the results, varying from 0 to 66%. Only one study published data about vesicles. Jarupanich and colleagues reported that, at 3 months after study initiation, 18% of their patients experienced vesicles at least once during the study treatment period. In cases of MDTS, one patient in the 'one E2 spray arm' and one in the 'two placebo sprays arm' experienced itching and one patient in the 'one E2 spray arm' experienced vesicles. Few patch studies presented data about edema and burning sensation, and no such reactions were presented with the MDTS.

Discontinuation rates due to local skin reactions
In patch studies, the discontinuation rates due to local skin reactions were significant. The drop-out rate ranged from 0 to 12% (see Supplemental Figure S6 at http://dx.doi.org/10.1080/113697137.2016.1221919). The E2 MDTS had a favorable local tolerability profile in this respect: only one patient (who received a placebo spray) was withdrawn from the
study due to a local skin reaction (0.4%). After termination, the rash resolved without treatment\(^2\).

**Discussion**

Vasomotor symptoms especially can cause a significant burden for women with menopause\(^3\) and are associated with significantly worse quality of life\(^4\), making VMS one of the primary targets of treatments. HRT is widely accepted for alleviating VMS\(^5,6\). Transdermal HRT seems to have a lower risk for venous thromboembolism than oral administration\(^6\). Transdermal routes include gel, patch or, more recently, the metered-dose transdermal spray. Especially patches are used widely. MDTS, as the most recent E2 delivery mode, has achieved good efficacy results and has a local safety profile similar to patches\(^17\). It was suggested that the E2 MDTS had additional application advantages. Our objectives were to study the efficacy and tolerability of the E2 MDTS compared to E2 patches in women with postmenopausal hot flushes. However, the efficacy of E2 patches and the E2 MDTS had never been compared directly to each other, and thus an indirect comparison in a NMA needed to be applied\(^18,19\). The tolerability outcomes were compared in a descriptive manner based on a systematic literature review as the outcomes were not directly comparable quantitatively.

In NMA, all treatments but one (the lowest E2 dose: 14 \(\mu\)g/day) resulted in a significantly greater mean difference in the relative change of the number of hot flushes than placebo. In the pairwise comparisons, the treatments showed a dose–response pattern, consistent with the probability of the most effective treatment analysis. These dose–effect results support the validity of the analysis, which provided evidence that, when applied in similar doses, the MDTS and patches have similar efficacies in preventing hot flushes.

In local skin reactions, the E2 MDTS seems to perform better than patches. The cumulative incidence of application site reactions compared to patches is low and almost no difference can be observed between the placebo and active MDTS arms. The detailed results were similar for erythema and skin irritation. The E2 MDTS seems to have a very advantageous local tolerability profile. Limited evidence is available for itching, vesicles, edema and burning sensation, and no clear difference can be identified between the delivery forms. These skin reactions can significantly influence the compliance of the patients, and, if preliminary results were confirmed, this would strengthen the favorable local tolerability profile of the E2 MDTS.

The most important limitation of our analyses regarding the efficacy is the indirect nature of the comparison, which assumes consistency, i.e. valid inference about the relative effect of the MDTS compared to patches via a third common comparator, placebo. However, in our view, there is no major concern about this in regard to the relative change measure analyzed, and the found dose–response relationship further supports this hypothesis. Another limitation was that we included only those studies in which the differences between the treatment arms in the percentage change of the frequency of hot flushes from baseline to week 12 were reported or could be estimated from the published data. This led to the exclusion of some studies in which hot flushes were the outcome but this effect measure could not be extracted. As the availability of the chosen effect measure is not likely to be related to the results themselves, this selection did not bias our results but somewhat decreased the precision. Regarding the safety analysis, the variety of the length of studies to which the cumulative incidences of the side-effects were referred prevented us from pooling the results quantitatively. Nevertheless, the review of the safety results could provide evidence for the different local safety profiles of the two studied application modes.

In summary, our review provides evidence that the efficacy of the E2 MDTS on vasomotor symptoms is similar to the efficacy of E2 patch treatment in similar doses, and the MDTS treatment has a better safety profile for local skin reactions.

**Conflict of interest** The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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