



VAGINAL ESTROGEN THERAPY AND THE RISK OF RECURRENCE IN WOMEN WITH A HISTORY OF BREAST CANCER

TERAPIA DE ESTRÓGENOS VAGINALES Y RIESGO DE RECURRENCIA EN MUJERES CON ANTECEDENTE DE CÁNCER DE MAMA

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ABSTRACT

Breast cancer remains the most common malignant neoplasm and one of the leading causes of mortality in women, making it a significant target for global health efforts and a public health priority. Through the use of innovative therapies, survival rates have improved, leading to the emergence of associated conditions such as genitourinary menopausal syndrome. Hormonal therapy is employed for managing this condition, significantly alleviating its symptoms and, in some cases, serving as the sole solution. The most commonly utilized approach is vaginal estrogen therapy. Nevertheless, there have been reports of a potential risk of breast cancer recurrence associated with its use. In the Spanish-speaking context, there is limited evidence discussing this topic. A search was conducted across PubMed, ScienceDirect, and MEDLINE databases, using the terms "Vaginal Estrogen Therapy," "Recurrence," and "Breast Cancer." It was determined that, on a global scale, vaginal estrogen therapy is an effective and safe therapeutic option for managing genitourinary menopausal syndrome in women with a history of breast cancer. This therapy does not appear to increase the risk of recurrence, with the exception of those undergoing treatment with aromatase inhibitors. For these individuals, alternative therapies are recommended to mitigate this potential risk.

Keywords: Estrogens; Vaginal Creams; Foams, and Jellies, Breast Neoplasms; Risk Factors; Recurrence. (Source: MESH-NLM)

RESUMEN

El cáncer de mama sigue siendo la neoplasia maligna más frecuente y una de las mortales en mujeres, considerándose un importante objetivo de la salud global y prioridad en salud pública. Con el uso de terapias innovadoras, ha mejorado la supervivencia, apareciendo condiciones asociadas, como el síndrome genitourinario menopáusico. La terapia hormonal, se utiliza para el manejo de esta condición, mejorando sustancialmente la sintomatología, e incluso, siendo en algunos casos la única solución. La más utilizada, es la terapia de estrógenos vaginales. Sin embargo, se ha descrito un posible riesgo de recurrencia de cáncer de mama con su uso. En habla hispana, no existe evidencia que haya discutido este tópico. Se llevó a cabo una búsqueda en las bases PubMed, ScienceDirect y MEDLINE, utilizando los términos "Terapia de estrógenos vaginales", "Recurrencia" y "Cáncer de mama". Se encontró, que, de forma global, la terapia de estrógenos vaginales es una opción terapéutica eficaz y segura en el manejo del síndrome genitourinario menopáusico en mujeres con antecedente de cáncer de mama, sin incrementar el riesgo de recurrencia, a excepción de aquellas tratadas con inhibidores de la aromatasa, en quienes se recomienda el uso de otras terapias para evitar acarrear este riesgo.

Palabras clave: Estrógenos; Cremas, espumas y gelatinas vaginales; Neoplasias Mamarias; Factores de Riesgo; Recurrencia. (Fuente: DeCS- BIREME)

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INTRODUCTION

Breast cancer remains the most common malignancy and one of the deadliest in women (ranking fourth), generating an unsustainable disease burden worldwide, being considered an important global health goal and a public health priority^(1,2). In 2020, 2.3 million new cases were diagnosed, with approximately 690,000 deaths⁽¹⁻⁴⁾. It is estimated that by the year 2040, the incidence will be close to 3 million new cases and 1 million deaths per year, due to the growth and aging of the population⁽¹⁾.

Despite this discouraged outlook, new antineoplastic therapies provide tools that can favorably modify the survival rate⁽⁵⁾. Nevertheless, other conditions associated with the survival and recovery of these women may emerge and be the objective of both primary and specialized care, such as, for example, cancer recurrence in the medium or long term^(4,5). Menopausal genitourinary syndrome (MGS) usually appears at menopause, secondary to decreased estrogen production, causing vulvovaginal and vesicourethral symptoms⁽⁶⁾. These progressive symptoms are accentuated according to the peak of hypoestrogenism, considerably affecting the quality of life of the woman who suffers from it. Hormone therapy (HT) can be used to manage this condition, substantially improving the symptoms, and even being, in some cases, the only solution^(7,8). This can be both vaginal (VHT and systemic SHT), the first being more frequently used⁽⁷⁾.

Nonetheless, in those cases of women with a history of estrogen receptor-positive breast cancer, evidence suggests that there is an increased risk of recurrence, without knowing exactly whether it is prudent or not to use it, or whether it is feasible or not to use it during the adjuvant or neoadjuvant process⁽⁷⁻⁹⁾. Taking into consideration the high incidence of breast cancer, increasingly at younger ages, as well as the frequent symptoms of moderate to severe MGS, in addition to the initiatives to have scientific evidence that facilitates the understanding of the health-disease process in cancer breast cancer, and promotes evidence-based clinical practice^(10,11), it is necessary to know what the

most recent and best-quality evidence has concluded. Based on the above, the objective of this review is to analyze the current evidence regarding the risk of breast cancer recurrence in women who require VHT.

METHODS

A literature search was performed using the terms "Vaginal estrogen therapy", "Recurrence" and "Breast cancer", together with their synonyms, in the PubMed, ScienceDirect and MEDLINE databases. To select the articles, inclusion criteria were established, giving priority to original studies, systematic reviews, and meta-analyses that focused on evaluating the risk of breast cancer recurrence in women who received vaginal hormone therapy. Articles had to be available in full text. Articles published up to the year 2023 were included, as well as those that described risk factors associated with breast cancer recurrence in women and manifestations after adjuvant or neoadjuvant therapy in these cases. No exclusion criteria were defined. Effect measures were expressed in their original measures, such as frequencies, percentages, confidence intervals (CI), mean difference (MD), risk difference (RD), relative risk (RR), or odds ratio (OR).

RESULTS

Factors associated with the risk of breast cancer recurrence in women. In general, several factors are associated with the recurrence of breast cancer, either positively or negatively. Associated with therapies, one of which is often frequently used in medical practice, are statins. Harborg et al.⁽¹²⁾ carried out a cohort study where they evaluated the association between the use of statins and the risk of breast cancer recurrence in 14,773 postmenopausal Danish women treated with aromatase inhibitors for breast cancer diagnosed in early stages.

During a 5-year follow-up period, the authors found an incidence of 32 cases per 3,163 person-years of follow-up among patients exposed to statins, and 612 cases per 45,655 person-years of follow-up among unexposed patients, giving an incidence rate (per 1000 people/year) of 10.12 (95% CI: 6.92 – 14.28) vs. 13.40 (95% CI: 12.36 – 14.51), respectively.





After a multivariate analysis, they found that using any statin was associated with a 5-year reduction in the risk of recurrence of up to 28% (HR 0.72; 95% CI: 0.50 – 1.04). Therefore, they found that those women treated with aromatase inhibitors for breast cancer and who used statins had a lower risk of recurrence in the medium term⁽¹²⁾. Ahern et al.⁽¹³⁾, conducted a prospective cohort study using the same Danish database, finding that, in 18,769 women followed for a median time of 6.9 years, the use of simvastatin (lipophilic statin) was associated with ten fewer recurrences per 100 women after 10-year follow-up (RD -0.10, 95% CI -0.11 to -0.08), compared to those not receiving statins.

The use of hydrophilic statins was associated with approximately the same risk as not using statins (RD 0.05, 95% CI -0.01 to 0.11). Thus, it was concluded that simvastatin, a highly lipophilic statin, was associated with a reduced risk of breast cancer recurrence in women with a history of stage I to III carcinoma⁽¹³⁾.

Having this evidence is essential, since some authors state that the risk of breast cancer recurrence remains for up to 32 years after remission⁽¹⁴⁾. Associated with the characteristics of the neoplasm, diagnosis before the age of 40, estrogen receptor-positive tumors, treatment with conservative surgery, 4 or more affected lymph nodes, a primary tumor measuring 40 mm or more, among other variables; are potential positive predictors for recurrence⁽¹⁴⁾. Lafourcade et al.⁽¹⁵⁾, through a cohort study initiated in the 1990s in France, with a median follow-up of 7.2 years for 4,926 women, there were 1,334 cases of recurrence and 469 deaths.

On this occasion, it was found that large tumors (HR 1.64; 95% CI: 1.33 - 2.01 vs. HR 4.70; 95% CI: 2.27 - 9.75) of high grade (HR 1.90; 95% CI: 1.36 – 2.66 vs. HR 6.54; 95% CI: 2.02 – 21.18), with axillary node involvement (HR 1.54; 95% CI: 1.26 – 1.86 vs. HR 5.23; 95% CI: 2.63 – 10.42), and estrogen or progestin receptor-negative tumors (HR 2.14; 95% CI: 1.70 – 2.70 vs. HR 9.76; 95% CI: 4.39 – 21.75), had a higher risk of recurrence and death, respectively.

Smoking after diagnosis was specifically associated with a higher risk of recurrence compared to never having smoked (HR 1.55; 95% CI: 1.16 – 2.07)⁽¹⁵⁾. With these results, the authors expressed the need to recognize and design strict follow-up and education programs to reduce the risk of recurrence, considering that some aspects related to lifestyle could significantly impact this risk.

Phytoestrogens are chemical compounds with the ability to mimic the action of endogenous estrogens. The main phytoestrogens are isoflavones, common in the Asian diet (where, coincidentally, the incidence of breast cancer is lower compared to other regions of the world), where there is a high consumption of soy. Some authors have associated the consumption of these phytoestrogens through soy consumption with a reduction in the risk of recurrence and/or mortality in breast cancer. But what does the evidence say? A very recent systematic review⁽¹⁶⁾ found that, of 7 studies included with more than 18,500 women, only one found no general benefits in terms of soy consumption and recurrence of this type of cancer. However, those studies that did find associations demonstrated that these were heterogeneous.

Two studies found reduced risk of recurrence only in postmenopausal women; four studies found reduced risk of recurrence and death in women with tumors sensitive to hormones or receiving hormone therapy. It should be noted that no adverse effects were found in terms of soy consumption, and recurrence or mortality events. So, although in a non-specific way, the consumption of soy (phytoestrogens) could have benefits on the prognosis of recurrence and death of breast cancer⁽¹⁶⁾. Other innovative studies have described that the suspension of endocrine therapy⁽¹⁷⁾, body mass index⁽¹⁸⁾, and other factors, are also positively correlated with recurrence up to 20 years after diagnosis^(17,18). Considering the above, other exposures associated with this prognosis must also be taken into account, and work must be done to reduce the risk of recurrence and mortality in women with a history of breast cancer (Figure 1).

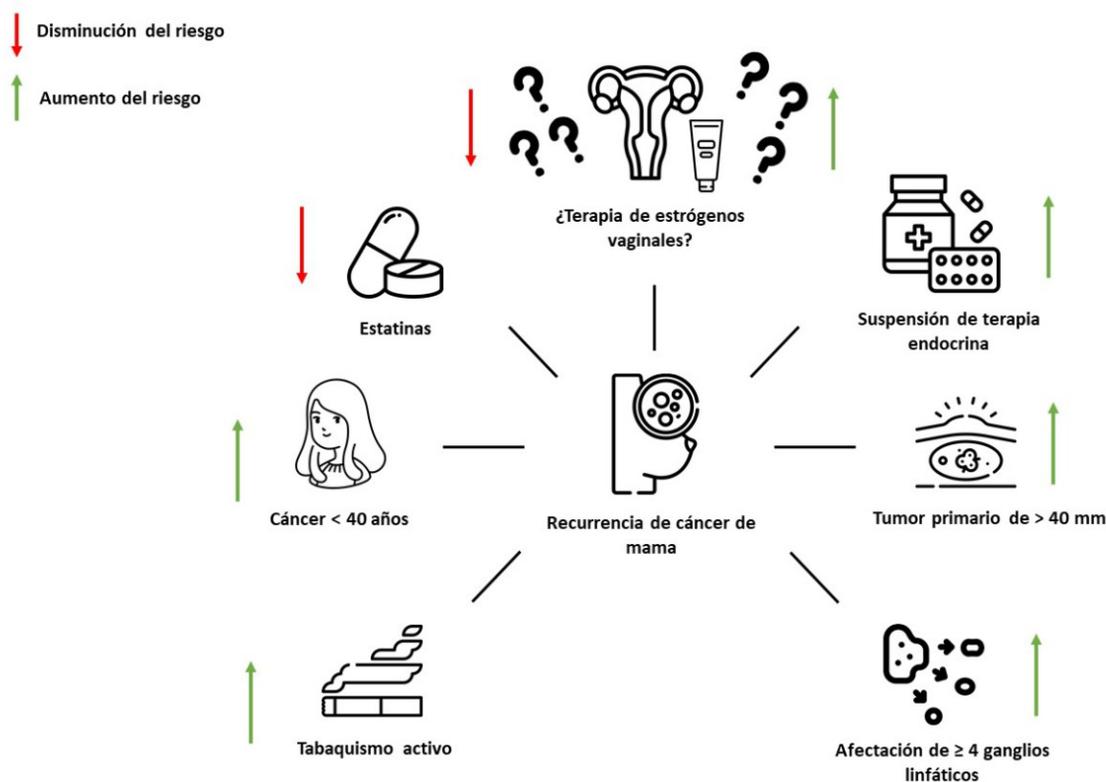


Figure 1. Summary of some factors positively or negatively associated with breast cancer recurrence. Source: authors.^(12,13,14,15,17)

Manifestations after antineoplastic therapy in women with breast cancer history

Considering that the peak incidence of breast cancer diagnosis oscillates between the fifth and sixth decade of life, peri and postmenopausal manifestations are very frequent, to which the symptoms are added after chemotherapy. This mixed picture tends to be more aggressive, can last up to 15 years after treatment, occurs in up to 72% of cases, and can further affect the morbidity, survival, functional capacity, and quality of life of the woman. Some studies reveal that women with this history have a greater number of symptoms and these vary according to age, type of chemotherapy received, pathological history, consumption of medications for comorbidities not related to malignancy, etc.

Among the most commonly reported manifestations or diagnoses are cough, respiratory, skin and urinary infections, fatigue, poor sleep quality, lymphedema (HR 8.6; 95% CI: 6.3-11.6), chest pain, osteopenia (HR 2.1;

95% CI: 1.8 – 2.4) and osteoporosis (HR 1.5; 95% CI: 1.2 – 1.9)⁽¹⁹⁻²¹⁾. In the emotional sphere, compared to control groups, women with a history of breast cancer have a higher risk of obtaining lower scores on the mental and physical quality of life scales, as well as depressive symptoms ($p=0.03$) and anxiety ($p<0,001$)⁽²²⁾.

For all of the above, emphasis has been placed on the support care needs for the proper and timely management of these conditions.

Recurrence in general (59.1%), access to the best medical care (52.7%), access to complementary therapy service (51.5%), changes in beliefs (48.2%), and expectations about the survival (47.6%), are some of the concerns associated with manifestations in survivors with breast cancer. These correlate with the patient's age, time since diagnosis, and quality of life ($p < 0,01$)^(23,24). Comprehensive care also includes screening for cardiometabolic conditions associated with chemotoxicity. Hamood et al.⁽²⁵⁾ carried out a case-control study with 2,246 surviving women of



breast cancer, finding that having used hormone therapy (HR 2.40; 95% CI: 1.26-4.55), tamoxifen (HR 2.25; 95% CI: 1.19 – 4.26) and aromatase inhibitors (HR 4.27; 95% CI: 1.42 – 12.84), was associated with increased risk of developing diabetes. in an average time of 6 years⁽²⁵⁾.

While evaluating metabolic risk and cardiovascular events in women with breast cancer and undergoing treatment with aromatase inhibitors, it has been described that this group of drugs increases the probability of a cardiovascular event (OR 1.16; 95% CI: 1.04 – 1.30), compared to tamoxifen⁽²⁶⁾. And although a possible association between the use of these two agents and dementia in survivors has also been described, some meta-analyses have confirmed that the available evidence is insufficient to establish a precise estimate (HR 1,04; IC 95%: 0,83 – 1,03)⁽²⁷⁾. This panorama demonstrates that women with a history of breast cancer, who were eventually administered neoadjuvant therapy, have a much wider range of manifestations and syndromes (mainly postmenopausal), compared to control groups. Therefore, timely and personalized treatment is essential to maintain or improve the quality of life of these women⁽²⁸⁾.

Vaginal estrogens and other therapies for managing moderate to severe menopausal genitourinary syndrome in women with a history of breast cancer: which is better?

Moderate to severe MGS in women with a history of breast cancer is probably one of the most significant clinical pictures, since it affects two systems, the reproductive and urinary⁽²⁹⁾. The symptoms and predisposition to urinary tract infections, and the limitation of sexual activity due to dyspareunia, dryness, among other manifestations, must be managed to avoid the alteration of other spheres⁽²⁹⁾.

As mentioned, vaginal estrogens are a useful therapy, but they may have adverse events in these cases.

What does the evidence say about its safety and efficacy in this risk group?

More than 5 years ago, a series of cases with 18-year follow-up showed that those women who survived

breast cancer and who used VHT, did not observe changes in breast density when they were periodically evaluated by mammography⁽³⁰⁾. At the time, it was established that the use of low doses of VHT could be safe^(30,31). The foregoing, supported by the consensus recommendations of the "North American Menopause Society and The International Society for the Study of Women's Sexual Health", who, through a panel of 16 international experts, stated that VHT should be used as a second line, in the management of the MGS⁽³²⁾.

However, it is necessary to take into account other available therapies and weigh the benefit-risk balance, compared with VHT. Jha et al.⁽³³⁾ conducted a systematic review and meta-analysis, where they evaluated the impact of vaginal laser therapy for MGS in breast cancer survivors. 10 studies with a total of 354 women were included, evidencing that this therapy was effective in the treatment of MGS, improving the vaginal sexual health index (DM -11,35; IC 95%: -13,35 a -12,05), and the score obtained from the visual analog scale for dyspareunia (MD 2.22; 95% CI: 1.98 - 2.46) and vaginal dryness (MD 2.72; 95% CI: 2.50 - 2.93)., as well as sexual function and general satisfaction with short-term results (83.5%), without relevant adverse events⁽³³⁾. Quick et al.⁽³⁴⁾ carried out a trial study with 64 women, to evaluate the feasibility and preliminary efficacy of fractionated CO2 therapy in EMS in female breast cancer survivors. Patients received 3 intervention cycles each month and were then followed up to the fourth month. It was found that 88.1% of the participants did not present serious adverse events, and that there was a considerable reduction in the vaginal evaluation scale (DM -0,99; IC 95%: -1,19 a -0,79), Female Sexual Function Index (DM 9,67; IC 95%: 7,27 – 12,1), and the Urinary Distress Index (DM -8,85; IC 95%: -12,75 a -4,75).

It should be remarked that, representatively, these women had hormone-positive cancers (63%), were stage I or II (86%), received endocrine therapy (92%), and were managed with aromatase inhibitors (68%). . Thus, they were able to demonstrate that fractionated CO2 laser therapy is viable and reduces symptoms in the short term, being a powerful tool to consider in the management of MGS in women with these

characteristics of cancer⁽³⁴⁾. Other non-hormonal therapies consist of vaginal gels, lubricants and moisturizers, which temporarily alleviate the symptoms, but with insignificant results^(35,36). For its part, systemic hormonal therapy was demonstrated approximately 20 years ago (HABITS study), the significantly increased risk of breast cancer recurrence (HR 3.5; 95% CI: 1.5 – 8.1), mainly in women with hormone-positive cancer.

Which, at the time, generated controversy and led to the dissemination of a recommendation on the suspension of this type of treatment in women with a history of breast cancer⁽³⁵⁾. However, years later, a trial (Stockholm trial) found that, During a follow-up of approximately 4 years, there was no association between this type of therapy and risk of recurrence (HR 0,82; IC 95%: 0,35 – 1,9). Nevertheless, there was significant heterogeneity between the groups analyzed. Therefore, the researchers emphasized that there could be a risk in the use of VHT⁽³⁵⁾. Vaginal estrogens are administered at the vaginal level using tablets, creams or other presentations, at a low dose with local action and minimal systemic absorption⁽³⁶⁾.

Although it is presumed that the inherent risk of recurrence due to the high exposure is with the use of systemic hormone therapy, there is also evidence to suggest that VRT may positively influence this risk. But in which subgroups? Very recently, Cold et al.⁽⁹⁾ published the results of a cohort study in Danish women, with the aim of evaluating the risk of breast

cancer recurrence, in women using VHT vs. systemic hormone therapy. A total of 8,461 women with a history of early-stage estrogen receptor-positive non-metastatic cancer who had never used any of these therapies prior to diagnosis were included. After diagnosis, 1,957 used VHT and 133 systemic hormonal therapy, evidencing that, during a follow-up period of approximately 10 years for recurrence and 15 years for mortality, the adjusted relative risk of recurrence with the use of VHT was 1.08. (IC 95%: 0,89 – 1,32) vs. 1,05 (IC 95%: 0,62 – 1,78) for systematic hormone therapy.

However, when doing a subgroup analysis, it was found that the only significant estimate for recurrence was for those women who were treated with aromatase inhibitors (RR 1,39; IC 95%: 1,04 – 1,85). The overall mortality estimate for VHT was 0.78 (95% CI: 0.71 – 0.87) vs. 0.94 for systemic therapy (95% CI: 0.70 – 1.26)⁽⁹⁾. Thus, it was possible to conclude, based on the most recent and best-quality evidence, that the risk of recurrence in the use of VHT is only significant in those women with a history of breast cancer with the previously described tumor characteristics, and treated with aromatase inhibitors. This result is compatible with recommendations made by work committees of the *American College of Obstetricians and Gynecologists*⁽³⁷⁾, and reviews published by experts, who also mention other factors to consider, in the administration of this type of therapy in women with a history of breast cancer (Table 1)⁽³⁸⁾.

Table 1. Factors to consider when prescribing vaginal hormone therapy in women with a history of breast cancer.⁽³⁷⁾

Variable	In favor	Against
Tumor stage	Up to stage II – metastatic with poor life expectancy	From stage III – metastatic with prolonged life expectancy
Grade of disease	Low – intermediate	High
Lymph node involvement	No - < 4	Yes - > 4
Hormone sensitive cancer	Negative	Positive
Endocrine therapy	Tamoxifen	Aromatase inhibitors
Time since diagnosis	Significant	Recent



Symptom severity	Severe	Mild - Moderate
Use of previous non-hormonal therapies	Therapeutic failure	Unused – High rate of effectiveness
Effect on quality of life	Significant	No significant
Identification of additional modifiable risk factors	High probability of eliminating them	Low probability of eliminating them
Identification of additional non-modifiable risk factors	Relative	Relative

Source: authors.

But, it is necessary to mention that the available evidence on this topic comes almost entirely from developed countries, the behavior of this condition being unknown in countries such as Latin America, where the genetic and epigenetic characteristics differ significantly compared to those of other regions of the world. So, based on the overall high risk of developing cancer due to the Western diet, unhealthy lifestyle, ethnicity/race, and difficulties in timely access to breast cancer screening and control programs, it is presumed that in our region, this risk is greater than that described in the world literature.

Future perspectives

Taking as a reference the goals stipulated by international consensus on cancer control in low- and middle-income countries⁽³⁹⁾, like Latin Americans, as well as the phantom load generated by breast cancer in our region and the existing gap in the evidence on this topic^(40,41), Studies adapted to the sociodemographic, cultural, economic, and health context⁽⁴²⁾, should be designed to estimate the risk of recurrence and mortality, the efficacy and safety of these therapies, and women's perception of the results and their respective quality of life, to verify that MGS is solved with a therapy that is presumed to be highly effective, without unfavorably modifying the risk of breast cancer

recurrence in women. All of the above, to reproduce the evidence-based research model⁽⁴³⁾, produce valid and valuable research that can substantially impact the health outcomes of breast cancer and facilitate the process of health education in women. postmenopausal women⁽⁴⁴⁾ so that they are participants in their health care process and can live fully. As limitations, mention that this is a narrative review, which performs only a qualitative analysis of the available evidence, constituting insufficient evidence to support a recommendation or intervention in care practice, which must be based on higher quality evidence.

CONCLUSIONS

Based on the most recent evidence, overall, vaginal estrogen therapy is an effective and safe therapeutic option in the management of menopausal genitourinary syndrome in women with a history of breast cancer, without increasing the risk of recurrence, except for those treated with aromatase inhibitors, in whom the use of other therapies is suggested to avoid carrying this risk. Nevertheless, this phenomenon is clearly unknown in Latina women, so studies should be carried out that consider the variables typical of this population, which may influence the evolution and/or outcomes of the use of this therapy.

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have participated in the conception and design of the article, analysis and interpretation of data, writing of the article, critical review of the article and approval of the final version.

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