Physicians' Opinions Regarding Treatment with Hormone Therapy, Antidepressants and a Novel Estrogen Receptor Beta Agonist, Menerba for Vasomotor Symptoms

Running Head: TREATMENT OPTIONS FOR VASOMOTOR SYMPTOMS

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ABSTRACT

OBJECTIVE: To conduct qualitative and quantitative studies among physicians who treat women with menopause to evaluate current practices for treating vasomotor symptoms and to solicit their opinion about the use of an oral, novel, non-hormonal agent in clinical testing, Menerba, for the treatment of vasomotor symptoms.

DESIGN: Descriptive qualitative and quantitative studies were conducted by an independent survey group to allow physicians specializing in women's health to respond to questions about treatment practices for vasomotor symptoms.

RESULTS: 23 physicians participated in the qualitative study and 101 physicians participated in the quantitative study. In the qualitative survey, physicians cited the most commonly reported barriers to treatment for vasomotor symptoms for patients was the risk of breast cancer (74%) and cardiovascular disease (48%) associated with hormone therapy use. In the quantitative study, physicians report that the primary unmet medical need for the treatment of vasomotor symptoms is a safer alternative to hormone therapy with fewer side effects that does not sacrifice efficacy. The physicians in the qualitative study state that, if available, Menerba would be used as first-line therapy by 78% of physicians for the treatment of vasomotor symptoms, and 92% stated they would prescribe Menerba prior to prescribing an SSRI or SNRI.

CONCLUSION: Physicians and patients have concerns about the safety and tolerability of currently available treatments for vasomotor symptoms. Based upon phase 2 clinical trial results of Menerba, physicians would prescribe this novel, estrogen receptor beta agonist as first-line treatment for vasomotor symptoms if approved as a new drug.

Keywords: Menerba, MF101, vasomotor symptoms, menopause, hormone therapy, hot flashes

INTRODUCTION

There are approximately 40 million women of menopausal age in the United States. This population is expected to increase dramatically in the next decade as the "baby boom" generation continues to enter this age group. Approximately 75% to 85% of menopausal women experience significant and unpleasant side effects while transitioning through menopause and approximately 15% of postmenopausal women continue to experience hot flashes into their 60s.[1] Prior to the first publication of the Women's Health Initiative (WHI) results in 2002, hormone therapy (HT) was a popular, long-term treatment for menopausal symptoms and conditions related to estrogen deprivation[2], with total worldwide sales exceeding $3.5 billion per year in 2001.

In July 2002, the WHI Data and Safety Monitoring Board (DSMB) stopped the estrogen plus progestogen trial early, which enrolled over 16,000 women, due to the increased risk for breast cancer among the participants taking HT when compared to placebo.[3-5] The full results of that trial showed that the most commonly prescribed HT poses significantly increased risks for a number of serious adverse effects including:

- breast cancer;
- deep-vein thrombosis;
- pulmonary embolism;
- stroke;
- coronary heart disease; and
- dementia.

The FDA issued six "black box" warnings for all estrogen-containing formulations for HT. A black box warning is the strongest type of warning the FDA can require for a drug, and is

generally reserved for drugs that may lead to serious injury or death. Recently published data also shows that HT also increases the risk for ovarian cancer and increased the number of deaths from lung cancer, in particular deaths from non-small-cell lung cancer.[6, 7]

Following the publication of the WHI study results, sales of HT drugs dropped by more than 50% and the number of prescriptions written by physicians has dramatically decreased.[8] Concurrently, demand for over-the-counter herbal supplements, which have unproven safety and efficacy profiles, has increased, with approximately 80% of menopausal women using herbal supplements for vasomotor symptoms (VMS).[9]

Two other classes of drugs, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have been shown to be effective in the treatment of hot flashes, although they are not FDA-approved for this indication.[10] The FDA recently declined approval of the first non-hormonal SNRI under review for the treatment of postmenopausal VMS. The FDA instead issued an "approvable" letter and requested additional safety data with regards to the drug.

Menerba, in clinical development, represents a new class of receptor sub-type selective estrogen receptor modulators (SERMs) for the treatment of VMS. Menerba has been designed to selectively modulate the estrogen receptor beta (ERβ) to provide an improved safe profile over existing therapies for this indication.[11] In brief, the currently available estrogen therapies used to treat menopausal symptoms are non-selective to both of the two known estrogen receptors, alpha and beta. Unlike currently available non-selective estrogens contained in all hormone therapies, Menerba does not activate the estrogen receptor alpha (ERα), which is known to be implicated in both breast and uterine cancer formation[11]. Menerba has distinct chemical structural differences from steroidal estrogens, and from selective estrogen receptor modulators (SERMs), which result

in its receptor subtype selectivity, its different pharmacological profile, and its improved safety profile. To date, the aggregate of preclinical and clinical studies demonstrate that Menerba will not increase the risks for either breast or uterine cancer. In addition, due to the absence of ERβ in the liver, Menerba will not result in an increased risk for venous thromboembolic events or clotting, a finding confirmed by animal studies.

A double-blind, placebo-controlled phase 2 clinical trial evaluating the safety, tolerability and efficacy of Menerba for the treatment of postmenopausal VMS was conducted in the US.[12] In the trial of 217 postmenopausal women, Menerba 10 g/day was extremely well tolerated and resulted in a statistically significant reduction in hot flashes when compared to placebo after 12 weeks of treatment. The results also indicated a favorable safety profile and statistically significant efficacy with the higher of two doses of Menerba tested. There was one statistically significant side effect associated with the Menerba treatment, an increase in loose stools (3% in the placebo group vs. 12% in the Menerba groups) with a statistically significant benefit from a reduction in constipation. (This one side effect was most likely due to the presence of soluble fiber in the plant-based extract and for the phase 3 clinical trial, manufacturing process changes have been implemented to removed the soluble fiber and mitigate this one side effect). There were no differences among the groups in the number of women who reported vaginal bleeding and there were no cases of endometrial hyperplasia, a hallmark of uterine cancer risk.

Qualitative and quantitative methods are ideally suited to gather in-depth information regarding the opinions and practice patterns of physicians. The goals of this study were to obtain detailed qualitative and quantitative information from physicians specializing in women's health to: (1) review current treatment practices for VMS associated with menopause, (2) evaluate unmet needs in the VMS therapeutics arena, (3) understand receptivity toward a botanically-

based drug in development for VMS, and (4) determine how Menerba might be incorporated into current treatment algorithms given available data from a double-blind, placebo-controlled clinical trial of 217 postmenopausal women with moderate to severe VMS.

METHODS

Two in-depth, structured, online, qualitative and quantitative survey approaches were used to elicit physicians' practicing patterns about HT and attitudes about Menerba as a new treatment for VMS. The study team developed an interview guide consisting of open- and closed-ended questions on these topics. The first part of the survey dealt with the physicians' feelings regarding current therapies for VMS. The second part of the survey required physicians to read a product profile of Menerba (which was referred to as Product X) and provide professional opinions regarding Menerba as a potential treatment option for VMS. A description of the mechanism of action of Menerba was also included in the product profile as well as data relating to safety, tolerability and efficacy derived from a phase 2 double-blind, placebo-controlled, randomized clinical trial.

In order to be eligible for the panel, physicians had to meet the following criteria:

a. board certified medical doctor in internal medicine (PCP) or obstetrics and gynecology (OB/GYN),
b. 2-30 years of clinical experience,
c. Currently practicing medicine in the United States,
d. >75% of professional time spent in clinical care,
e. treat a minimum number of VMS patients per month,

    -50 patients per month for OB/GYNs

-10 patients per month for PCPs

f. no conflict of interest with the sponsor of the study based on disclosures of past and current consulting relationships.

Physicians who participated in the qualitative study logged onto the discussion multiple times during the survey, answering questions and reading posts from other participating physicians. One author performed the role of moderator, and posed follow-up questions to expand, probe and clarify responses as necessary.

The participating physicians in both the qualitative and quantitative surveys were from academic hospitals and private practices across the United States and had at least 2 years of clinical experience and spent at least 75% of their time in clinical practice. Twelve physicians board certified in internal medicine and eleven physicians board certified in obstetrics and gynecology participated in the web-based qualitative survey. Fifty physicians board certified in internal medicine and 51 physicians board certified obstetrics and gynecology participated in the web-based quantitative survey. The average number of years in clinical practice for the 23 participating physicians in the qualitative study was 15 years (range 5-27) and the average number of patients treated for VMS per month was 77 (range 20-225). In the quantitative study, the average number of years in clinical practice for the 101 participating physicians was 15 years (range 3-30) and the average number of patients treated for VMS per month was 64 (range 10-200). The surveys were conducted in March and April of 2008 by Panel Intelligence LLC, and paid for by Bionovo, Inc.

RESULTS

Qualitative Study

A professional qualitative research firm prepared verbatim transcription reports of the panel discussion from the qualitative survey. A summary of the qualitative survey is below.

Question 1. Please describe your current treatment approach to VMS associated with menopause. What is your initial choice of therapy? What medication(s) do you use next? Please explain your thought process.

Physicians reported reviewing the patients' medical history as well as the severity and frequency of symptoms as part of their initial approach to treating VMS associated with menopause. For women experiencing mild hot flashes, lifestyle changes such as exercise, diet, smoking cessation and over-the-counter (OTC) preparations are commonly recommended. The majority of the physicians reported using the lowest dose of estrogen (or estrogen plus progestogen therapy for women with an intact uterus) for moderate to severe hot flashes. Physicians in the survey reported that 35% of their patients going through menopause are prescribed HT. When there are known contraindications to the use of HT for VMS, physicians reported using antidepressant agents such as SSRIs or SNRIs. Since the release of data from the Women's Health Initiative (WHI) trial, some physicians now require patients to sign an "Informed Consent" prior to prescribing HT for VMS.

Question 2. What medications do you prescribe in patients who refuse to take HT or for whom HT is contraindicated?

The most commonly recommended treatments for VMS for patients who refuse to use HT were over-the-counter herbal supplements. SSRIs were also cited as alternative treatments for VMS.

Question 3. In your consideration of treatment options, how do you stratify VMS patients? How do you think of patients differently based on their age, the severity of symptoms, duration of symptoms, other medical co-morbidities, etc? What percentage of your VMS patients have tried OTC therapies for their symptoms prior to seeking your assistance with prescription medications?

Classification and rating of both the frequency and severity of hot flashes by patients was the most commonly reported method of stratifying patients prior to considering treatment options. Other factors included: age, medical history, family history, medications, and surgical versus natural menopause. Physicians reported 38% (range 5%-90%) of their patient population had used some form of over-the-counter treatment prior to seeking care from their physician.

Question 4. What do you perceive to be the greatest barriers to treatment for VMS from the perspective of both the physician and patient?

The greatest barriers to treating VMS from the physicians' perspective were: a) the increased risk of breast cancer with HT use, b) the increased risk for cardiovascular disease with HT use, c) the misconception of the results from the WHI and, d) the medical-legal risk associated with prescribing HT treatments.

The most common reported barrier to treatment for VMS for patients was the risk of breast cancer associated with HT use, cited by 74% of the physicians. The second most common

concern for patients was the risk of cardiovascular disease associated with HT, cited by 48% of the physicians.

Question 5. What do you see as the greatest unmet needs in the area of treatment of VMS?

The overwhelming majority of physicians reported the greatest unmet need is for a safe therapy that would not lead to abnormal uterine bleeding or cause increased risks for breast cancer, cardiovascular disease or thromboembolic events.

Question 6. What is your threshold for safety, efficacy and tolerability for a new agent being introduced to treat VMS? What type of improvement would you need to see in the number and severity of hot flashes? For this question, please provide your answers in the form of percent change.

For a new therapy to treat VMS, physicians want a drug that can reduce the number of hot flashes by 63%-65%. Physicians would be satisfied with a new therapeutic agent for VMS with a side effects profile that caused untoward effects in 14%-19% of patients. Acceptable side effects would include: nausea, breast tenderness, weight gain, headache, insomnia, dry mouth and GI tolerability issues. Additionally, physicians reported a 15%-17% dropout rate would be acceptable for patients taking a new therapy.

Question 7. What is your opinion of Menerba? What do you think are its strengths and weaknesses?

The strengths of Menerba reported were: no adverse effects on breast or uterine tissues, no major risks associated with HT, excellent tolerability, high compliance, good efficacy, reduction in body mass index and overall minimal side effects.

The weaknesses reported were: reduction in hot flashes, small sample size of clinical trial and diarrhea as a side effect.

Question 8. Please describe the patients for which you think Menerba would be most appropriate. In your answer, please comment on such characteristics as: age, severity, frequency, and duration of symptoms; prior therapies to treat VMS; medical co-morbidities; and any other features that you think are significant.

The overwhelming majority of physicians stated Menerba would be an appropriate therapy for any women going through menopause, regardless of age or severity of menopausal symptoms, given that the side effects of Menerba were minimal. In addition, a number of physicians added that Menerba would be an ideal treatment for menopausal women with increased risks for either breast or uterine cancers and for women with other contraindications to HT.

Question 9. If it were available, how would Menerba fit into your current treatment algorithm for VMS? Would you use it alone or in combination with other therapies? Please explain your reasoning behind your answer.

If available, Menerba would be used as a first-line therapy by 78% of physicians for the treatment of VMS. In addition, 92% of the physicians stated they would prescribe Menerba prior to prescribing either an SSRI or SNRI.

Quantitative Study

The following summarizes the results of the quantitative survey**.**

Question 1. Considering your patients you treat for VMS, what percentage of your patients can be classified into mild, moderate or severe (based on the severity of VMS)?

	Symptom Severity	**% of Patients Treated for VMS in a Month**
Total	Mild	40.2%
	Moderate	39.7%
	Severe	20.1%
PCP	Mild	43.7%
	Moderate	37.8%
	Severe	18.5%
OB/GYN	Mild	36.7%
	Moderate	41.6%
	Severe	21.7%

Question 2. Considering all of your patients who present with VMS at the 3 severity levels, what percentage receives prescription treatments?

Percent of VMS Patients Receiving Prescription Medications			
	Mild VMS	Moderate VMS	Severe VMS
Total	21.9	44.6	67.6
PCP	19.9	37.0	62.2
OB/GYN	23.9	52.1	73.0

Question 3. What percentage of your patients take over-the-counter medications for VMS before coming to you?

PCPs reported 47% and the OB/GYNs reported 41%. PCPs and OB/GYNs combined reported 44%

Question 4. Would you prescribe a new SNRI for VMS that was shown to reduce moderate to severe hot flashes by 64% and had the following side effects: nausea (39%), dry mouth (21%), dizziness (19%), generalized body aches (19%), insomnia (17%), constipation (17%), somnolence (16%), abnormal vision (6%) and hypertension (5%).

45.5% of the physicians reported yes and 54.5% reported no.

Question 5. Considering your patients treated with prescription therapies for their VMS, what percentage are on the following therapies for 1st line and 2nd line treatment?

Current Prescription Treatment of VMS		
	First-Line Therapy	Second-Line Therapy
Hormone Therapy		
PCP & OB/GYN Combined	63.0%	53.6%
PCP	48.0%	43.2%
OB/GYN	77.7%	63.9%
SSRI/SNRIs		
PCP & OB/GYN Combined	38.4%	48.3%
PCP	53.7%	57.6%
OB/GYN	23.5%	39.2%
Other prescription therapies (gabapentin, clonidine, etc.)		
PCP & OB/GYN Combined	5.3%	7.3%
PCP	7.9%	8.3%
OB/GYN	2.7%	6.3%

Note: In some cases physicians' responses did not total 100%.

Question 6. What percentage of your patients stop using HT for VMS due to the side effects associated with treatment?

PCPs reported that 29% and OB/GYNs reported that 21% of patients stop using HT due to the side effects. PCPs and OB/GYNs combined reported that 25% of patients stop due to the side effects.

Question 7. What percentage of your patients stop using SSRI/SNRIs for VMS due to the side effects associated with treatment?

PCPs reported that 30% and OB/GYNs reported that 35% of patients stop using SSRI/SNRIs for VMS due to the side effects. PCPs and OB/GYNs combined reported that 33% of patients stop SSRI/SNRIs due to the side effects.

Question 8. What percent of your VMS patients:

a. *express concerns about taking HT for VMS,*
b. *refuse to take HT for VMS,*
c. *express concerns about taking antidepressants for VMS, and*
d. *refuse to take antidepressants for VMS.*

Patient Concerns Regarding Treatment for VMS			
Concern Expressed	**PCP & OB/GYN Combined: Percent of Patients**	**PCP: Percent of Patients**	**OB/GYN: Percent of Patients**
Express concern taking HT for VMS	61.3%	55.6%	66.9%
Refuse to take HT	27.0%	26.9%	27.1%
Express concern taking antidepressants for VMS	38.7%	37.8%	39.6%
Refuse to take antidepressants for VMS	28.9%	25.4%	32.3%

Question 9. Based on the product profile of Menerba (Product X), what is your overall opinion based on a 7 point scale, with one extremely unfavorable, 4 neutral opinion and 7 extremely favorable?

Physician reaction to Menerba Profile			
	PCPs & OB/GYNs Combined	**PCPs**	**OB/GYNs**
Favorable (rating of 6 or 7 on 7 point scale)	69%	72%	67%
Slightly Favorable (rating of 5 on 7 point scale)	18%	14%	22%
Total	87%	86%	89%

Question 10. What percentage of your patients are on the current first line of treatment for VMS and in 12 months, if Menerba were approved, what percent of patients would be on HT and SSRI/SNRI?

Physicians	**Current Use**		**Future Use**	
	HT	SSRI/SNRI	HT	SSRI/SNRI
PCPs & OB/GYNs Combined	63.0%	38.4%	38.3%	24.6%
PCPs	48.0%	53.7%	27.9%	35.4%
OB/GYNs	77.7%	23.5%	48.5%	13.9%

DISCUSSION

In a previous study of physicians' opinions and views regarding the WHI trial many reported confusion and fear among both healthcare providers and patients regarding the use of HT[9]. The results of our qualitative and quantitative surveys are in line with previously conducted surveys and general views regarding the use of HT among postmenopausal women. It is clear, alternative treatments to HT are urgently needed.

To date there are no approved alternative treatments to HT for the treatment of women with VMS. Menerba is a novel, estrogen receptor beta agonist drug in development for the treatment of postmenopausal VMS. From the qualitative and quantitative surveys, it is clear that physicians are enthusiastic to prescribe Menerba to their patient population as a safe alternative therapy to reduce VMS.

In both the qualitative and quantitative surveys, a range between a third and upwards to almost half of the patients seen by physicians for their VMS had already used at least one form of an over-the-counter medication prior to their first office visit. Results from the quantitative survey show typical prescribing pattern differences between PCPs and OB/GYNs. Namely, OB/GYNs are more likely than PCPs to prescribe HT for first-line treatment of VMS (77.7% vs. 48.0%), whereas PCPs are more likely than OB/GYNs to prescribe SSRI/SNRIs or other prescription therapies for first-line treatment of VMS (61.6% vs. 26.2%).

In the qualitative survey, the most commonly reported barrier to treatment for VMS for patients was the risk of breast cancer associated with HT use, cited by 74% of the physicians. The second most common concern for patients was the risk of cardiovascular disease associated with HT, cited by 48% of the physicians. These responses indicate that the results of the WHI study have influenced patient perspectives on the safety of HT. In the quantitative study, physicians from both groups report that the primary unmet medical need for the treatment of VMS is for a safer alternative to HT with fewer side effects that does not sacrifice efficacy. These physicians estimate that 56% (PCPs) to 67% (OB/GYNs) of their VMS patients express concerns about using HT for the treatment of VMS.

The physicians in the qualitative study state that, if available, Menerba would be used as a first-line therapy by 78% of physicians for the treatment of VMS. In addition, 92% of the physicians stated they would prescribe Menerba prior to prescribing either an SSRI or SNRI. If Menerba were approved, the percentage of future use for HT or SSRI/SNRI is significantly reduced with p-value < 1e-4 based on the permutation test of 10,000 random permutations.

CONCLUSION

The results of the WHI studies unveiled serious health risks associated with HT that resulted in a precipitous drop in the number of prescriptions written by physicians for HT. Despite the decline in use of HT for VMS, no new therapies have been approved by the FDA for this indication resulting in a large unmet need for the 40 million women transitioning through menopause in the United States. In the aftermath of the WHI trials, an area of interest lies in physicians' opinions regarding their current treatment practices for menopausal VMS and their receptivity toward a novel, estrogen receptor beta agonist drug, Menerba, for the treatment of this important quality of life issue.

Physicians and their patients have concerns about the safety and tolerability of the currently available FDA approved treatments for VMS, specifically breast cancer risk and cardiovascular disease associated with HT use. Based upon phase 2 clinical trial results of Menerba evaluated for postmenopausal VMS, physicians would prescribe this novel, estrogen receptor beta agonist as first-line treatment for VMS if approved as a new drug.

Appendix 1: Product Profile of Menerba (Called Product X in the Survey)

Product X represents a new class of selective estrogen receptor modulator (SERM) for the treatment of VMS of menopause, or "hot flashes." It selectively modulates the estrogen receptor beta (ERβ) to provide a safe and effective alternative to existing therapies.

It is administered orally as a flavored powder packaged in a sachet.

In preclinical studies, Product X inhibits breast and uterine cancer tumor formation and it inhibits bone resorption through the release of osteoprotegrin. In a phase 2 trial of 217 postmenopausal women, Product X (50 mg of ER beta compounds) was statistically superior to placebo (p-value = 0.05) at 12 weeks in the reduction of all hot flashes and had a 62% reduction of the moderate to severe hot flashes. It was also observed that Product X 50 mg was 2.3 times more likely to result in 50% or more reduction in all hot flashes when compared to placebo (p-value= 0.03).

The only side effect associated with treatment was an increase in loose stools (3% in the placebo group vs 12% in the Product X groups). Product X did not increase vaginal bleeding, breast tenderness, estradiol levels, blood pressure and there were no cases of endometrial hyperplasia, a hallmark of uterine cancer risk. In addition, treatment with Product X 50 mg/day led to a statistically significant decrease in both weight loss and BMI.

At the conclusion of the study, compliance with treatment was 91% and the drop-out rate was 2%.

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