Assessment of the tolerance and effectiveness of a food supplement Sérélys® (Femal®) for menopausal women

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Following the publication of the WHI study, a large number of women have stopped their hormone replacement treatment or have not started the latter and are suffering from hot flushes and night sweats amongst other things. In this context we have studied the effectiveness and tolerance of a new natural product amongst menopausal women: Sérélys® (Femal®).

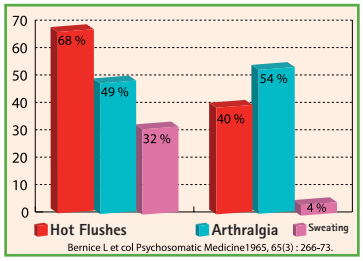

Figure 1: Hot flushes, sweating and arthralgia after the menopause for women of 45-54 and 55-64 years of age.

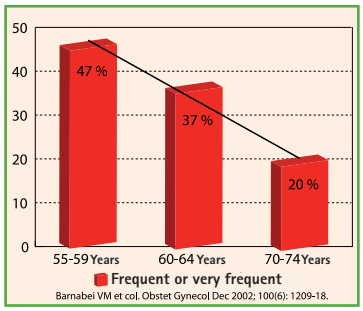

Figure 2: Persistence of hot flushes according to age [n=2763 (HERS). Average = 18 years post menopause. Age = 67 (55-88) 99% = non-hysterectomies]

Hot flushes and night sweats are one of the most common signs of a lack of oestrogen caused by the menopause. The length of these symptoms varies enormously. If they are extremely frequent during the first few years after the menopause (figure 1) they will continue for 20 % of women from 70-74 years of age (figure 2).
HRT (Hormone Replacement Treatment), from the time that it brings a sufficient dosage of oestrogen, makes these heat-related symptoms disappear within 10 to 15 days for the large majority of women concerned.
The WHI study published 6 years ago, because it compared the increase in breast cancer and cardiovascular risks for women using these treatments, nowadays no longer makes people take any notice.
The consequences of the debate: almost half of women who would normally use HRT either preferred not to start it or to stop it of their own accord or on the advice of their doctor.
The consequences of stopping HRT are amongst other things a substantial increase in the number of women complaining of hot flushes and night sweats.
The alternatives to HRT are represented by the beta-alanine (Abufène®), considered by many people as not very effective, the veralipride (Agréal®), withdrawn from the market, and the soya isoflavones, which were severely discredited in the joint report by the AFFSAPS and the AFFSA drawn up in 2005 by patients and doctors.
In this context we have studied the effectiveness/tolerance of a new natural product amongst menopausal women: Sérélys® (Femal®) whose active agent is composed of pollen cytoplasmic extracts making it of interest. This product has already been used in Europe since 1999. It has been the subject of several studies, two of which were a double blind against placebo, which showed it was of interest in the treatment of hot flushes and night sweats associated with the menopause.
Here we report on a trial in which 102 French doctors participated (91 % gynaecologists) having included 417 women.

Method

• Population
417 menopausal women participated in the trial.

Inclusion criteria
The women included:
- were informed of the trial methods;
- are menopausal (regardless of age and symptoms of the menopause);
- have a range of symptoms which are related to the menopause: hot flushes, night sweats, sleep disorders, mood swings…

Exclusion criteria
- hot flushes and/or night sweats not associated with the menopause;
- known allergy to one of the product ingredients;
- taking medication which might interfere with the trial;
- pregnancy and breast feeding.

• Product
The treatment consists of taking 2 tablets of Sérélys® orally per day for 84 days.
Sérélys® contains 3 active agents: vitamin E (antioxidant ingredient), purified pollen extract (GC Fem) and a mixture of cytoplasmic pollen and pistil extracts (PI 82), ingredients which are full of antioxidant enzymes (similar to the superoxide dismutase) and natural non-steroid anti-inflammatories.
The pollen and pistil are grown from selected species (Poaceae, grasses) and harvested separately according to a standardised procedure. The cultivation and harvest are carried out in

fields divided up by the type of plant in accordance with the recommendations of the "European Medicine Agency".
The procedure of cytoplasmic extraction is undertaken in accordance with the Good Practices of Manufacture making it possible to extract the active part of the grain of pollen (the cytoplasm) from its rigid watertight husk. A filtration stage makes it possible to reject the pollen husks, thus eliminating the part, which might be potentially allergenic. A final check by HPLC and GC makes it possible to verify the conformity of concentration of the active agents. Bacteriological and fungal checks are also carried out.
Thanks to a standardised procedure for mixing the extracts, each tablet therefore contains 40 mg of GC Fem and 120 mg of PI 82 as well as 5 mg of vitamin E. The method described above makes it possible to exclude potential allergens ensuring full safety of use (no contraindication for patients who are allergic to pollen) and a constant concentration of the active agents in each tablet.

• Method
This is an open multi-centre study of 12 weeks, whose aim is to assess the effectiveness and tolerance of Sérélys®.
The women taking part in the trial have two consultations: C1 (on J0) and C2 (on J84) at the end of the assessment.
102 investigating doctors (the large majority of whom are self-employed gynaecologists) involved 417 volunteers in this way. During each consultation, the visual analogical scales (VAS) and a questionnaire concerning specific factors of the menopause were completed and then analysed.
During the first consultation (C1 on J0), the methodology and the aims of the trial were explained to the women included in the trial (as well as questioning and a clinical examination). Medical and surgical history and current treatments were also listed. The questionnaire and the VAS established for this purpose were completed by each person in order to characterise and rate each specific factor : hot flushes, sweats, irritability, fatigue, sleep, quality of life…
Lastly, it is recommended to the women to take 2 tablets of Sérélys® per day orally until the end of the trial.
During the second consultation (C2 on J84), twelve weeks later, further questioning combined with a clinical examination are again carried out to look for any possible undesirable results. The same factors as those determined during the first consultation are analysed then rated (with the aid of the questionnaire and the VAS). Any comments by patients are noted in an additional questionnaire. In the same way, the comments by the investigating practitioners are also taken into account and noted in an additional questionnaire.

• Evaluation criteria

Effectiveness
The effectiveness is assessed by using a questionnaire and visual analogical scales (VAS) for the following factors : hot flushes and sweats (frequency, intensity, timing of occurrence, discomfort caused…) ; irritability; fatigue; sleep; quality of life.
The questionnaires are processed descriptively. The data resulting from the appraisal of the volunteers by VAS was subjected to statistical analysis.
The VAS scales (see figure below) make it possible to assess the various symptomatic factors of the menopause.
The analogical scales are lines of 100 mm in length on which the woman must make a mark (vertical line) depending on the seriousness of the discomfort experienced. If marked at the extreme left of the line, the vertical line means that the discomfort is considered non-existent. If marked at the extreme right, the line means that the discomfort is considered to be at a maximum. The distance separating the extreme left of the line and the mark is associated with the intensity of the discomfort. It is therefore possible to carry out a statistical analysis of the women's judgement of the form of discomfort under consideration, quantify its development during the trial and verify whether any variation is statistically significant.
For each of these data, there are comparisons of averages observed with the same subjects (paired series).
The test carried out is therefore a bilateral parametric test (test of t by Student) if the distribution of the differences follows the normal rule (verified by a test W by Shapiro Wilk) or a non-parametric test (Wilcoxon test) in the event of any doubt on this condition. The risk of 1st type α is fixed at 0.05. The software used is the following: Software SAS, version 9.1. (SAS Institute Inc. Cary, North Carolina, USA).

Tolerance
The tolerance is assessed by using a rating scale of 4 levels used by the investigating doctor in accordance with the complaints reported by the volunteers and in accordance with the data resulting from the clinical examination. The 4 rating levels are as follows.
1 = Excellent tolerance: Absence of any undesirable functional or clinical effect.
2 = Good: functional or clinical symptoms particularly mild and brief, felt or noticed at the start of the trial, then disappeared never to reappear.
3 = Average: undesirable effect showing only moderate and fleeting functional symptoms or objectively minor symptoms, felt or noticed several times during the trial.
4 = Poor: undesirable effect showing objectively clear symptoms or operational symptoms, which were not moderated in their intensity and/or fleeting in their duration.

Intensity of hot flushes

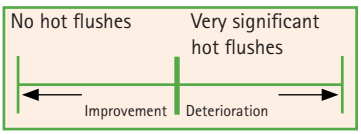

Table 1: Features of the sample

Average age (years)	54,4
Average weight (kg)	63,1
Height (cm)	162,4
BMI (kg/m2)	23,9

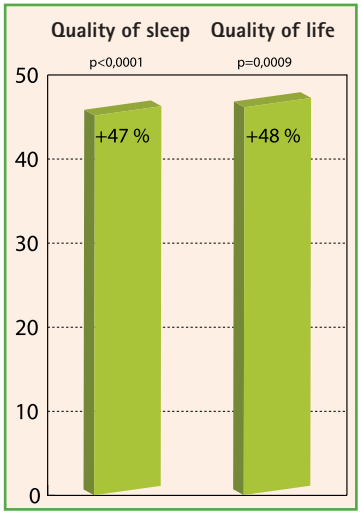

Figure 4: Improvement in the quality of sleep and quality of life on J84

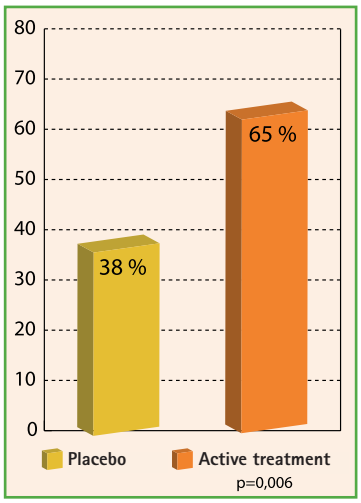

Figure 5. Hot flushes, % of respondents in the active treatment and placebo groups. Two thirds of patients respond to the active treatment.

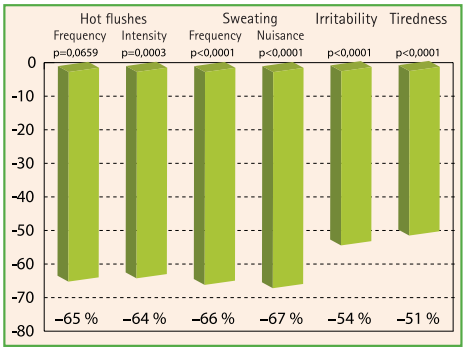

Figure 3: Reduction in symptoms on J84

Results

The assessment of the effectiveness takes account of 373 volunteers, with 44 files having been removed from the analysis owing to a lack of a date for consultations or not complying with the criteria of exclusion concerning medication authorised during the trial.
Only the visual analogical scales (VAS) completed during the 2 consultations were taken into account.
Table I covers the data concerning the averages for age, weight, height and body mass index. The age is an average of 54.4 years. Only one patient is 37 years old and all the others are over 40 years of age.

• Effectiveness

The visual analogical scales (VAS)

All the parameters studied and in particular the hot flushes and night sweats improved significantly between the first consultation (C1) and the second (C2) 84 days later. Figure 3 regroups the results of the effectiveness measured with the help of analogical scales.
The quality of sleep and the quality of life of the volunteers included in the trial also improved significantly as is shown in figure 4.

Special case of hot flushes (table II)

For inclusion (C1 :
- only 3.4 % of volunteers do not have any hot flushes;
- 28.6 % have one or two hot flushes per day;
- 68 % have hot flushes frequently, between 3 and 6 times per day or more.

At the end of the trial (C2):
- 85.6 % no longer experience hot flushes or only 1 to 2 times per day;
- 14.3 % have hot flushes frequently, between 3 and 6 times per day or more than 6 times per day.

After analysing the questionnaires (table III), it can be noted:
- an improvement in hot flushes: their frequency and intensity declined considerably, the discomfort they cause is clearly reduced;
- an improvement in episodes of sweating: their frequency declined, the discomfort is reduced;
- a clear improvement in irritability and feeling tired;
- a marked improvement in the quality of sleep (sleep much more “refreshing”);
- an improvement in the quality of life.

Overall assessment of the women (table IV)

- 93 % of the women thought the product was « very effective » or « quite effective » in improving discomfort associated with the period of the menopause;
- 97 % thought the acceptability of the product was « very good » or « quite good »;
- 93 % thought the product was « very effective » or « quite effective » in improving the quality of life associated with the symptoms experienced during the menopause;
- 77.5 % would « definitely » be happy to continue the treatment, 19 % would be happy to continue it « at a pinch » and 2.5 % would not be happy to do so at all.

Overall assessment of the prescribing doctors

- 93.5 % of the doctors thought the product was « very effective » or « quite effective » in improving discomfort associated with the period of the menopause;
- 97 % of doctors intend to regularly prescribe or advise Sérélys® in this context.

• Tolerance

Tolerance is rated by the investigating doctor depending on the side effects reported by the women in the sample and the data resulting from the clinical examination. Tolerance was not assessed for one patient who had an operation for breast cancer one month after inclusion, although in this case, attribute ability to the treatment studied has of course been ruled out.

Tolerance amongst the 416 women in the sample:
- excellent for 98.32 %;
- good for none of them;
- average for 0.96 % of them: irritability and over-activity (attribute ability not shown), stomach problems ended when another woman stopped taking the tablet (attribute ability not shown), itching (not documented) and glaucoma (attribute ability ruled out);
- poor for 0.72 % of them: migraine, digestive problems not mentioned, rhinitus of an « allergic » type (symptoms having disappeared when the treatment stopped for each of these volunteers).

Discussion

Practitioners, gynaecologists in particular, are faced with a growing demand for strategies able to relieve hot flushes and menopausal sweats.
Winther et al had already shown the effectiveness of Sérélys® for menopausal women in

particular concerning the frequency and intensity of hot flushes.
In this study, which was random double blind against placebo, there is a difference of 20 to 30 % between the placebo group and the group undergoing treatment (figure 5). The results of this study confirm those already observed previously. Taking account of the large number of investigating doctors and patients included, the results observed seem to be a fair reflection of the benefits obtained from taking this product on a daily basis. The blood dosages of FSH, oestrogen, testosterone and SHBG taken during previous studies did not show any change in their concentrations for patients under Sérélys®. The test on the mouse Wistar is negative. The search for phyto-oestrogens in the active agents of the product is also negative. A hormonal type action is therefore ruled out.
It seems to be of interest to carry out complementary investigations with the aim of discovering the action mechanism. The field of anti free radicals still needs to be explored in relation to the powerful anti-oxidant force of Sérélys®.
The observations carried out in current practice lead to reinforcing the importance of observing the treatment, some women indicated an improvement during the first 15 days, others much later (up to one and a half months). Moreover, it seems that the effectiveness of the product continues to progress during the first 6 months of use.

Conclusion

On the basis of this study and previous ones, the cytoplasmic pollen extract (Sérélys®) offers significant effectiveness on the most frequent problems related to over-heating: hot flushes and sweats in particular, bringing about a significant improvement in the quality of life of patients.
These good results are directly linked to sticking to the treatment: two months minimum at the rate of 2 tablets per day (to be repeated).
Good tolerance of the product, the absence of phyto-oestrogens in its composition and its non-hormonal action mechanism enable it to be safely suggested to women who suffer from hot flushes and menopausal sweats.

Table II

		C 1	C 2
HOT FLUSHES – FREQUENCY *Are your hot flushes frequent?*	0 = No hot flushes	3,4 %	25,9 %
	1 = 1 or 2 times per day	28,6 %	59,7 %
	2 = 3 to 6 times per day	45,6 %	13,5 %
	3 = More than 6 times per day	22,4 %	0,9 %

Table III

		C 1	C 2
HOT FLUSHES – Frequency	0 to 2 times per day	32 %	85,6 %
	3 to 6 times per day (and more)	68 %	14,4 %
HOT FLUSHES – Intensity	Insignificant or minor	27,3 %	85 %
	Significant to very significant	72,7 %	15 %
HOT FLUSHES – Occurrence	No hot flushes	3,5 %	24,7 %
	Only during the day	18,9 %	34,1 %
	Only during the night	16,4 %	19,5 %
	During the day AND night	61,2 %	21,7 %
HOT FLUSHES – Nuisance	Not annoying or only slightly	17,8 %	83,1 %
	Fairly to very annoying	82,2 %	16,9 %
SWEATING – Frequency	0 to 2 times per day	53,9 %	91,5 %
	3 to 6 times per day (and more)	46,1 %	8,5 %
SWEATING – Nuisance caused	Not annoying or only slightly	34,3 %	87,4 %
	Fairly to very annoying	65,7 %	12,6 %
SWEATING – Occurrence	No sweating	18,3 %	44,1 %
	Only during the day	9,8 %	14,8 %
	Only during the night	32,8 %	26 %
	During the day AND night	39,1 %	15,1 %
IRRITABILITY	None to very little	52 %	85,8 %
	Average to substantial	48 %	14,2 %
FATIGUE	None to very little	44,3 %	77,8 %
	Average to substantial	55,7 %	22,2 %
REFRESHING SLEEP	Very refreshing to quite refreshing	39,1 %	82 %
	Not very refreshing to not at all	60,9 %	18 %
QUALITY OF LIFE	Very good to good	23,5 %	79,3 %
	Average to poor	76,5 %	20,7 %

Table IV

				Nombre	%
How do you assess the effectiveness of this product on improving the problems associated with the menopause? *3 volunteers did not express an opinion on this item.*	1	=	Very effective	85	23 %
	2	=	Quite effective	263	70 %
	3	=	Not very effective	19	5 %
	4	=	Completely ineffective	3	1 %
How do you assess the acceptability of this product (in terms of constraints in taking it, any taste of the tablets etc.) *3 volunteers did not express an opinion on this item.*	1	=	Very good	239	64 %
	2	=	Quite good	123	33 %
	3	=	Average	8	2 %
	4	=	Poor	-	-
Effectiveness of the product on the quality of life, chiefly linked to the symptoms which you experience (hot flushes, sweating, sleep.....) *4 volunteers did not express an opinion on this item.*	1	=	Very effective	104	28 %
	2	=	Quite effective	241	65 %
	3	=	Not very effective	21	5 %
	4	=	Completely ineffective	3	1 %
Would you be happy to use this product on a regular basis? *3 volunteers did not express an opinion on this item.*	1	=	Yes definitely	289	77,5 %
	2	=	Yes at a pinch	71	19 %
	3	=	No, not at all	10	2,5 %

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Acknowledgements

The authors would like to thank the 102 investigating doctors who participated in this study on the effectiveness and tolerance of Sérélys®.