

Safety of the Synthetic Retinoid Fenretinide: Long-Term Results From a Controlled Clinical Trial for the Prevention of Contralateral Breast Cancer

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Purpose: To describe the pattern of occurrence of adverse events commonly arising during treatment with fenretinide, a synthetic retinoid under investigation for cancer prevention.

Patients and Methods: The series includes 2,867 women accrued in a trial aimed at assessing the effect of fenretinide on the prevention of second breast malignancy. Women were randomly assigned to receive no treatment (1,435 patients) or 5-year fenretinide treatment (1,432 patients). In terms of disease recurrence in the breast, the trial showed a possible beneficial effect of the compound in premenopausal women, and an opposite trend in postmenopausal women. End points considered for safety assessment were the occurrence of diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, disorders of the ocular surface, and abnormal laboratory values.

Results: The most common adverse events were diminished dark adaptation (cumulative incidence,

19.0%) and dermatologic disorders (18.6%). Less common events were gastrointestinal symptoms (13.0%) and disorders of the ocular surface (10.9%). In comparison, incidence figures in the control arm were 2.9% for diminished dark adaptation, 2.9% for dermatologic disorders, 5.4% for gastrointestinal symptoms, and 3.2% for disorders of the ocular surface. Symptoms occurring during fenretinide treatment tended to recover with time. No between-group difference was observed for the occurrence of laboratory data abnormalities. Overall, 63 (4.4%) treatment discontinuations were caused by adverse events.

Conclusion: Given the number of patients involved in the study and the prolonged intake of the drug, the experience on fenretinide tolerability can be considered sufficiently reassuring to justify further testing of the retinoid.

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RETINOIDS, THE natural and synthetic analogs of vitamin A, have demonstrated antitumor effects in preclinical models^{1,2} and are being evaluated in clinical trials of cancer prevention.³ However, the use of these molecules as preventive agents is limited by their toxicity. *N*-(4-hydroxyphenyl)retinamide (fenretinide or 4-HPR), a synthetic derivative of all-*trans* retinoic acid, showed low toxicity compared with other retinoids^{4,5} and high activity in inhibiting mammary carcinogenesis in animal models.⁶ For these properties, fenretinide was selected for a breast cancer prevention trial. The final results of this study have recently been published.⁷ The trial investigated the effect of fenretinide on the prevention of second breast malignancy in women with early breast cancer. The results obtained showed a possible beneficial effect of the compound in

premenopausal women, and an opposite trend in postmenopausal women. Fenretinide was well tolerated, considering that treatment discontinuation owing to adverse events was uncommon (4.4%) and the occurrence of laboratory abnormalities was not different between the experimental and the no-treatment control arm. However, adverse events such as diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, and disorders of the ocular surface were not uncommonly reported during fenretinide treatment. The purpose of the present paper is to describe the pattern of occurrence of these events as well as of laboratory abnormalities with time, and to assess whether menopausal status had an influence on these events.

PATIENTS AND METHODS

A detailed description of the study protocol has been published elsewhere.⁸ Briefly, women with stage I breast cancer or ductal carcinoma-in-situ were enrolled from 10 Italian Institutions, coordinated by the Istituto Nazionale Tumori of Milan. Admitted were women aged 30-70 years, treated with ablative or conservative (plus radiotherapy) surgery, who had received no adjuvant chemotherapy or hormone therapy, and without evidence of local relapse or distant metastases before study entry. Additionally, to be eligible the patients should have normal liver and metabolic function tests and normal WBC, RBC, and platelet counts.

Menopause at the time of study entry was defined as the absence of menstruation for at least 1 year. Hysterectomized patients without

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bilateral salpingo-oophorectomy were considered premenopausal if they were younger than 51 years.

Women were randomly assigned to receive no treatment or fenretinide (R.W. Johnson Pharmaceutical Research Institute, Springhouse, PA), 200 mg PO daily for 5 years (two capsules, 100 mg each, at dinner). A placebo control was not incorporated into the study design because of the long duration of intervention, the large size of the capsule, and the objective nature of the main end point. Moreover, all women were observed by use of the same procedures throughout the study period, and the radiologists who examined the mammograms were blinded to the allocated treatment arm. Because fenretinide administration is associated with a decrease in plasma retinol levels,⁹ a 3-day drug holiday at the end of each month was adopted to minimize diminished adaptation to darkness. Patient compliance to treatment was evaluated by counting the unused capsules.

Treated and untreated women had the same clinical and laboratory follow-up. Follow-up assessments included physical examination and blood chemistry determinations every 6 months; mammography, chest x-ray, and liver ultrasonography every year; and bone scan at 18, 36, and 60 months after randomization (or when required by the occurrence of clinical symptoms).

The occurrence of adverse events was assessed by questioning the patient. Adverse events were defined as subjective complaints or abnormalities at physical examination or any disease not related to tumor recurrence. Their severity was graded using the World Health Organization toxicity criteria, with slight modifications.⁸

A specific questionnaire was adopted for visual disturbances⁸ and was submitted to the patients of both groups. The three items of the questionnaire focused on dark adaptation, vision in poor luminosity, and recovery after dazzling. The outcome was judged positive if at least two items were positive, doubtful when only one item was positive, and negative otherwise. In case of a positive or doubtful questionnaire, the patient underwent ophthalmologic evaluation, including electroretinogram and, in a subgroup of subjects, dark-adaptometry tests.¹⁰ Approximately one third of such patients did not undergo electroretinogram because of the presence of concomitant diseases (eg, severe myopia, cataract, disorders of the retina such as rupture or diabetic retinopathy) that might themselves contribute to explain the symptoms or produce abnormal electroretinogram findings.

When compared with dark adaptometry in a subset of patients,¹¹ the sensitivity of subjective perception was 50% and the specificity 78% when including the doubtful questionnaire response in the positive category.

Temporary or permanent dose reduction (100 mg daily) or treatment discontinuation was allowed by the protocol in case of severe adverse events, possibly documented by objective abnormalities of electroretinogram or laboratory values.

Statistical Methods

The pattern of occurrence as a function of time for each of the investigated adverse events (diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, disorders of the ocular surface, laboratory abnormalities) was assessed in terms of incidence, cumulative incidence, and prevalence for each year of follow-up. Incidence reflects the occurrence of symptoms for the first time within a given yearly interval, whereas prevalence reflects the occurrence of symptoms for the first time or as a recurrence or persistence in a given year. Incidence and prevalence estimates tend to overlap if symptoms recover in a short time; otherwise, for long-term adverse events, prevalence figures exceed incidence estimates.

Incidence and cumulative incidence estimates, as well as statistical comparisons between cumulative incidence curves, were obtained with

the life-table method.¹² Prevalence estimates for each year of follow-up were obtained by counting the women who reported the symptoms, for the first time or repeatedly, among those who were still at risk during the same period.

For diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, or disorders of the ocular surface, cumulative incidence was estimated in both study arms, whereas the temporal pattern of occurrence was detailed for the treatment arm but not for the control arm, in consideration of the small number of events in the latter. Because of the lack of a placebo control group, statistical comparison between the two study arms was not deemed appropriate. In contrast, such a comparison was performed for laboratory data given their objective nature.

All the analyses were performed using the SAS software.¹³ Probability values reported are two-sided. Values of *P* less than .05 were considered significant.

RESULTS

The study was started in March 1987, and the recruitment of patients was closed in July 1993. A total of 2,867 assessable women were randomly assigned to the fenretinide arm (1,432 patients) or the control arm (1,435 patients). The two groups were well matched for all host, tumor, and treatment characteristics considered.⁷ As of September 1998, the median follow-up duration was 97 months. Twenty-six (0.9%) patients, nine in the fenretinide group (four during intervention and five after treatment completion) and 17 in the control arm, were lost to follow-up.

Treatment compliance as assessed by pill counting was high (median value, 98%; interquartile range, 95% to 100%). Such a level of compliance was maintained throughout the 5-year intervention period.

Overall Incidence of Adverse Events

Table 1 reports the total occurrence of events such as diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, and disorders of the ocular surface in the two study arms, whereas detailed incidence and prevalence estimates in the fenretinide arm are listed in Table 2.

In terms of 5-year cumulative incidence (Table 2), the most common adverse events among women receiving fenretinide were diminished dark adaptation and dermatologic disorders (19.0% and 18.6%, respectively). As reflected by yearly incidence figures, the rate of occurrence of both types of events tended to decrease with time. Prevalence figures showed a similar trend and were not much higher than incidence estimates, consistent with the tendency of the symptoms to recover. In agreement with such a finding, clinical observation showed that symptoms mostly recovered spontaneously and did not require permanent treatment discontinuation (Table 1) or dose reduction.

Lower 5-year cumulative incidence figures were observed for gastrointestinal symptoms (13.0%) and disorders

Table 1. Total Occurrences of Adverse Events Among the 1,432 Women in Fenretinide Arm and 1,435 in the Control Arm

	Fenretinide Arm			Control Arm	
	No. of Events	%	Treatment Discontinuation	No. of Events	%
Diminished dark adaptation	221	15.4	25	34	2.4
Dermatologic disorders	234	16.3	20	36	2.5
Skin dryness	82			11	
Mucosal dryness	59			6	
Pruritus	44			15	
Urticaria	37			—	
Dermatitis	33			4	
Other	36			9	
Gastrointestinal symptoms	159	11.1	3	66	4.6
Dyspeptic syndrome	87			35	
Nausea	44			11	
Abdominal pain, diarrhea, other	59			33	
Disorders of the ocular surface	119	8.3	—	36	2.5
Ocular dryness	44			18	
Lacrimation	34			14	
Conjunctivitis	34			4	
Other	6			—	

of the ocular surface (10.9%). However, the temporal pattern of occurrence differed for the two types of event. As observed for diminished dark adaptation and dermatologic disorders, the rate of occurrence of gastrointestinal symptoms tended to decrease with time, and prevalence figures overlapped incidence estimates. In contrast, for ocular surface disorders, the rate of occurrence was substantially stable as a function of time, and prevalence estimates showed a slight trend toward an increase. Overall, these adverse events prompted treatment discontinuation in 48 patients.

In the control arm, 5-year cumulative incidence estimates were 2.9% for diminished dark adaptation, 2.9% for dermatologic disorders, 5.4% for gastrointestinal symptoms, and 3.2% for disorders of the ocular surface. Therefore, between-group differences were 16.1% for diminished dark adaptation, 15.7% for dermatologic disorders, 7.6% for gastrointestinal symptoms, and 7.7% for disorders of the ocular surface.

Of the 221 patients in the fenretinide group with a positive or doubtful ophthalmologic questionnaire, 139 (63%) underwent electroretinography: 11 abnormal questionnaires (positive or doubtful) were confirmed by a positive electroretinography; 11 patients with abnormal questionnaire had a doubtful electroretinography result; the other 117 electroretinography results were negative. Therefore, considering electroretinography as the gold standard for detecting nyctalopia, the positive predictive value of the questionnaire was only 8% for definitely abnormal electroretinography.

Three patients of the control group (one with a positive questionnaire and two with negative questionnaire and

visual complaints) underwent electroretinography with negative results.

Table 3 reports total occurrences of laboratory test abnormalities, whereas incidence and prevalence estimates for laboratory test abnormalities are listed in Table 4. For liver function tests, the 5-year cumulative incidence figures were 9.4% in the fenretinide arm and 8.5% in the control arm. The difference was not statistically significant ($P = .5280$). For lipid profile, the 5-year cumulative incidence figures were 9.1% in the fenretinide arm and 9.7% in the control arm. The difference was not statistically significant ($P = .5832$). For hematologic tests, the small number of abnormal events (Table 3) did not allow us to obtain reliable incidence and prevalence estimates.

In 12 patients treatment was discontinued because of laboratory test abnormalities. Such a number, combined with that of the 48 patients who discontinued treatment for visual, dermatologic, or gastrointestinal adverse events and three additional women with allergic reactions, yields a total of 63 (4.4%) discontinuations owing to possibly drug-related adverse events.

Table 2. Incidence and Prevalence Estimates by Year of Follow-Up for Adverse Events in the Fenretinide Arm

	I, (%)	SE	CI, (%)	SE	Prev, (%)	SE
Diminished dark adaptation						
Year 1	6.7	0.68	6.7	0.68	6.7	0.68
Year 2	4.7	0.64	11.1	0.88	6.7	0.75
Year 3	4.2	0.65	14.8	1.02	7.5	0.86
Year 4	2.6	0.56	17.0	1.11	6.0	0.83
Year 5	2.4	0.58	19.0	1.18	5.8	0.88
Dermatologic disorders						
Year 1	11.3	0.86	11.3	0.86	11.3	0.86
Year 2	4.2	0.62	15.1	0.99	6.1	0.73
Year 3	2.5	0.52	17.2	1.06	4.1	0.66
Year 4	1.0	0.36	18.1	1.09	2.0	0.50
Year 5	0.6	0.29	18.6	1.11	1.3	0.43
Gastrointestinal symptoms						
Year 1	7.1	0.70	7.1	0.70	7.1	0.70
Year 2	2.6	0.48	9.5	0.81	3.5	0.55
Year 3	1.6	0.41	11.0	0.88	2.4	0.49
Year 4	1.4	0.40	12.3	0.94	1.6	0.43
Year 5	0.8	0.33	13.0	0.97	0.8	0.32
Disorders of the ocular surface						
Year 1	2.2	0.40	2.2	0.40	2.2	0.40
Year 2	1.9	0.40	4.0	0.55	2.2	0.41
Year 3	3.4	0.57	7.3	0.77	4.1	0.62
Year 4	2.2	0.50	9.3	0.88	4.4	0.70
Year 5	1.7	0.48	10.9	0.97	3.7	0.69

NOTE. Abbreviations: I, yearly incidence; CI, cumulative incidence; Prev, prevalence.

Table 3. Total Occurrences of Abnormal Laboratory Tests

	Fenretinide Arm			Control Arm	
	No. of Events	%	Treatment Discontinuation	No. of Events	%
Abnormal liver function tests (AST, ALT, total bilirubin, alkaline phosphatases)	106	7.4	9 (0.6%)	107	7.4
Mild	59	4.1		49	3.4
Moderate	34*	2.4	4	34	2.4
Severe	13†	0.9	5	24‡	1.7
Abnormal lipid profile (total cholesterol and triglycerides)	101	7.1	3 (0.2%)	119	8.2
Mild	85	5.9		98	6.8
Moderate	11	0.8	1	16	1.1
Severe	5§	0.3	2	5	0.3
Abnormal hematologic tests (hemoglobin, WBC, and platelets)	16	1.1		7	0.5
Mild	2	0.1		4	0.3
Moderate	11	0.7		3	0.2
Severe	3	0.2		—	

*Gilbert's disease in one patient.

†Hepatitis in five patients.

‡Hepatitis in four patients.

§Familial hypertriglyceridemia in two patients, alcoholism in one patient.

||Diabetes in one patient.

Comparison Between Premenopausal and Postmenopausal Women

Cumulative incidence curves of events such as diminished dark adaptation, dermatologic disorders, gastrointestinal symptoms, and disorders of the ocular surface in the

fenretinide arm according to menopausal status are shown in Figs 1-4.

The curves were substantially overlapping and did not statistically differ between premenopausal and postmenopausal women when considering diminished dark adaptation ($P = .4436$) or dermatologic disorders ($P = .8082$). As regards gastrointestinal symptoms (Fig 3), a more favorable trend was observed for premenopausal women. The 5-year cumulative incidence estimates were 11.4% in premenopausal women, compared with 14.4% in postmenopausal women. Although not statistically significant, a low probability value was obtained ($P = .0639$). Similar results were obtained for disorders of the ocular surface. The 5-year cumulative incidence estimates were 9.4% in premenopausal women, compared with 12.2% in postmenopausal women ($P = .1499$).

The cumulative incidence curves of abnormal lipid tests according to menopausal status for the two treatment arms are shown in Fig 5. Lipid profile abnormalities were clearly less frequent in premenopausal women than in postmenopausal patients in both groups. In the treatment arm, 5-year cumulative incidence estimates were 5.2% in premenopausal women and 12.7% in postmenopausal women ($P < .0001$). The values in the control arm were 5.6% in premenopausal women and 13.7% in postmenopausal women ($P < .0001$). In contrast, the curves were overlapping for liver function tests both in the fenretinide arm ($P = .4118$) and the control arm ($P = .9471$).

Table 4. Incidence and Prevalence Estimates by Year of Follow-Up for Abnormal Liver and Metabolic Function Tests

Laboratory Tests	Yearly Incidence				Cumulative Incidence				Prevalence			
	Fenretinide		Control		Fenretinide		Control		Fenretinide		Control	
	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Abnormal liver function tests (any of AST, ALT, total bilirubin, alkaline phosphatases)												
Year 1	3.1	0.47	2.2	0.39	3.1	0.47	2.2	0.39	3.1	0.47	2.2	0.39
Year 2	1.4	0.35	1.8	0.37	4.5	0.58	3.9	0.53	1.7	0.38	2.4	0.43
Year 3	2.2	0.46	2.1	0.43	6.6	0.71	5.9	0.66	2.6	0.50	2.8	0.49
Year 4	1.9	0.46	1.6	0.39	8.4	0.82	7.4	0.75	2.4	0.51	2.3	0.47
Year 5	1.2	0.39	1.2	0.37	9.4	0.89	8.5	0.81	1.7	0.47	2.1	0.48
Abnormal lipid profile (any of total cholesterol and triglycerides)												
Year 1	1.6	0.35	2.6	0.43	1.6	0.35	2.6	0.43	1.6	0.35	2.6	0.43
Year 2	2.5	0.46	2.5	0.44	4.1	0.56	5.0	0.60	3.2	0.52	3.2	0.50
Year 3	2.2	0.46	1.6	0.38	6.2	0.71	6.6	0.69	3.0	0.54	2.5	0.47
Year 4	1.7	0.44	2.0	0.44	7.8	0.81	8.4	0.79	3.1	0.58	2.8	0.52
Year 5	1.4	0.43	1.4	0.39	9.1	0.89	9.7	0.86	2.9	0.60	3.0	0.58

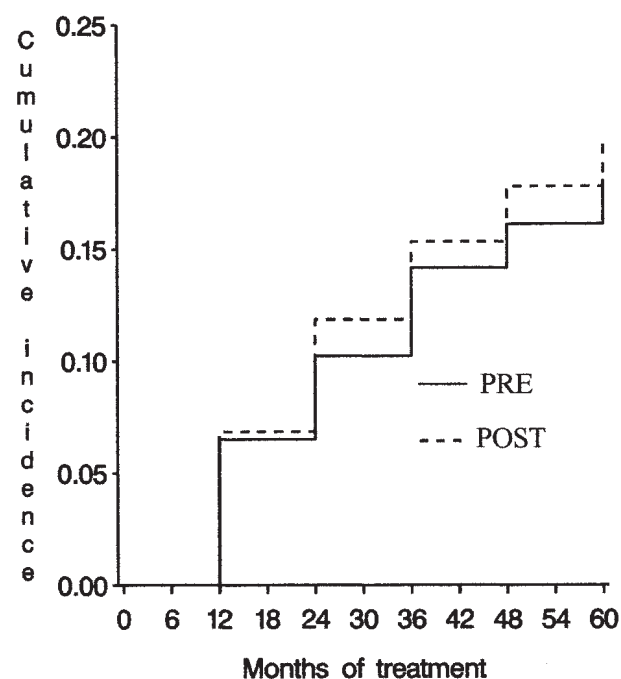


Fig 1. Cumulative incidence of diminished dark adaptation during fenretinide treatment by menopausal status.

DISCUSSION

The aim of the present study was to provide further insight into the safety and long-term tolerability of fenretinide. As recently noted,⁷ adverse events such as diminished dark adaptation and disorders of the ocular surface, dermatologic disorders, and gastrointestinal symptoms were not uncommon during the 5-year treatment period. Also, liver function, lipid profile, and hematologic laboratory tests were considered in the present study as they play a key role for safety assessment and are frequently altered during treatment with other retinoids.¹⁴

The proportion of patients reporting diminished dark adaptation estimated in a 5-year treatment period was close to 20%, compared with approximately 3% in the control group. As regards the temporal pattern of such an event, diminished dark adaptation was more likely to occur at the beginning of treatment, but it may still appear for the first time during the fifth year, and it tends to recover spontaneously even without treatment discontinuation. Diminished dark adaptation was an expected adverse event, inasmuch as fenretinide is known to decrease plasma retinol levels.⁹ A 3-day drug holiday at the end of each month was adopted to minimize, but clearly not eliminate, the occurrence of the symptom. In previous studies, plasma retinol levels were shown to correlate with the occurrence of visual complaints¹⁵ as well as with retinal psycho-

physical impairment, as assessed by dark adaptometry test.¹¹ Retinol level thresholds for the occurrence of mild or moderate functional impairment were shown to be 160 or 100 ng/mL, respectively.¹¹

Other ophthalmologic symptoms were disorders of the ocular surface, mainly represented by ocular dryness and lacrimation. Compared with diminished dark adaptation, disorders of the ocular surface were less frequent during fenretinide treatment, their cumulative incidence at 5 years being approximately 11% (3.2% in the control arm). Furthermore, they had a different temporal pattern of appearance, as their prevalence slightly increased with time. In a previous study, disorders of the ocular surface were unrelated to plasma retinol levels and were favored by older patient age.¹⁵ It was shown also that fenretinide induces a slight loss of goblet cells and metaplasia of epithelial cells of the conjunctiva as measured by conjunctival impression cytology,¹¹ an effect consistent with a lower vitamin A supply at the ocular surface.¹⁶

Dermatologic disorders were mainly subjective, being mostly represented by skin or mucosal dryness and pruritus. Their cumulative incidence amounted to approximately 19% at 5 years in the fenretinide arm and approximately 3% in the control arm. The major incidence of dermatologic adverse events was in the first treatment year (11.3%) and

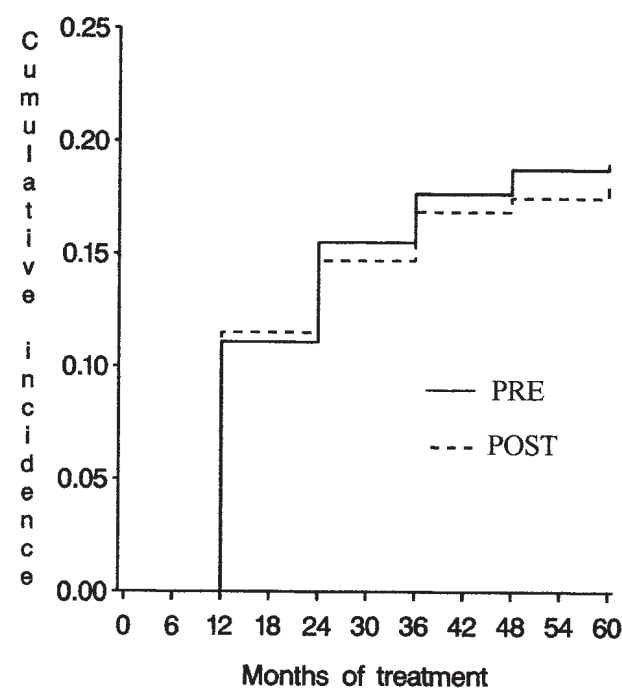


Fig 2. Cumulative incidence of dermatologic disorders during fenretinide treatment by menopausal status.

strongly declined in the fourth (1.0%) and fifth years (0.6%). The mild grade of dermatologic symptoms was demonstrated by the small number of patients who discontinued treatment for such a reason (20 of 234 who experienced this type of complaint). Prevalence figures paralleled incidence estimates as these symptoms had the tendency to recover spontaneously.

Also gastrointestinal symptoms were mainly of subjective nature (dyspeptic syndrome, nausea, abdominal tenderness), rarely prompted treatment discontinuation (only three patients of the 159 who experienced such symptoms), and tended to recover spontaneously. The cumulative incidence rose to 13% at 5 years, the occurrence of gastrointestinal complaints being mostly concentrated in the first year of treatment (7.1%) and gradually decreasing thereafter to low levels in the fourth (1.4%) and fifth years (0.8%). Of note, the incidence of such complaints was fair also in the control group (5.4%).

Tests of liver function, lipid profile, and blood cell counts were not influenced by fenretinide administration. This result is important as hepatic toxicity is a well-known side-effect of other retinoids.¹⁴

As regards the role of menopause, we observed that such a factor did not affect the occurrence of visual and dermatologic disturbances, whereas a more favorable trend was observed for

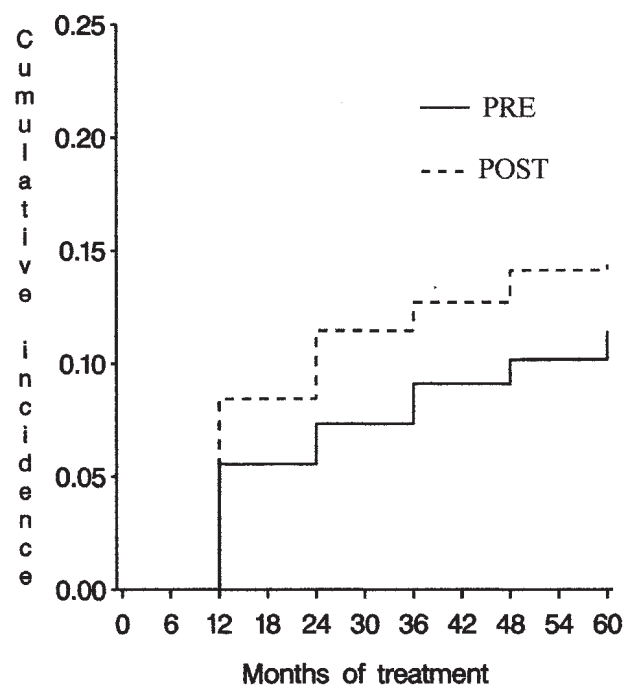


Fig 3. Cumulative incidence of gastrointestinal symptoms during fenretinide treatment by menopausal status.

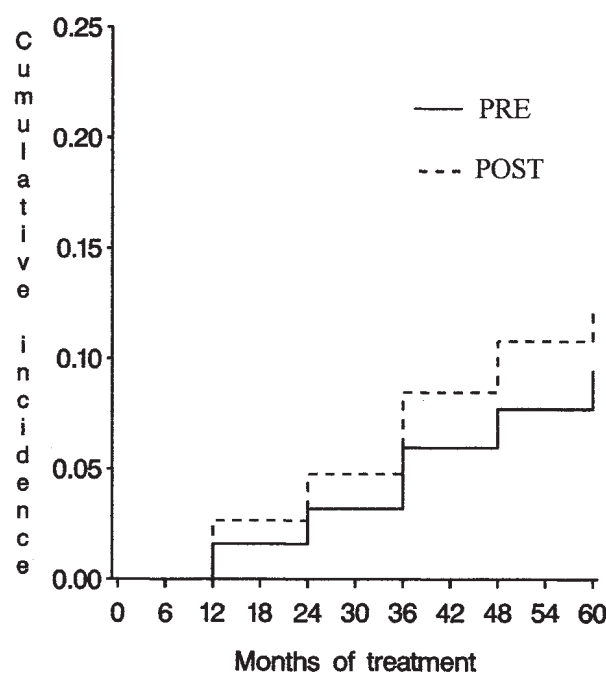


Fig 4. Cumulative incidence of disorders of the ocular surface during fenretinide treatment by menopausal status.

gastrointestinal symptoms and disorders of the ocular surface in premenopausal women. In these patients, the occurrence of symptoms was approximately 3% less frequent than in postmenopausal women. The observed association between ocular surface disorders and menopause is consistent with the already mentioned predisposition of older patients to exhibit the symptom.¹⁵ Likewise, lipid metabolism abnormalities, although not affected by fenretinide treatment, were less frequent in premenopausal women.

We are aware of some limitations of this study. First, the lack of a placebo-controlled group hampered a reliable quantification of subjective adverse events actually related to treatment. In particular, for disturbances in dark adaptation, it is reasonable to believe that the incidence of events actually related to fenretinide administration was lower than that reported. Because patients were informed before study entry about the risk of having visual complaints during treatment, some degree of over-reporting was likely to occur. Furthermore, when compared with electroretinography, the questionnaire was shown to have a low positive predictive value, and its reliability in incidence quantification is therefore questionable. Second, attention was focused on common adverse events. The assessment of rare adverse reactions requires larger numbers of patients than those achieved in this study. Nevertheless, we think that some important conclusions can be drawn.

The final results of the trial⁷ showed an interaction between fenretinide and menopausal status, suggesting a

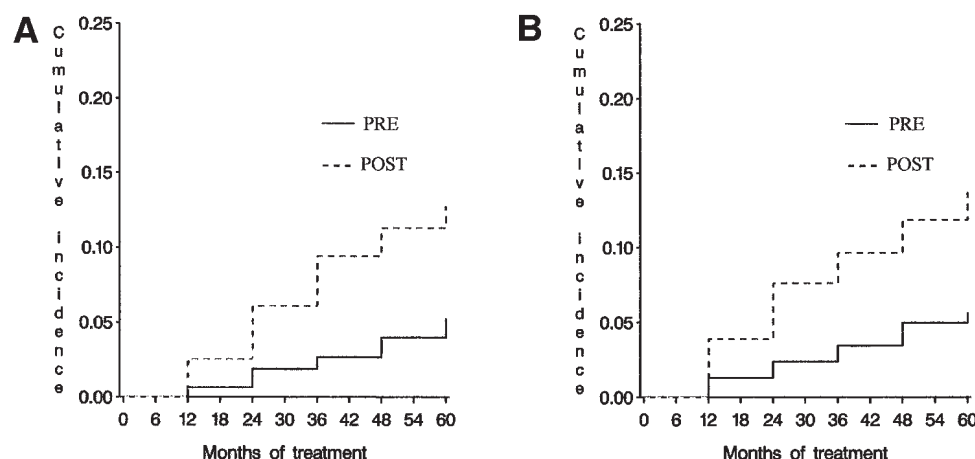


Fig 5. (A) Cumulative incidence of abnormal lipid profile of fenretinide group during treatment by menopausal status. (B) Cumulative incidence of abnormal lipid profile of control group during intervention plan by menopausal status.

possible beneficial effect of the retinoid on second breast cancers in premenopausal women. The efficacy of fenretinide in reducing the risk of first breast cancer in young women at increased risk is thus being investigated in combination with tamoxifen. Given the large number of patients involved in the study and the prolonged intake of the drug, we believe that the experience on fenretinide tolerability can be considered reasonably reassuring. The incidence of typical side effects up to approximately 20% was relatively high and might prevent many women from using fenretinide for breast cancer prevention. However,

clinical symptoms were often of minor importance, tended to recover spontaneously, and required permanent treatment discontinuation in a minority of cases. Fenretinide at 200 mg per day did not affect safety factors or cause side effects typical of other retinoids, such as decreased bone density, ligament calcification, and skeletal hyperostosis,¹⁷ and was shown by laboratory studies to be less teratogenic.⁵ Therefore, from the above findings and considerations, further trials of fenretinide do not seem to be contraindicated by drug safety and tolerability considerations.

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