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Long-term Tolerability of Fenretinide (4-HPR) in Breast Cancer Patients

N. Rotmensz, G. De Palo, F. Formelli, A. Costa, E. Marubini, T. Campa, A. Crippa, G.M. Danesini, M. Delle Grottaglie, M.G. Di Mauro, A. Filiberti, M. Gallazzi, A. Guzzon, A. Magni, W. Malone, L. Mariani, M. Palvarini, M. Perloff, M. Pizzichetta and U. Veronesi

A group of 53 patients initially participating in a phase I trial with the synthetic retinoid fenretinide was assessed for the long-term tolerability of this compound. The patients were evaluated after 42 months of drug intake at a dose of 200 mg/day, including a 3-day drug interruption at the end of each month, by the following examinations: a dermatological visit; an ophthalmological evaluation including an ophthalmological questionnaire and an electroretinogram (ERG); a study on blood chemistry and plasma retinol levels; a study on bone densities and on skeletal X-rays; and finally a psychological evaluation including various tests for anxiety, depression and overall mood. The results show that prolonged administration of fenretinide is well tolerated. No acute nor severe toxicity was observed and thus this compound can be considered a good candidate for chemoprevention trials in a variety of patient populations.
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INTRODUCTION

CLINICAL RESEARCH on retinoids, the analogues of vitamin A, has been very limited in oncology as compared to the numerous experimental investigations into these substances. Both vitamin A and retinoids have demonstrated activity in modulating cellular growth and maturation [1]. They have consequently been tested as both preventive and therapeutic agents in human malignancy. However, most retinoids are stored in the liver, having the potential to cause hepatotoxicity, thus limiting their use.

The need to test an effective and safe retinoid has led to the study of fenretinide (N-(4-hydroxyphenyl)retinamide, 4-HPR), a synthetic retinoid demonstrated to be efficacious and relatively non-toxic in preclinical experiments. It has the property of reducing the incidence of carcinogen-induced mammary cancers in rats [2], and of accumulating in the mammary gland.

The aforementioned characteristics of fenretinide led to the idea in one of US—U Veronesi—of using this compound for the prevention of contralateral breast tumours. Although preclinical studies showed that adverse reactions to fenretinide are less frequent than those reported for other retinoids [3], and that, unlike natural compounds, i.e. retinol and retinyl esters, fenretinide does not accumulate in the liver [4], a preliminary clinical study at the dose of 800 mg/day showed abnormal retinal function. This side-effect reversed rapidly upon drug cessation and was presumably related to the high dose administered [5]. As there was no adequate phase I study, a trial was started in January 1986 at the Istituto Nazionale Tumori of Milan, with the aim of comparing different doses of fenretinide administration vs. a placebo arm [6]. The sample consisted of 101 patients initially randomised into four groups: fenretinide at the dose of 100 mg/day (25 patients), 200 mg/day (26), 300 mg/day (25) or placebo (25). After 6 months of intervention, the data showed no significant alteration in blood chemistries or any major dermatological side-effects. There was minimal hepatic toxicity (1 case of mild increase of transaminases). Nevertheless, 1 case of impaired dark adaptation, confirmed by an electroretinogram (ERG), occurred at 24 weeks of intervention in a patient taking a daily dosage of 300 mg. The symptoms disappeared 9 days after drug interruption, again confirmed by an ERG (in addition, this patient had glaucoma). After the first 6 months of intervention, all subjects continued fenretinide at a dosage of 200 mg/day, with a 3-day drug interruption at the end of each month. This monthly break was based upon observations that both in rats [7] and in humans [8], fenretinide lowers plasma retinol levels; since vitamin A deficiency is associated with impaired dark adaptation, this pause should allow for a recovery of plasma retinol levels. Between the 6th and the 12th month of intervention, no further toxicities were observed [6].

As the chemoprevention population under investigation is without evidence of malignant disease, the first question to be answered concerns the definition of a non-toxic dose. The

Correspondence to N. Rotmensz.
N. Rotmensz, G. De Palo, F. Formelli, A. Costa, T. Campa, G.M. Danesini, M.G. Di Mauro, A. Filiberti, A. Guzzon, A. Magni, L. Mariani, M. Pizzichetta and U. Veronesi are at the Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan; E. Marubini is at the Institute of Medical Statistics and Biometry; A. Crippa and M. Delle Grottaglie are at the Neurological Institute "C. Besta"; M. Gallazzi is at the Orthopedic Institute "Gaetano Pini", Milan, Italy; W. Malone and M. Perloff are at the National Cancer Institute, Bethesda, Maryland, U.S.A.; and M. Palvarini is at the Department of Dermatology, University of Milan, Milan, Italy.
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second deals with the evaluation of tolerability after prolonged administration of the compound.

In March 1987, a large-scale randomised phase III trial was started at the Istituto Nazionale Tumori of Milan, with the goal of administering fenretinide for the prevention of contralateral breast carcinoma [9]. As the schedule planned a 5-year fenretinide administration at 200 mg/day—including a 3-day drug interruption at the end of each month—versus a control group, it was decided to administer the drug at the same dosage (200 mg/day) to the patients from the phase I trial. Since this sample had a longer exposure to the compound, it may have helped evaluate tolerability after prolonged administration.

DRUGS, PATIENTS AND METHODS

Fenretinide, administered in capsules of 100 mg was supplied by McNeil Pharmaceuticals (Spring House, Pennsylvania, USA).

A group of 53 patients, who were already participating in the phase I trial of fenretinide [6] was assessed for this long-term tolerability study and was evaluated during and after 42 months of drug intake (Table 1). These patients were followed every 4 months with clinical examination, laboratory determinations and ophthalmological evaluation as reported previously [6]. Long-term tolerability was assessed through dermatological examination, ophthalmological evaluation and blood chemistry. Skeleton X-ray and bone mineral densities were performed, since the reported side-effects of retinoids include ligament calcification [10], skeletal hyperostosis [11] and decreased bone mass associated with an increased risk of fractures [12]. Furthermore, as neuropsychiatric changes were reported in a phase I study of retinol in cancer patients [13], a standardised psychological evaluation was conducted.

Dermatological examination

This was performed by a dermatologist and included an interview with the patient and an examination of skin and oral mucosa.

Table 1. Patients according to initial distribution and number of months in the trial

		Months						
Treatment (mg)	*n*	6*	12	18	24	30	36	42
Placebo	25	20[a]	17[b]	13[c]	13	13	13	11[d]
100	25	22[e]	21[f]	19[g]	17[h]	16[f]	16	16
200	26	25[f]	23[h]	18[i]	18	18	17[f]	14[j]
300	25	22[k]	18[l]	15[m]	13[n]	12[f]	12	12
Total cases	101	89	79	65	61	59	58	53

*After the first 6 months, all patients received the same dosage of fenretinide 200 mg/day, including a 3-day drug interruption at the end of each month.

(a) refusal 2, metastases 1, protocol violations 2; (b) metastases 2, intercurrent event 1; (c) refusal 2, metastases 1, intercurrent event 1; (d) other primary 1, liver dysfunction 1; (e) metastases 3; (f) refusal 1; (g) metastases 1, contralateral tumour 1; (h) refusal 2; (i) refusal 3, metastases 1, intercurrent event 1; (j) other primary 1, contralateral tumour 1, pathological ERG 1; (k) refusal 2, pathological ERG 1; (l) metastases 2, local recurrence 1, abnormal ophthalmological questionnaire with normal ERG 1; (m) refusal 2, other primary 1; (n) intercurrent event 1, contralateral tumour 1.

Table 2. Ophthalmological questionnaire

Q.	Do you see less well in the evening than in normal daylight?
Q.	Can you adapt easily when going from the light to dimness? (Driving into a tunnel or going into a cinema, when a film is being shown).
Q.	Have you noted any changes in how you adapt?
Q.	Can you adapt well to darkness? (Getting up to go to the bathroom or looking for the light switch in the cellar).
Q.	Do you have any difficulty when driving at the time of the sunset?
Q.	When you are in dim light can you distinguish the outlines of objects well?
Q.	When you pass from a dimly lit room or place to a strongly lit one, are you dazzled? (Leaving a tunnel or leaving a subway station) If yes, for how long?

If no more than 3 out of 7 questions had a positive answer, the questionnaire was considered "negative"; when 4 questions were answered positively, it was quoted "doubtful"; when more than 4 questions were positive, the questionnaire was considered as definitely "positive".

Ophthalmological evaluation

This included an ophthalmological questionnaire, a clinical examination and an electroretinogram (ERG). The questionnaire was designed by us, based upon symptoms likely to occur with fenretinide administration (Table 2).

The clinical examination included monocular determination of visual acuity, colour vision evaluation, examination of the anterior segment and lens, measurement of the intraocular pression, determination of the visual fields and fundus oculi examination.

The ERG was carried out using an Amplaid MK7 electrodiagnostic computer system. The employed parameters were the standards proposed by the Amplaid MK7 for ERG recording. The selected intensity of the flash was 1.5 joules. A blue filter was applied to the lamp for the rod ERG registration. For the cone ERG recording, a white light stimulus was used. The eyelid silver plate electrodes in Ag/Ag cl (Seagull) were chosen. After 30 min from the mydriatic instillation (tropicamide 1%), the patients were fully adapted to the dark for 15 min. One eye at a time was tested: while the contralateral eye was occluded, the rod ERG was performed with the flash at 20 cm distance from the head of the patients. After a brief adaptation to the light, the patients underwent the cone ERG. The parameters of A and B waves of the cone and rod ERG were measured by a computer system. The latency, amplitude and morphology of the waves were evaluated comparing the results with normal values accepted in the electrophysiology division of the Neurological Institute "C. Besta".

Blood chemistry and plasma retinol levels detection

The common laboratory values [aspartase aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatases, total bilirubin, cholesterol, triglycerides, blood sugar, blood urea nitrogen (BUN), creatinine, haemoglobin, haematocrit, WBC, RBC and platelets] were performed at baseline, every 4 months during follow-up and at 42 months.

Plasma retinol level was measured at the time of the ERG evaluations, in order to assess the association between plasma retinol level reduction by fenretinide and abnormal retinal function [8].

The procedure for plasma retinol detection has been described previously. Briefly, blood samples were collected in heparinised

tubes wrapped in aluminium foil. Plasma was separated by centrifugation and stored at −20°C until analysis for retinol content by high performance liquid chromatography (HPLC) [8]. All the assays were performed in the dark.

Bone mineral densities

These were measured on the lumbar spine (L2-L4) by dual photon absorptiometry with ^{153}Gd source (Norland 2600) and additional measurements at the distal radius by single photon absorptiometry with ^{125}I source (Norland 278) [14, 15].

Skeleton X-rays

Radiographical parameters included costal cartilages, posterior cervical ligaments and iliolumbar ligaments.

Psychological evaluation

The IPAT (Institute for Personality and Ability Testing) anxiety test [16], the IPAT depression test [17] and a self-scoring mood questionnaire [18] were used for this assessment.

The first two tests are questionnaires to be completed by the patients themselves, consisting of 40 items which collect information on anxiety and depression. Patients with scores of 8, 9 and 10 are very likely to develop anxiety and depression. In a "normal" population, a pathological score is generally found in 16% of the cases.

The self-scoring mood questionnaire consists of 15 items in pairs of positive/negative paradoxical adjectives (i.e. calm–very nervous). The score ranges from −45 to +45.

RESULTS

Overall results

Table 1 gives a detailed description of the patients' status, based upon the number of months of participation in the study, with reference to the reasons for leaving the trial.

As toxicities occurring during the first year of exposure to the compound have been reported previously [6], a brief summary of the toxicities in 79 patients between the 13th and the 42nd month is shown in Table 3.

It is worth noting that out of the 20 patients refusing to continue into the trial (Table 1), 11 had no side-effects at all, while mucous dryness (5 patients), pruritus (3 patients), increased triglycerides (3 patients), increased cholesterol (1 patient), headache (1 patient), nausea (1 patient), dyspeptic syndrome (1 patient) and impaired dark adaptation with negative ERG (1 patient) have been noted in the others.

Table 3. Toxicity in 79 patients treated from the 13th to the 42nd month according to the protocol

Mucous dryness	9
Impaired dark adaptation	7*
Increased triglycerides	4
Dyspeptic syndrome	2
Increased transaminases	1†
Muscle pain	1
Headache	1
Dizziness	1
Pruritus	1
Epigastric pain	1

*Confirmed by pathological ERG in 3 cases.
†Already present during the first 6 months but persisting thereafter.

Table 4. Retinol plasma levels in 4 patients with a pathological ERG

Time to occurrence of pathological ERG	Retinol level (ng/ml)	Outcome	Retinol level (ng/ml)
24 wk*	80	Normal ERG at 9 days	240
24 mo	158	Normal ERG at 4 mo	508
40 mo	42	Normal ERG at 4 mo	317
41 mo	80	Doubtful ERG at 9 mo	518

*Patient receiving 300 mg/day during the first 6 months of the study.

Long-term tolerability results

The results reported below are not always related to the whole sample of 53 cases as not all of them accepted to undergo the proposed examinations.

Results of the dermatological examination include observations on 51 patients who underwent a visit at baseline and at 42 months. At the second visit, 41 patients had no symptoms at all. Among the remaining 10 patients, 6 had some degree of alopecia (2 having this finding at baseline), 5 had nail fragmentation, 2 had xerosis, 1 had urticaria and one had pruritus.

The ophthalmological evaluation, including the completion of the ophthalmological questionnaire and an ERG examination, was performed on all 53 participants. Besides the patient reported earlier [6] and described in the introduction, a total of 7 patients reported impaired dark adaptation (a positive ophthalmological questionnaire), but only 3 were confirmed by a pathological ERG. All 3 had low plasma retinol concentrations, considering that the average found in the placebo group was 493 (S.D. 121) ng/ml [8]. The first patient had a pathological ERG after 24 months of treatment with a retinol plasma level of 158 ng/ml (Table 4). Intervention was suspended, the ERG controlled after 4 months returned to normal values; the retinol rose to 508 ng/ml and the patient then restarted the drug. The ERG was normal at 42 months. The second case had a pathological ERG at 40 months with a retinol level of 42 ng/ml. The ERG, repeated after 4 months of treatment interruption, returned to normal with a retinol level of 317 ng/ml, and the patient recommenced the drug. The third case had a pathological ERG at 41 months (retinol level was 80 ng/ml). She stopped treatment as she still had some abnormalities in one eye after 9 months with a retinol value of 518 ng/ml. The incidence rate of pathological ERG, 0.61% at 37–42 months, is reported in Table 5.

Table 5. Incidence rate of pathological ERG

Time (min)	Incidence rate (mo)*	
≤6	1/550	†0.18%
7–12	0/476	
13–18	0/409	
19–24	1/369	0.27%
25–30	0/361	
31–36	0/343	
37–42	2/325	0.61%

*Women-months of exposure.
†Patient receiving 300 mg/day during the first 6 months of the study.

Mild increases in triglycerides were observed in 4 patients, but did not necessitate alterations in drug dose. In 1 patient a mild increase of transaminases was observed. This patient underwent a liver scan which showed an echographic pattern consistent with steatosis. Hepatic markers were positive for hepatitis B; a liver biopsy showed a pattern of diffuse steatosis. No alterations of the common laboratory values nor of the urine analysis, BUN or creatinine were seen.

Bone density evaluation was not carried out at baseline. It was first performed on the lumbar spine of 47 patients (6 patients refused the examination) at 42 months. 35 were found to have normal values, 6 were borderline and another 6 had pathological values. Of these 12 patients, 6 had a single photon absorptiometry on the forearm as it was thought that the amount of fat tissue could have caused difficulties in interpreting the results. 3 out of these 6 patients showed normal values. Among the remaining 9 patients, 5 cases presented additional risk factors, e.g. a long period of time since menopause and low milk consumption [19]. 4 had definitely abnormal values.

The skeleton X-ray evaluation was performed at the baseline visit and 42 months after the start of the trial in 17 patients (all the others underwent a bone scan). No ligament calcification or skeletal hyperostosis were found.

40 patients accepted to undergo the psychological evaluation which was first performed 4–5 months after the start of the trial and then at 36 to 42 months. In our sample, the score of the anxiety test was pathological in 33% of patients at the first assessment and in 43.5% at the second. The depression test was considered pathological in 40% of cases at the first evaluation and in 47.5% of the cases at the second, i.e. there was no appreciable difference between the two evaluations.

A larger difference between the median of the two evaluations was found for the self-scoring mood questionnaire. The median was 15.5 at baseline and 6.5 at 42 months; but here, the overall score was still positive and one explicit hypothesis could be that the patients developed a kind of euphoric mood at the beginning of the preventive treatment. With time, this enthusiasm decreased, without reaching negative values.

DISCUSSION

Limiting factors in the use of any vitamin A analogue are that large pharmacological doses are usually required to reach therapeutical efficacy, and that, in most individuals, high dosages of retinoids produce significant side-effects. With few exceptions, toxicity occurs only after excessive ingestion of vitamin A: in most cases, side-effects are reversible and usually disappear within a few hours or days after drug withdrawal [20]. Toxical signs due to large doses of vitamin A and/or retinoids can be grouped into four categories [21]: (1) central nervous system abnormalities, which include increased cerebrospinal fluid pressure, pseudotumour cerebri, headache, nausea, ataxia and anorexia; (2) liver problems, including hepatomegaly, hepatotoxicity, enhancement of collagen formation in liver, and probably hyperlipaemia; (3) bone abnormalities, including joint pains, long-bone thickening, hypercalcaemia, and calcification of the soft tissues; and (4) skin and other epithelial defects, including excessive dryness, scaling, cheilitis, chapping, desquamation, brittle nails and alopecia.

However, due to the increasing attention paid to possible chemopreventive effects of retinoids, interest has focused on chronic tolerability of these compounds rather than on acute toxicity. Additional issues have to be addressed such as ophthalmological tolerability and teratogenicity [22]. The spectrum of congenital defects induced by synthetic retinoids seems to be identical to that induced by retinoic acid, as does the mechanism of embryopathic action [23]. The following comments may be made based upon our results. Ocular toxicity was represented by impaired dark adaptation which appears to be dose-related since the incidence after a 200 mg daily dose is lower than the incidence reported by other authors after a 800 mg [5] or a 300 mg [24] daily dose. The incidence rates reported in Table 5 suggest an increasing trend in the number of pathological ERGs with the duration of drug intake. However, due to the small sample size, this finding should be considered with extreme caution.

The effect on vision may be attributed to interference by this agent with vitamin A [25]. A reduction in serum retinol levels in patients receiving fenretinide has indeed been reported [8, 26], together with a proportional decrease in retinol binding protein (RBP) [8, 27]. Moreover, this seems to be confirmed by the fact that, after interruption of treatment, retinol levels increased and the toxic ocular symptoms disappeared.

From the dermatological standpoint, the main side-effects of retinoids are mucocutaneous dryness, skin atrophy and skin vulnerability [28]. Abnormal cutaneous photosensitivity has also been reported for some vitamin A synthetic analogues [29] and severe nail distrophy has been described [30]. Fenretinide failed to produce similar side-effects at the reported dosage of 200 mg/day. Although some hair loss, nail fragmentation, pruritus, etc. were present in the list of complaints of our patients, the dermatological tolerability of fenretinide is good, even after more than 3 years of administration.

Retinoid-induced skeletal changes are well known and long-bone effects in humans have been reported both in hypervitaminosis A [31] and as a result of retinoid therapy in terms of bone thinning since 1954. The potential use of retinoids in orthopaedic practice to stimulate bone remodelling has even been suggested [32]. In our experience with fenretinide, we cannot draw conclusions for the 4 cases of abnormality in bone metabolism by densitometric evaluation since neither control nor baseline data are available. We can only say that contrary to the findings for hypervitaminosis A [12], no fractures were observed.

While large increases in triglyceride levels seem to be limited to subjects with pre-existing hypertriglyceridaemia, smaller increases in triglyceride, cholesterol and HDL cholesterol are very common in patients treated with synthetic retinoids [33]. Fenretinide did not seem to cause hyperlipidaemia in our series, but this is definitely an important issue to be clarified because of potential impact upon cardiovascular diseases.

In his review of 652 patients treated with retinoids for dermatological diseases, Cunningham indicated that about one third of them would develop some liver function abnormality [34]. On the other hand, from extensive evaluations of liver function, histology and ultrastructure in a group of patients preselected for potential hepatotoxicity and treated with etretinate, Roenigk found no significant damage to the liver [35].

In our series, one patient had mild liver dysfunction at 42 months of intervention. Other side-effects reported in the literature, such as necrotising vasculitis [36] were not found in our sample of patients. Similarly, no psychological adverse reactions were observed, thus confirming the preliminary observation of our group [37].

In conclusion, no severe acute toxicity or chronic toxicity has developed in our series of 53 patients given 200 mg of fenretinide daily, with a 3-day hiatus each month, for up to 42 months. Although longer term tolerability of this synthetic retinoid needs

to be further evaluated, fenretinide may be considered to be a good candidate for chemopreventive trials in a variety of patient populations.

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