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Long-term Tamoxifen Citrate Use and Potential Ocular Toxicity

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• PURPOSE: To estimate the prevalence of abnormalities in visual function and ocular structures associated with the long-term use of tamoxifen citrate.

• METHODS: A single-masked, cross-sectional study involving multiple community and institutional ophthalmologic departments was conducted with a volunteer sample of 303 women with breast cancer currently taking part in a randomized clinical trial to determine the efficacy of tamoxifen (20 mg/day) in preventing recurrences. Participants included women who had never been on drug (n = 85); women who had taken tamoxifen for an average of 4.8 years, then been off the drug for an average of 2.7 years (n = 140); and women who had been on tamoxifen continuously for an average of 7.8 years (n = 78). Women were evaluated by questionnaire, psychophysical testing, and clinical examination to determine any abnormalities in visual function and the comparative prevalences of corneal, lens, retinal, and optic nerve pathology.

• RESULTS: There were no cases of vision-threatening ocular toxicity among the tamoxifen-treated participants. Compared with nontreated participants, the tamoxifen-treated women had no differences in the activities of daily vision, visual acuity measurements, or other tests of visual function except for color screening. Intraretinal crystals (odds ratio [OR] = 3.58, P = .178) and posterior subcapsular opacities (OR = 4.03, P = .034) were more frequent in the tamoxifen-treated group.

• CONCLUSIONS: Women should have a thorough baseline ophthalmic evaluation within the first year of initiating tamoxifen therapy and receive appropriate follow-up evaluations. (Am J Ophthalmol 1998;125:493–501. © 1998 by Elsevier Science Inc. All rights reserved.)

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TAMOXIFEN CITRATE (TAM) IS A NONCORTICOSTEroidal oral antiestrogen. It is used in the treatment of advanced breast cancer and as an adjuvant therapy after surgical resection. Tamoxifen is structurally similar to drugs, such as chloroquine,

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chlorpromazine, thorazine, and amiodarone, that are known to have ocular side effects. Previous studies have suggested that the use of regular, low-dose tamoxifen (20 to 40 mg/day) may be associated with abnormalities of visual functioning (visual acuity) and ocular structures (refractile crystalline deposits in the retina, macular edema, corneal opacities, lens changes, optic neuritis).[1]

METHODS

THE PARTICIPANTS IN THE TAMOXIFEN OPHTHALMIC Evaluation Study (TOES) were drawn from the B-14 trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP), which was designed to evaluate the efficacy of tamoxifen in the prevention of disease recurrence among women with primary operable breast cancer.[2-4] Patients received treatment with tamoxifen (10 mg orally twice a day) or placebo.

The TOES was a single-masked (medical staff), cross-sectional investigation of a subset of patients from the B-14 trial. TOES patients were classified a priori into three groups: patients who had never been given tamoxifen from the time of their recruitment into B-14 until their TOES evaluation (TAM-NONE); patients who had been given tamoxifen for some length of time but had quit taking the drug for any reason before their TOES evaluation (TAM-ON/OFF); and patients who had continuously taken tamoxifen from the time of their recruitment into B-14 until their TOES evaluation (TAM-CONT). The TOES protocol was approved on February 1, 1993, by the Human Subjects Institutional Review Board at the University of Pittsburgh School of Medicine and renewed on an annual basis. Approvals were also received from local institutional review boards in the collaborating centers.

Patients were eligible for inclusion in TOES if they were enrolled in the B-14 trial, had remained in the study for at least 1 year, and had not suffered a disease recurrence by the time of the eye examination. TOES participants were recruited from eight NSABP collaborating institutions and examined at five ophthalmic centers: (1) University of Pittsburgh (TOES headquarters) and Allegheny General Hospital, Pittsburgh, Pennsylvania; (2) Hôtel-Dieu, Jewish General Hospital, and Montreal General Hospital, Montreal, Quebec, Canada; (3) Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada; (4) Michigan State University, East Lansing, Michigan; and (5) Mount Sinai Medical Center, Cleveland, Ohio (Appendix).

On an Ophthalmic and Medical Evaluation Form, data were collected on conditions that would predispose the patient to decreased vision or retinal dysfunction, including amblyopia, strabismus, significant refractive error, glaucoma, cataracts, age-related macular degeneration, diabetes, previous visual loss, and medical or surgical ophthalmic treatment. A second questionnaire addressed current and past visual symptoms using modifications of the Activities of Daily Vision Scale.[5]

Psychophysical testing assessments involved visual acuity and color vision testing. Best-corrected visual acuity measurements were determined in accordance with the Early Treatment Diabetic Retinopathy Study (ETDRS).[6] Color vision deficits were assessed by a Farnsworth D-15 desaturated panel of color chips, and color confusion scores were calculated.[7] Two undilated tests of macular function were administered, the SKILL card[8] and macular automated static perimetry on the Humphrey perimeter.[9,10]

The ophthalmic examination consisted of a slit-lamp biomicroscopic examination of the cornea, iris, and lens, and biomicroscopic examination of the fundus. Participating ophthalmologists reviewed the problems of identifying refractile crystalline deposits in the retina using tamoxifen case history data and photographic evidence.[11,12] A 4-point scale for age-related maculopathy was constructed based on a proposed international grading system.[13]

Lens opacifications were identified as present or absent based on LOCS III standard photographs.[14,15] Thresholds (N3, C3, P2) were chosen so that the presence of opacification would probably affect visual acuity. Fundus photographs and retroillumination views of the lenses were taken by certified photographers and sent to the Wisconsin Fundus Photograph Reading Center for an independent evaluation.

Because the administration of tamoxifen represents a systemic exposure, its potential effects were evaluated at the level of the person rather than by eye. Exceptions to this approach occur with the measures of visual function and the assessment of age-related maculopathy. The TOES analysis involved screening

a large number of outcome measures for statistical significance. We made an a priori decision to carry out hypothesis testing using one-sided alternatives, with the tamoxifen groups expected to demonstrate the more adverse score. Initial analyses compared participants in the group who had never taken tamoxifen (TAM-NONE) with those who had ever taken tamoxifen (TAM-POS). The TAM-POS group consisted of the TAM-ON/OFF and TAM-CONT participants. Subsequent analyses compared participants who discontinued tamoxifen to those who had taken the drug continuously in order to investigate the possibility that ocular toxicities receded or reversed themselves once the drug had been discontinued. Distributions of continuous variables were found to be non-normal, and nonparametric statistics, such as those of the Wilcoxon-Mann-Whitney and the Kruskal-Wallis tests, were used. Chi-square tests were employed for categoric variables except when numbers became small and the exact test had to be substituted. Exact Poisson confidence intervals were placed on prevalence rates. *P* values were not adjusted for multiple comparisons in order to maximize the power to detect negative consequences of tamoxifen use.

Required sample sizes were estimated on the basis of findings in prior studies.[16] The TOES was designed to have an 80% or greater statistical power to identify small differences (for example, 4%) between the study groups in the prevalence of intraretinal crystals associated with macular edema.

RESULTS

A TOTAL OF 464 B-14 PATIENTS WERE CONTACTED FOR participation in the TOES; 161 (35%) declined to participate. The remaining 303 patients took part in the TOES: 85 in the TAN-NONE group, 140 in the TAM-ON/OFF group, and 78 in the TAM-CONT group. It was found that the patients who declined to participate in the TOES were significantly older than the patients who appeared for their examinations (median ages, 68 and 64 years, respectively; $P < .001$). However, the patients who declined to participate in the TOES were distributed among the three study groups in proportions that were similar to the patients who completed their evaluations. There were no statistically significant differences among the three study groups with regard to the distribution of age or potentially confounding comorbid conditions (Table 1).

In regard to the masking of ophthalmic technicians and ophthalmologists, the ophthalmic technicians reported that 11 participants (3.6%) had disclosed information regarding their tamoxifen status, and the ophthalmologists reported that only two patients (0.7%) disclosed similar information.

Regarding subjective and psychophysical tests of visual function, there was no evidence (Table 2) of any tamoxifen-related decrements in visual function based on the results of visual acuity measurements, the SKILL card, automated perimetry, or the Activities of Daily Vision Scale. The tamoxifen-treated groups did show poorer median color confusion scores. The differences between the TAM-NONE and TAM-POS groups were statistically significant for both the right eye (medians, 19.1 vs 23.6, respectively; $P = .023$) and the left eye (medians, 19.0 vs 24.2, respectively; $P = .037$). Comparisons of the TAM-NONE with the TAM-CONT group (see Table 2 for medians) were statistically significant for the right eye ($P = .038$), whereas comparisons with the larger TAM-ON/OFF group were statistically significant for both the right ($P = .039$) and the left ($P = .046$) eyes. When diabetic participants (n = 29; Table 1) were removed from the sample, these group differences were slightly reduced.

No statistically significant differences were found among the study groups with regard to the prevalence of corneal opacities; neither were there statistically significant differences in the frequencies of unilateral and bilateral aphakic and pseudophakic participants in the three study groups (Table 3). The prevalences of nuclear sclerosis, cortical opacities, and posterior subcapsular opacities were compared among study groups using participants with one lens or both lenses present. No statistically significant differences were found in the frequencies of nuclear sclerosis or cortical opacities among the study groups.

Fourteen (67%) of the 21 participants reported to have posterior subcapsular opacities had unilateral involvement; five (24%) of these individuals were pseudophakic in the fellow eye (Table 3). Two of the participants with posterior subcapsular opacities had reportedly been taking corticosteroids for more than 6

TABLE 1. Ages, B-14 Study Characteristics, and Comorbid Conditions and Center Recruitment Stratified by TOES Groups at the Time of the TOES Examination

Variable	TAM-NONE (n = 85)	TAM-ON/OFF (n = 140)	TAM-CONT (n = 78)
Mean age (yrs [SE])	62.4 (1.1)	63.1 (0.8)	62.9 (1.2)
Age distribution (yrs [%])			
≤49	13 (15.3)	17 (12.1)	9 (11.5)
50–69	45 (52.9)	78 (55.7)	44 (56.4)
≥70	27 (31.8)	45 (32.2)	25 (32.1)
B-14 study characteristics			
Mean yrs on trial (SE)	8.9 (0.2)	7.5 (0.2)	7.6 (0.2)
Mean mos on TAM (SE)	0 (0)	57.8 (0.2)	84.9 (2.46)
Mean mos off TAM (SE)	—	32.2 (2.1)	0 (0)
Total mos taking TAM (n [%])			
0 mos on TAM	85 (100)	0 (0)	0 (0)
1-60 mos on TAM	0 (0)	140 (100)	2 (2.6)
>60 mos on TAM	0 (0)	0 (0)	76 (97.4)
Comorbid conditions			
Diabetes mellitus (n [%])			
Self-report and/or ophthalmologist	7 (8.2)	13 (9.3)	9 (11.5)
Macular degeneration (n [%])			
Right eye			
None/minimal	62 (73.8)	111 (79.3)	57 (73.1)
Mild	17 (20.2)	24 (17.1)	13 (16.7)
Moderate	4 (4.8)	5 (3.6)	6 (7.7)
Severe/advanced	1 (1.2)	0 (0)	2 (2.6)
Left eye			
None/minimal	64 (76.2)	112 (80.0)	58 (74.4)
Mild	12 (14.3)	19 (13.6)	12 (15.4)
Moderate	8 (9.5)	8 (5.7)	6 (7.7)
Severe/advanced	0 (0)	1 (0.7)	2 (2.6)

B-14 = the B-14 trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP)[2-4]; TOES = the Tamoxifen Ophthalmic Evaluation Study; TAM = tamoxifen citrate; TAM-CONT = patients who had continuously taken tamoxifen from the time of their recruitment into B-14 until their TOES evaluation; TAM-NONE = patients who had never been given tamoxifen from the time of their recruitment into B-14 until their TOES evaluation; TAM-ON/OFF = patients who had been given tamoxifen for some length of time but had quit taking the drug for any reason before their TOES evaluation.

months, and a third participant had diabetic retinopathy. The initial comparison of TAM-POS vs TAM-NONE was statistically significant (odds ratio [OR] = 4.03, $P = .034$). Both the TAM-ON/OFF and TAM-CONT groups had similar prevalences of posterior subcapsular opacities (9.2% and 9.3%); statistical comparisons with the control group (TAM-NONE) yielded significant results for the TAM-ON/OFF group (OR = 4.02, $P = .046$) and marginally significant results for the TAM-CONT group (OR = 4.07, $P = .067$). When the participants with extended corticosteroid use were removed from the TAM-POS vs TAM-NONE comparison, the odds ratio became 3.61 ($P = .055$). With the additional removal of the patient with diabetic retinopathy, the odds ratio became 3.40 ($P = .069$).

Refractile crystalline deposits in the retina were reported by the ophthalmologists in 10 (3.3%) of the TOES participants (Table 3). Six of the cases were bilateral and four were unilateral. One eye was reported to have more than 10 crystals, whereas four eyes had five to 10 crystals and 11 eyes had one to four crystals. Nine cases were observed in participants treated with tamoxifen, four in the TAM-ON/OFF group, and five in the TAM-CONT group. One individual with bilateral intraretinal crystals was in

TABLE 2. Visual Function and Psychophysical Tests Stratified by TOES Groups

Variable	TAM-NONE (n = 85)	TAM-ON/OFF (n = 140)	TAM-CONT (n = 78)
Visual function			
Mean visual acuity (n [%])			
RE	83.7 (1.5)	83.2 (0.8)	81.8 (1.3)
LE	83.9 (1.1)	83.5 (0.7)	82.5 (1.1)
Color-confusion score (n)			
RE*			
Median	19.1	23.6	23.8
Median without diabetics	19.0	19.0	24.7
LE*			
Median	19.0	25.8	24.2
Median without diabetics	18.7	21.2	24.2
Activities of daily vision score (n [SE])†	89.9 (1.2)	90.9 (0.9)	91.2 (1.0)
Psychophysical testing			
SKILL card (mean [SE])			
RE			
High contrast	71.9 (0.99)	72.1 (0.73)	70.5 (1.3)
Low contrast	55.4 (0.87)	54.1 (0.92)	54.1 (1.1)
LE			
High contrast	72.8 (0.89)	73.3 (0.56)	71.8 (0.64)
Low contrast	54.7 (1.1)	54.2 (0.83)	53.9 (1.0)
Humphrey automated perimetry 10-2 (mean [SE])			
RE			
Mean deviation	−1.53 (0.35)	−1.75 (0.33)	−2.09 (0.57)
Pattern standard deviation (PSD)	1.93 (0.19)	1.89 (0.13)	1.91 (0.18)
Short-term fluctuation	1.33 (0.067)	1.40 (0.054)	1.39 (0.086)
Corrected PSD	1.19 (0.20)	1.06 (0.14)	1.17 (0.18)
Foveal threshold	34.96 (0.30)	34.16 (0.49)	34.26 (0.47)
LE			
Mean deviation	−1.43 (0.77)	−0.74 (0.56)	−1.04 (0.88)
Pattern standard deviation (PSD)	1.85 (0.16)	2.07 (0.13)	1.87 (0.16)
Short-term fluctuation	1.25 (0.062)	1.39 (0.064)	1.36 (0.091)
Corrected PSD	1.17 (0.16)	1.34 (0.14)	1.16 (0.15)
Foveal threshold	34.96 (0.32)	34.29 (0.35)	34.94 (0.28)

*$P < .05$; see text for details.
†n = 82, 140, and 76, respectively, for TAM-NONE, TAM-ON/OFF, and TAM-CONT.

the TAM-NONE group. The overall prevalence of intraretinal crystals in the tamoxifen-treated participants (TAM-POS) was 4.1% (95% confidence interval [CI], 1.9% to 7.7%) and 6.4% (95% CI, 2.1% to 14.3%) for the TAM-CONT group compared with 1.2% (95% CI, 0.03% to 6.4%) in the TAM-NONE group. The prevalence of intraretinal crystals in cases identified by the ophthalmologists was greater in the TAM-POS group compared with the TAM-NONE group (OR = 3.62, $P = .178$). The TAM-CONT subgroup had a higher odds ratio for intraretinal crystals (OR = 5.75, $P = .086$) than did the TAM-ON/OFF subgroup (OR = 2.47, $P = .37$). Participants with clinically identified intraretinal crystals were not different statistically from other TOES participants with regard to subjective and psychophysical measures of visual function.

The fundus photographs independently graded by the Wisconsin Fundus Photograph Reading Center were intended to serve as confirmation of the oph-

TABLE 3. Ocular Structures: Pathology of Cornea, Lens, Retina, and Optic Nerve Stratified by TOES Groups

Variable	TAM-NONE	TAM-ON/OFF	TAM-CONT
Cornea			
Corneal opacities (n [%]) (n = 303)	3 (3.5)	7 (5.0)	7 (9.0)
Lens			
Aphakic or pseudophakic (n [%]) (n = 303)			
Unilateral	2 (2.4)	7 (5.0)	2 (2.6)
Bilateral	4 (4.7)	10 (7.1)	3 (3.9)
Nuclear sclerosis (n [%]) (n = 286)*	21 (25.9)	36 (27.7)	22 (29.3)
Cortical opacities (n [%]) (n = 286)*	11 (13.6)	18 (13.8)	15 (20.0)
Posterior subcapsular opacities† (n [%]) (n = 286)*	2 (2.5)	12 (9.2)	7 (9.3)
Corticosteroids >6 mos	0 (0)	1 (0.8)	1 (1.3)
Diabetes mellitus	0 (0)	1 (0.8)	0 (0)
Retina			
Intraretinal crystals (n [%]) (n = 303)			
Ophthalmologists			
Unilateral	0 (0)	1 (0.7)	3 (3.9)
Bilateral	1 (1.2)	3 (2.1)	2 (2.6)
Macular edema (n [%]) (n = 303)			
Ophthalmologists			
Unilateral	1 (1.2)	1 (0.7)	1 (1.3)
Bilateral	0 (0)	3 (2.1)	2 (2.6)
Optic nerve			
Optic neuropathy (n = 301)	2 (2.4)	1 (0.7)	1 (1.3)

*This n = 286 is composed of unilateral and bilateral phakic subjects (81, 130, and 75, respectively, for TAM-NONE, TAM-ON/OFF, and TAM-CONT).
†$P < .05$; see text for details.

thalmologists' findings. The Wisconsin Fundus Photograph Reading Center reported seven unilateral cases of intraretinal crystals; however, in only a single instance did the Wisconsin Fundus Photograph Reading Center identify crystals in an eye that was positive on the ophthalmologists' examinations. Of the six cases identified only by the Wisconsin Fundus Photograph Reading Center, three were in the TAM-ON/OFF group and three were in the TAM-CONT group.

Because of the lack of agreement regarding intraretinal crystals between the Wisconsin Fundus Photograph Reading Center and the ophthalmologists, a reliability study was carried out using two independent National Eye Institute retina experts. The National Eye Institute ophthalmologists demonstrated poor reliabilities ($\kappa < 0.3$) for recognizing intraretinal crystals from the fundus photographs of patients who were identified as having crystals on clinical examination and even poorer agreement with the cases independently identified by the Wisconsin Fundus Photograph Reading Center. Because of the unreliability of the photographic assessments, the six unique cases of intraretinal crystals identified by the Wisconsin Fundus Photograph Reading Center were not included in the prevalence estimates in Table 3.

There was a greater frequency of macular edema in the TAM-POS (OR = 2.79, $P = .296$) and TAM-CONT (OR = 3.36, $P = .279$) groups compared with the controls. Of the seven cases of macular edema reported among tamoxifen-treated participants, only two cases were associated with intraretinal crystals. Neither of these subjects had evidence of diabetic retinopathy or retinal vascular disease. The prevalence of intraretinal crystals in association with macular edema for the tamoxifen-treated portion of

our study population was 0.9%, with 0.7% in the TAM-ON/OFF group and 1.3% in the TAM-CONT group. There was no evidence that cases of macular edema were associated with deterioration in visual acuity measurements or other tests of visual function.

DISCUSSION

THE PARTICIPANTS IN THIS STUDY HAD A TOTAL OF 1,226 person-years of tamoxifen exposure, with an overall mean exposure time of 5.6 years. Our TAM-CONT group had an average exposure time of 7.8 years, with a maximum individual exposure of 12.8 years. These are the longest cumulative exposure times that have been reported. We also had a series of patients (TAM-ON/OFF) who had been exposed to tamoxifen for an average of 4.8 years, then had been off drug for an average of 2.7 years, thereby permitting us to explore the possibility that certain tamoxifen-related toxicities are permanent (intraretinal crystals) and that others recede (macular edema) with the termination of the drug. Unlike other studies of tamoxifen-related ocular toxicities, the present study used a drug-free control group and masked the clinical investigators to the exposure status of the participants.

Two limitations need to be noted regarding the TOES data. First, there were no baseline assessments of visual function and ophthalmic pathology among the B-14 patients. Hence, it is impossible to guarantee that the TOES participants were ophthalmically similar before the initiation of tamoxifen treatment. Second, at the time of the TOES evaluations, the participants were unmasked with regard to their treatment status during a portion of the B-14 trial. A bias may have been created if eligible subjects had different motivations for participation in the TOES depending upon whether they received tamoxifen during the initial phase of the B-14 trial.

Regarding positive findings, both eyes of women in the TAM-POS group had statistically significant increases in the color confusion scores compared with the eyes of women in the TAM-NONE group. Disturbances in color perception have been recognized as early indications of retinal dysfunction from diabetic retinopathy,[16-18] age-related maculopathy,[19,20] and optic nerve dysfunction. When patients with these conditions were removed from our series, the significance of these differences was slightly reduced. Age-related maculopathy levels were not associated with poorer color confusion scores, and no evidence was found to suggest optic nerve dysfunction associated with tamoxifen use. There were no associations between color confusion scores and adverse levels of subjective or psychophysical measures of visual function, nor was there an association between poorer color confusion scores and other potential manifestations of tamoxifen ocular toxicity (for example, posterior subcapsular lens opacities and intraretinal crystals).

This is the first study of tamoxifen to observe an increased frequency in the development of posterior subcapsular cataracts in humans. There is some precedent from studies in rats and in vitro studies.[21,22] Postmenopausal estrogen replacement therapy has also been shown to cause an increase in the prevalence of posterior subcapsular cataracts.[23] The similar prevalences of posterior subcapsular opacities in the TAM-ON/OFF and TAM-CONT groups suggests that if tamoxifen does increase the risk of posterior subcapsular opacities, this effect occurs within the first 5 years of drug exposure.

The prevalence of individuals with intraretinal crystals in this study is similar to the prevalence reported by Pavlidis and associates[24] and higher than that reported by Heier and associates.[25] The number of crystals observed in the eyes of the tamoxifen-treated TOES participants is comparable to the numbers reported in other screening programs.[25,26] However, less than 1% of the TAM-POS participants had macular edema and intraretinal crystals. None of the individuals with intraretinal crystals demonstrated a decrement in visual function.

Regarding negative findings, the data from visual acuity measurements, the SKILL card, the Activities of Daily Vision Scale, and automated macular perimetry showed no evidence of a decline in visual function associated with the use of tamoxifen.

No evidence was found of an association between tamoxifen treatment and corneal or optic nerve pathology. Nuclear sclerosis and cortical opacities in the lens were not associated with tamoxifen treatment. The corneal opacities that have been reported[27,28] may be coincidental because of the high prevalence of map-dot-fingerprint dystrophy that has been reported in the general population.[29] None of

Appendix

Recruitment and Examination of Patients by Ophthalmologist and Center

Center	No. of Patients Examined (% of those contacted)	Study Groups as a % of Patients Examined (n [%])		
		TAM-NONE	TAM-ON/OFF	TAM-CONT
A	137 (57.8)	37 (27.0)	64 (46.7)	36 (26.3)
B	60 (83.3)	10 (16.7)	30 (50.0)	20 (33.3)
C	48 (87.3)	21 (43.8)	17 (35.4)	10 (20.8)
D	38 (55.9)	10 (26.3)	20 (52.6)	8 (21.1)
E	20 (62.5)	7 (35.0)	9 (45.0)	4 (20.0)

the tamoxifen-treated TOES participants demonstrated the pattern of extensive refractile crystalline deposits in the retina, macular edema, and associated vision loss that has been described in case reports. We found no evidence that women treated with tamoxifen had a higher prevalence or greater severity of age-related maculopathy than drug-free controls did.

Based on these data, it would be prudent to recommend that women have a thorough baseline ophthalmic evaluation within 1 year of the initiation of tamoxifen treatment. The American Academy of Ophthalmology currently recommends that normal adults have a complete eye examination at least every 2 years. It would be reasonable to conduct examinations in asymptomatic women with normal baseline evaluations at least as frequently as is recommended for normal eye care. More frequent examinations would be warranted when the patient has early cataract formation or other ocular pathology, or when she has noted any changes in the nature of her vision. The clinical evaluation should include slit-lamp biomicroscopy of the anterior and posterior segments in combination with a handheld indirect lens or contact lens.

The discovery of a limited number of intraretinal crystals in the absence of macular edema or visual impairment does not seem to warrant the discontinuation of tamoxifen. Decisions about the discontinuation of the drug should be made within the context of the patient's concerns and the circumstances that prompted the use of tamoxifen. The presence of age-related maculopathy is not a contraindication to the use of tamoxifen.

The observed prevalence of posterior subcapsular opacities for women on tamoxifen is potentially troublesome. These opacities are indistinguishable from those that occur spontaneously or from exposure to other medications, such as systemic or ocular corticosteroids. Clinical experience with these drugs[30] suggests that these opacities are generally not reversible after drug cessation and can progress after the medications have been stopped. Women taking tamoxifen should be advised that there is preliminary evidence suggesting that tamoxifen may increase the chance of developing cataracts. However, should these cataracts be observed, there is little reason to terminate the medication unless there is evidence of other ocular toxicity.

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