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REVIEW ARTICLE

Tamoxifen-Associated Eye Disease: A Review

By Susan G. Nayfield and Michael B. Gorin

Purpose: **The oral antiestrogen tamoxifen has demonstrated efficacy in the treatment of metastatic breast cancer and as adjuvant therapy in early-stage disease. Clinical trials of tamoxifen in chemoprevention of breast cancer among high-risk women have focused attention on potential adverse effects of long-term tamoxifen use, including the possibility of ocular toxicity. This review evaluates the published case reports, clinical series, and clinical trial data on ocular toxicities attributed to tamoxifen. Clinical issues of surveillance, differential diagnosis, and management of tamoxifen-related eye disease are discussed.**

Design: **National Library of Medicine online bibliographic services were used to identify case reports and clinical studies of ocular adverse effects that occurred in patients receiving tamoxifen published through the fall of 1994. The medical literature relevant to issues raised by the reports and studies was similarly identified and reviewed.**

Results: **Case reports and case series identify crystalline retinal deposits, macular edema, and corneal changes as potential tamoxifen ocular toxicities. Extensive retinal lesions and macular edema with visual impairment have been reported in a few patients receiving high-dose tamoxifen. Less extensive retinal changes may occur in patients receiving low doses for long periods, and isolated retinal crystals may be observed in patients without visual symptoms.**

Conclusion: **Ocular toxicity is uncommon in the current clinical setting of long-term, low-dose tamoxifen use. Physicians should be aware of the potential for ocular toxicity among patients receiving the drug and should assure appropriate surveillance and prompt evaluation of visual complaints.**

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TAMOXIFEN is an oral antiestrogen that is commonly used in the treatment of advanced breast cancer and as adjuvant therapy following surgical resection of early-stage disease. Observations from adjuvant clinical trials that tamoxifen decreased the occurrence of new cancers in the contralateral breast have led to implementation of a large randomized clinical trial to test the drug's efficacy in preventing breast cancer among women at increased risk.[1]

An association between tamoxifen and ocular disease was first recognized in 1978, with four case reports of ocular toxicity among patients receiving high-dose tamoxifen as treatment for metastatic breast cancer.[2] Since that time, case reports have suggested that ocular toxicity may occur at lower doses currently used as standard therapy,[3-12] and one recent study found that the cumulative incidence of tamoxifen-associated eye disease may be as high as 6% in the latter setting.[10]

While the true incidence and severity of tamoxifen-related eye disease is not known, widespread use of the drug in breast cancer patients emphasizes the need for awareness of potential adverse ocular effects. This report addresses current knowledge regarding tamoxifen's effects on the eye by reviewing the medical literature on reported ocular complications of tamoxifen therapy, exploring possible models for ocular injury, and discussing diagnosis and evaluation of patients with suspected tamoxifen-related eye disease.

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TAMOXIFEN OCULAR EFFECTS

The first cases of ocular toxicity due to tamoxifen were reported by Kaiser-Kupfer and Lippman[2] in 1978 among women receiving extremely high-dose tamoxifen (120 to 320 mg/d) for metastatic breast cancer. Since that time, sporadic case reports and small cross-sectional or prospective studies have appeared in the medical literature.

Case Reports and Case Series

At least 21 cases of tamoxifen-related ocular toxicity have been reported as individual case reports, case series, or within cross-sectional or prospective studies (Table 1).[2-14] Ophthalmologic findings attributed to tamoxifen in these cases include intraretinal crystalline deposits (often associated with macular edema), keratopathy, and optic neuritis.

Retinal changes, described most frequently, include small refractile or crystalline dot-like deposits that are white to yellow in color. These usually occur in the nerve fiber and inner plexiform layers of the retina, predominantly in the area surrounding the macula, which is the central portion of the retina responsible for central vision and high-resolution visual acuity. These deposits may appear in clusters in the paramacular areas. Extensive

Table 1. Cases of Tamoxifen-Associated Ocular Disease Reported in the Medical Literature, 1978 to Present

First Author/Year	Age (yrs)	Total Dose (g)/Daily Dose (mg)	Duration of Tamoxifen Therapy	Prior Chemotherapy	Eye Exam Before Visual Changes	Decreased Central Visual Acuity	Reversible Acuity Changes	Macular Edema	Intraretinal Crystals	RPE Changes	Corneal Opacities	Optic Neuropathy	Lens Changes	Comments
Kaiser-Kupfer/1978[2]	69	108/240	17 mos	+	+	+	–	+	+	–	–	–	NR	
	65	115/240	17 mos	+	–	+	–	+	+	+	+	–	NR	
	49	230/320	27 mos	+	–	+	NR	+	+	–	+	–	NR	
	54	151/240	21 mos	–	–	–	NR	+	+	–	+	–	NR	
McKeown/1981[13]	63	158/180	34 mos	+	+	+	–	+	+	+	–	–	+	Visual symptoms at 17 mos of therapy (90 g); tamoxifen continued. Vf-peripheral constriction. ERG nl.
Vinding/1983[3]	64	8.1/30	9 mos	NR	–	+	+	–	–	+	+	–	NR	Drusen, macular hemorrhage. Vf-Paracentral scotomas.
	65	12.0/30	14 mos	NR	–	+	NR	–	+	+	+	–	+	Reticular degeneration, drusen. Vf-Peripheral constriction.
Pugesgaard/1986[4]	50	6/30-40	6-7 mos	–	–	+	+	–	–	–	–	+	–	
Griffiths/1987[5]	42	7.7/20	16 mos	–	–	+	+	+	–	–	–	–	–	Visual symptoms at 11 mos of therapy; tamoxifen continued.
Ashford/1988[6]	42	0.4/20	3 wks	–	–	+	+	–	–	–	–	+	–	
Gerner/1989[7]	44	22.8/30-40	26 mos	+	–	–	+	(+)	+	–	–	–	–	Vf-nl. Macular cysts. No leakage on angiogram.
de Jong-Busnac/1989[3]	63	7.2/40	NR	NR	–	–	–	–	–	+	–	–	–	Diabetes on medication. Perifoveal pigment changes, arteriole attenuation. Vf-Constricted. ERG-Low amplitudes.
	61	43.8/40	NR	NR	–	–	–	–	–	+	–	–	–	Arteriole attenuation. Vf-nl. EOG abn. ERG abn.
Costa/1990[14]	51	205/80	7 yrs	–	–	+	–	+	+	–	–	–	–	Hypertension on medication. Vf-paracentral scotomas. ERG nl. EOG nl.
Bentley/1992[9]	72	73/40	60 mos	–	+	+	–	–	–	+	–	–	–	Diabetes, drusen. Vf-Central depression. Color abn. ERG nl.
Pavlidis/1993[10]	NR	6.0/20	10 mos	NR	+	+	+	+	+	NR	See comment	–	NR	One case with corneal opacities (case not specified).
	NR	16.2/20	27 mos	NR	+	+	+	+	+	NR		–	NR	
	NR	18.6/20	31 mos	NR	+	+	+	+	+	NR		–	NR	
	NR	21/20	35 mos	NR	+	+	+	+	+	NR		–	NR	
Chang/1992[11]	68	81/20-40	9 yrs	–	–	+	+	+	+	+	–	–	+	
Chern/1993[12]	50	230/20	3 yrs	+	–	+	–	–	+	+	–	–	NR	

Abbreviations: mos, months; yrs, years; EOG, electrooculogram; ERG, electroretinogram; NR, not reported; RPE, retinal pigment epithelium; Vf, visual fields; nl, normal; abn, abnormal.

deposits are often associated with macular edema, ie, the accumulation of fluid within the retinal cellular layers, and impaired visual acuity. Acuity may improve with resolution of the macular edema, but observations suggest that the number and size of retinal deposits do not change with cessation of tamoxifen. Changes in the retinal pigment epithelium (RPE) have also been described, both in central and peripheral areas. Isolated refractile deposits or a small number of deposits have been noted in patients receiving low daily and total doses of tamoxifen; these often occur without macular edema and may not be associated with changes in visual acuity.

Corneal opacities described in patients receiving long-term tamoxifen include subepithelial deposits,[10] whorls,[2] and lines or linear opacities.[2,3] The whorl-like or linear subepithelial opacities, white to brown in color, are often bilateral and occur in the inferior and occasionally the central portions of the cornea. Subepithelial lines may appear as obliquely oriented brown streaks or discreet horizontal lines in the center of the cornea and may occur in both eyes. Corneal changes may improve or resolve with discontinuation of tamoxifen therapy. Case reports suggest that these changes are not clinically significant and that retinal toxicity is the primary cause of visual morbidity.

Lens changes, noted in three cases in Table 1, consisted of bilateral mild to moderate nuclear sclerosis and/or subcapsular cataracts (anterior or posterior). It is unclear from the case reports whether lens changes were regarded as incidental age-related findings or were attributed to tamoxifen therapy.

The most common clinical abnormality among reported cases of symptomatic ocular toxicity was decreased central visual acuity, noted in 16 of 21 cases (76%). Ten of 16 patients with decreased acuity experienced improvement in their vision after tamoxifen was discontinued, although in one case the visual improvement was correlated with the resolution of a macular hemorrhage while the patient continued to receive tamoxifen. These findings are consistent with observations in 20 cases of tamoxifen-associated ocular toxicity reviewed by Szczesny and Steiner[15] that deterioration of vision was the first symptom in 85% of cases and that both development of ocular toxicity and potential improvement in visual acuity may be related to total cumulative dose of drug.

Initial reports of tamoxifen-associated ocular toxicity occurred in patients receiving high daily doses of tamoxifen for longer than 1 year and total cumulative doses of greater than 100 g.[2] Subsequently, three additional cases of toxicity at cumulative doses greater than 100 g have been reported. Intraretinal crystals were noted in all seven of these cases, macular edema was observed in six of seven, and corneal opacities were described in three patients. Findings among patients who received total cumulative doses less than 100 g have been less consistent. Eleven patients received cumulative doses up to 37 g (the approximate total dose for a patient completing 5 years of adjuvant therapy at 20 mg/d); retinal crystals were reported in six of these cases, macular edema in five, and corneal opacities in three. Among six patients who received cumulative doses up to 15 g (the approximate total dose for a patient completing 2 years of adjuvant therapy at 20 mg/d), retinal crystals were reported in one, macular edema in two, and corneal opacities in one. A consistent pattern of abnormalities was not apparent for other measures of visual function, such as color testing and visual fields. Similarly, electroretinograms and electrooculograms were normal in some cases and clearly abnormal in others.

The optic neuritis described by Ashford et al[6] is the only instance of toxicity reported for a total dose less than 1 g. The short interval between initiation of tamoxifen and development of the optic neuritis suggests an idiosyncratic reaction or noncausal association, despite the temporal relationship between clinical improvement and drug cessation. The bilateral optic neuritis reported by Pugesgaard and Von Eyben[4] in one patient occurred with 6 to 7 months of tamoxifen at 20 to 30 mg/d (total dose, 6 g); improvement occurred with discontinuation of tamoxifen and initiation of corticosteroids.

The variability of findings among reported cases suggests either that tamoxifen toxicity can be expressed in a highly variable fashion or that other diagnoses unrelated to tamoxifen must be considered. Interpretation of case reports that describe tamoxifen ocular toxicity is difficult, not only because of limited information in the published reports, but also because similar findings may be due to age-related eye disease or other common health problems or medications that are difficult to distinguish from true tamoxifen-related problems.

Cross-Sectional and Prospective Studies

Four small cross-sectional studies of women receiving conventional-dose tamoxifen for varying periods have addressed the prevalence or incidence of ocular findings associated with tamoxifen (Table 2). In 1979, Beck and Mills[16] reported no ocular changes attributable to the drug in 19 women who received tamoxifen for periods of from 3 months to 4 years. Ophthalmologic evaluation included assessment of near and distant visual acuity, tests of macular function, slit-lamp biomicroscopy, intraocular pressure measurement, and fundoscopic examination. Vinding and Nielsen[3] examined 17 patients receiving 20 to 30

Table 2. Cross-Sectional and Prospective Studies of Tamoxifen-Associated Ocular Toxicity

First Author/Year	Study Design	No. of Patients	Age (yrs) Range	Age (yrs) Mean	Daily Dose (mg)	Total Dose (g) Range	Total Dose (g) Mean	Duration of Therapy (mos) Range	Duration of Therapy (mos) Mean	Findings	Comments
Beck and Mills/ 1979[16]	Cross-sectional	19	54-84	63.9	20-40	NR		3-48	16	No cases of retinopathy or corneal lesions	Alternate explanations were identified in all patients with decreased visual acuity.
Vinding/1983[3]	Cross-sectional	17	57-82	67.5	20-30	5.8-15.0	10.6	7-25	16	2 cases of retinopathy; 4 cases of subepithelial corneal deposits	Prevalence of 11.8% for retinopathy, 23.5% for corneal lesions.
de Jong-Busnac/ 1989[8]	Cross-sectional	20	NR		40	NR		NR		2 cases of tapetoretinal degeneration	Prevalence of 10% for RPE changes.
Longstaff/ 1989[17]	Cross-sectional (with controls)	79 Patients 115 Controls	≤ 68	57.5	20-40	≤ 85	24.3	≤ 76	27	No cases of retinopathy; no differences in other findings between patient and control groups.	
Pavlidis/1992[10]	Prospective cohort	63	32-82	58	20	3.6-30	14.4	6-51	25	4 cases of retinopathy in 63 assessable patients	Exclusions for diabetes, hypertension, other oculotoxic drugs; 9/72 patients not assessable; incidence of 6.3% for retinopathy in assessable patients
Heier/1994[18]	Cross-sectional	135 (without visual symptoms)	44-89	65	20	1.2-87.6	17.2			2 cases of intraretinal crystals without macular edema; no corneal opacities	Prevalence of 1.5% for retinopathy.

Abbreviation: NR, not reported.

mg tamoxifen daily for up to 25 months. They reported retinopathy in two patients. They noted subepithelial changes in the center of the cornea in both patients with retinopathy and in two patients without retinal lesions. de Jong-Busac[8] examined 20 patients who received tamoxifen 40 mg/d and found two cases of tapetoretinal degeneration (retinal dysfunction associated with degenerative changes in the underlying RPE). These three studies are limited by the lack of baseline ophthalmic examinations or a suitable control group for comparison of clinical findings. However, the case series reported by Longstaff et al[17] compared ocular symptoms and findings in 79 women receiving 20 to 30 mg/d of tamoxifen for varying periods with those of 115 controls in a single-blind study design. Evaluation included assessment of visual acuity and slit-lamp and full fundoscopic examinations; no ocular toxicity attributable to tamoxifen was found.

In a recent prospective study, Pavlidis et al[10] reported four cases (6.3%) of ocular toxicity in 63 patients receiving tamoxifen 20 mg/d for varying durations. Examinations, performed at baseline and at 6-month intervals, included corrected visual acuity, slit-lamp examination, tonometry, grid testing, visual-field determination, and fundoscopy. Four patients complained of decreased visual acuity and had findings of macular edema and dot-like paramacular deposits; in addition, one patient had subepithelial corneal opacities. Macular edema regressed in all patients with discontinuation of tamoxifen and acuity returned to previous levels with slight residual monocular visual impairment in one patient. Duration of therapy in these patients ranged from 10 to 35 months, and total dose from 6 to 21 g.

Most recently, Heier et al[18] evaluated 135 asymptomatic patients receiving tamoxifen 20 mg/d for periods of 2 months to 12 years. Ocular examinations included visual acuity, central vision testing with the red Amsler grid, color vision testing with Ishihara pseudoisochromatic color plates, intraocular pressure measurements, slit-lamp examination, and dilated fundus examination. Intraretinal crystals consistent with tamoxifen retinopathy were observed in two of 135 patients (1.5%) who had received

10.9 g and 21.9 g total cumulative doses of tamoxifen; neither patient had impaired visual acuity, macular edema, or corneal opacities. Three patients in this study were found to have a solitary refractile macular lesion at the level of the inner retina on initial evaluation, which could not be confirmed at follow-up examination and which raises questions regarding transient toxicity or misinterpretation of other ocular lesions.

Experience From Adjuvant Clinical Trials

Prospectively collected information regarding ocular toxicity is available for 2,375 women who received tamoxifen alone or in combination with cytotoxic therapy in several large randomized clinical trials of adjuvant therapy for early-stage breast cancer[19] (Table 3). Among 926 patients who received tamoxifen, 11 reported ocular symptoms (cumulative incidence, 1.2%), and four of the 11 had ocular findings: keratitis (n = 1), retinal abnormalities (n = 2), and cataracts (n = 1). Other ocular complaints (eg, conjunctivitis, tearing, and blurring) were more common among patients on chemotherapy, reported by 5.2% (77 of 1,486) of those receiving cytotoxic therapy alone and 3.5% (51 of 1,499) of those receiving tamoxifen plus cytotoxic therapy. Similar complaints occurred in only 0.8% (seven of 926) of patients who received tamoxifen alone and in 0.7% (seven of 941) of patients who received placebo. These data suggest that ocular complaints are more frequent among patients who receive chemotherapy, alone or in combination with tamoxifen, and that there is little difference in ocular symptomatology between patients who receive tamoxifen alone and those who receive no treatment (observation or placebo controls).

PATHOGENESIS AND DIAGNOSIS OF TAMOXIFEN OCULAR TOXICITY

Pathophysiology

Little is known about the pharmacodynamics of tamoxifen and its metabolites in ocular tissues. Trace or undetectable amounts of tamoxifen and its metabolite N-desmethyltamoxifen (< 1% of serum concentrations) have been detected in CSF from patients receiving 20 to 40 mg/d,[20,21] which suggests that neither the protein-bound drug or the highly polar-free drug cross the blood-brain barrier easily at usual doses. However, analyses of brain metastases and adjacent brain tissue from patients with breast cancer have shown concentrations of tamoxifen and its metabolites up to 46-fold higher than in serum.[22] The ability of tamoxifen to concentrate in CNS metastases is consistent with clinical observations of remission of brain metastases from breast cancer among some patients receiving tamoxifen therapy[23-25] and has been attributed to the apparent absence of the blood-brain barrier in newly growing tumor vessels.[26] Disease stabilization and tumor regression have also been reported in patients with intracranial malignant gliomas who received tamoxifen following failure of other therapy.[27-29] This effect has been attributed to tamoxifen's ability to inhibit protein kinase C at micromolar concentrations and to the marked in vitro sensitivity of glioma cell lines to protein kinase C inhibition.[30]

Case reports in breast cancer patients of stabilization of optic nerve head metastases and reduction in the size of retinal metastases with tamoxifen therapy[31] suggest that the drug does penetrate the choriocapillaris and is exposed at least to the basal surface of the pigment epithelium. The extent of penetration into the retina and the vitreous is unknown and may vary in the presence of other conditions such as age-related macular disease and vascular disorders.

While the pathophysiology of retinal changes associated with tamoxifen is unclear, clinicopathologic correlation of clinical signs with histopathologic findings reported by Kaiser-Kupfer et al[32] indicate that the formation of the crystalline retinal deposits may be related to axonal degeneration. The intracellular location of the retinopathic lesions in the nerve fiber and inner plexiform layers of the retina, their similarity to nerve synapses by electron microscopy, and the demonstration of glycosaminoglycans in the deposits by histochemical methods support this concept.

Tamoxifen is structurally similar to other drugs with well-known retinal effects, including chloroquine[33,34] chlorpromazine,[35] thioridazine,[36,37] and tilorone.[38] Ultrastructural lesions associated with these agents may appear as lamellated or crystalloid inclusions in the neuroretina or as crystalloid bodies in the RPE. These amphiphilic compounds contain both a hydrophobic aromatic ring and a hydrophilic side chain with a positively charged nitrogen atom and are postulated to bind with polar lipids, inhibiting normal catabolism of the lipids and resulting

Table 3. Ocular Effects Reported in Cooperative Group Studies of Tamoxifen Therapy Alone or in Combination With Cytotoxic Chemotherapy

Ocular Effect	TAM (n = 926)	TAM + CTX (n = 1,449)	CTX (n = 1,486)	No RX (n = 941)
Visual complaints	6	1	0	3
Keratitis	1	0	0	0
Retinal abnormalities	2	0	0	0
Cataracts	1	0	0	0
Other*	1	50	77	4
Total (cumulative incidence)	11 (1.2%)	51 (3.5%)	77 (5.2%)	7 (0.7%)

NOTE. Data from ICI Pharmaceuticals Group.[19]

Abbreviations: TAM, tamoxifen; CTX, cytotoxic chemotherapy; No RX, no treatment (observed control or placebo).

*Includes conjunctivitis, tearing, blurring, swollen eyes, and nondefined complaints or symptoms.

in the accumulation of drug-lipid complexes in lysosomes.[39,40] Lullman and Lullman-Rauch[41] have demonstrated the development of a generalized lipidosis in rats treated subchronically with very–high-dose tamoxifen (100 to 130 mg/kg); the degree of lipidosis was dependent on the dose and duration of treatment. Imperia et al[42] hypothesized that retinal deposits described in patients who received long-term tamoxifen are formed by mechanisms similar to those associated with other amphiphilic agents, although the lesions examined by Kaiser-Kupfer et al[32] did not stain for lipid material.

Keratopathy has been reported with amiodarone,[43] chloroquine,[33] chlorpromazine,[35] tilorone,[38] and triparanol (MER 29).[44] The corneal lesions associated with these drugs are characterized as whorl-like distributions of intraepithelial opacities (verticilliate keratopathy), dot-like subepithelial deposits occasionally condensing into fine linear patterns, or diffuse clouding of the epithelium and anterior stroma. The deposits consist of lysosomal inclusions in the cytoplasm of the cells and are regarded as a manifestation of drug-induced lipidosis similar to the retinal lesions produced by many of these amphiphilic compounds.

While cataracts have been reported infrequently among patients who receive tamoxifen, lens changes have been observed in rats that received tamoxifen for long-term (2-year) toxicity studies.[45] Crescentic cataracts were significantly increased among animals in the high-dose (35 mg/kg) group, but only slightly increased in those who received lower doses (5 and 20 mg/kg). Few posterior suture cataracts and anterior lines were noted with increasing dose, and multiple zones of discontinuity (changes in refractive index) appeared at earlier onset as dose increased. Recently, Zhang et al[46] demonstrated that tamoxifen induces opacity in bovine lenses cultured in medium that contains concentrations of drug similar to serum levels achieved by usual doses. They postulate that tamoxifen's ability to inhibit cellular chloride channels contributes to cataract development by blocking these channels, which are necessary to maintain normal lens hydration and transmittance. However, without information regarding the presence of tamoxifen or its metabolites in the aqueous, it is difficult to conclude that tamoxifen poses a significant risk for cataract formation.

The observed reversibility of tamoxifen-related visual complaints suggests that the daily dose and duration of therapy may be more strongly associated with the ocular changes than the total or cumulative dose of tamoxifen, ie, low doses that do not exceed the body's ability to metabolize and excrete the drug may be tolerated for longer periods without retinal complications than larger doses that achieve much higher blood levels. This is consistent with the observation that the most striking cases of tamoxifen-associated retinopathy occurred in patients who received doses of at least 180 mg/d (Table 1), which could potentially enhance drug levels in the CSF and CNS tissues.

Differential Diagnosis

Because the incidence of breast cancer increases dramatically with age, interpretation of ophthalmologic findings in breast cancer patients who receive tamoxifen may be confounded by age-related eye disease or by ocular changes that complicate common medical problems such as diabetes and vascular disease.

Retinal changes attributed to tamoxifen are similar in appearance to findings in other rare and common retinal disorders. Age-related macular degeneration (maculopathy) is the leading cause of severe visual loss in persons over age 50, an age group that frequently receives long-term tamoxifen as adjuvant therapy for breast cancer. Early (nonneovascular) stages of age-related macular degeneration may be characterized by hard drusen associated with localized RPE abnormalities, soft drusen with generalized RPE dysfunction, and geographic atrophy. These fundus changes may predispose to the development of neovascular and exudative stages with irreversible central visual impairment.[47] The round, discrete yellowish-white deposits of hard drusen with associated pigmentary or trophic changes in the RPE may be mistaken for tamoxifen-related retinal changes on cursory examination. For example, macular degeneration was associated with drusen and/or peripheral reticular degeneration in three cases listed in Table 1. Diabetic retinopathy, idiopathic preretinal membranes, and idiopathic macular cysts or impending macular holes may be possible explanations for the findings in a number of these reports. Intraretinal exudates and macular edema may also occur with chronic nonischemic small-vein occlusions, in optic neuritis, or from idiopathic juxtafoveal telangiectasia.

Retinal lesions similar in appearance to those associated with tamoxifen may also occur with inherited metabolic disorders such as oxalosis,[48] nephropathic cystinosis,[49] Bietti's crystalline dystrophy,[50] Sjögren-Larsson syndrome,[51] and Alport's syndrome.[52] However, retinal changes are usually a late complication or an incidental finding in patients with systemic manifestations of the underlying metabolic disorder and an established diagnosis of the hereditary disease.

Other conditions with crystal-like retinal lesions include talc embolism[53] and canthaxanthin retinopathy.[54] Talc retinopathy is characterized by yellow-white intraarteriolar particles scattered in the paramacular area; these lesions represent emboli of talc particles to the reti-

nal circulation, which may occur when oral medications with talc fillers are dissolved for intravenous injection. Macular edema and dot- or flame-shaped retinal hemorrhages may accompany the arteriolar occlusion in some patients. Ingestion of canthaxanthin, a widely accepted orange food color, to produce a suntanned appearance may result in retinal deposition of glistening yellow particles, predominantly in superficial retinal layers around the macular depression. The retinal deposits are related to dose of canthaxathin, rather than to duration of treatment; however, the lesions may occur without intentional drug ingestion among individuals who are highly sensitive to canthaxathin as a food additive.[55]

Heier et al[18] emphasized the challenge of differentiating suspicious lesions from refractile crystals of tamoxifen retinopathy. Calcified drusen, reflections off the limiting membrane, and small epiretinal membranes were the most common findings initially identified as suspicious refractile macular lesions in their large cross-sectional study of asymptomatic patients. They suggest contact lens biomicroscopy to facilitate identification of these mimicking lesions.

Corneal changes similar to those associated with tamoxifen may occur with medication use as described earlier, in asymptomatic carriers of Fabry's disease (an X-linked deficiency of alpha-galactosidase A),[56] and in map-dot-fingerprint dystrophy (anterior membrane dystrophy and Cogan's microcystic dystrophy).[57] The presence of whorl-like subepithelial deposits in the absence of potentially causative medications warrants screening for Fabry's disease before the finding is attributed to tamoxifen, as these characteristic corneal lesions are present in 70% of female carriers and may predate skin and visceral signs in affected individuals.[56] Subepithelial lines and opacities such as those reported in map-dot-fingerprint dystrophy may occur in greater than 40% of the general population and 75% of persons older than age 50, independently of ocular symptoms and recurrent corneal erosions.[57] Brownish subendothelial deposits must be distinguished from iron deposition that occurs along the lower third of the aging cornea (Hudson-Stahli line), at the base of a keratoconus lesion (Fleisher's line), or at the junction of a pterygium (Stocker's line).

Recommendations for Women Currently Receiving Tamoxifen

Although the incidence and prevalence of tamoxifen-associated ocular toxicity appear to be low at usual doses of 20 to 40 mg/d, women receiving tamoxifen as treatment for breast cancer should have a complete eye examination before initiation of therapy to determine baseline visual function and document ocular findings that exist before tamoxifen exposure. Patients should be monitored carefully for visual complaints, and visual symptoms or clinical findings that develop during treatment should be fully evaluated.

The frequency for regularly scheduled ophthalmologic follow-up visits in asymptomatic patients receiving tamoxifen is unclear at present. For persons in the general population, the American Academy of Ophthalmology recommends a baseline comprehensive eye examination at approximately age 40 years followed by eye examinations every 2 to 4 years for adults ages 40 to 64 years and every 1 to 2 years for those $\geq$ 65 years.[58] However, they caution that the frequency of eye examination in the presence of acute or chronic medical disease or known risk factors for eye disease is widely variable. Annual ophthalmologic examinations for persons receiving tamoxifen is not inconsistent with these guidelines.

The most sensitive methods to detect early toxic retinopathy have not been firmly established. Because the majority of tamoxifen's effects occur in the macular region of the retina, testing of retinal function should include clinical and subclinical aspects of macular vision. Experience in patients with retinopathy related to chloroquine and phenothiazine use indicates that electrophysiologic studies (electroretinograms and electrooculograms) and color plates are relatively insensitive at early stages, becoming abnormal when there is already significant disruption of the pigment epithelium and retina.

Static perimetry of macular function can detect focal or diffuse increases in visual thresholds due to retinal or optic nerve dysfunction. Sequential measurements using an automated perimeter provide a sensitive, quantitative approach to assess changes in retinal function over time. Because retinal toxicity rarely causes a homogeneous elevation in retinal thresholds, these visual-field tests can detect threshold inhomogeneities within the macula, even if there is a general threshold elevation due to corneal or lens opacities.

The Amsler grid is frequently used in patients with age-related macular degeneration to detect subtle paracentral visual disturbances that indicate the development of subretinal neovascular membranes. Threshold Amsler testing allows the patient to adjust the threshold level of the visual target, which eliminates the confounding effects of lens and corneal opacities. Sophisticated quantitative hue and luminescence color matching may also provide early indications of macular dysfunction. The use of fluorescein angiography to detect retinal lesions should be discouraged unless there is clinical evidence of retinal thickening, intraretinal deposits, or retinal crystals. Other psychophysic tests of retinal function, such as glare recovery and quantitative macular photostress tests, are currently available in the clinical research setting.

While these studies may be highly sensitive in the detection of subclinical retinal dysfunction before impairment of visual acuity, their usefulness in the detection, evaluation, and monitoring of tamoxifen ocular toxicity has not been established. In addition, their findings are not specific for tamoxifen-related retinal changes. Thus, it is essential to exclude other common causes of macular dysfunction such as diabetic maculopathy, retinal vascular disease, and age-related macular degeneration before macular dysfunction is attributed to tamoxifen.

The findings reported by Heier et al[18] suggest that small numbers of retinal crystalline deposits may be observed in asymptomatic patients without compromise of visual acuity and raises the question of whether such isolated deposits may be transitory. The need to discontinue tamoxifen in asymptomatic patients with limited ocular changes has not been established. The potential reversibility of changes in visual acuity developing at low total cumulative doses of tamoxifen has led some physicians to continue tamoxifen in these patients under careful ophthalmologic surveillance.[5,6,10,11,18]

There is, at present, no evidence to suggest that macular degeneration predisposes to tamoxifen-related ocular toxicity or that its progression is accelerated by tamoxifen. Because of tamoxifen's demonstrated efficacy in controlling metastatic breast cancer and in preventing recurrence of early stage disease, women with macular degeneration should still consider taking tamoxifen on the advice of their physician. Routine ophthalmologic examinations in patients with macular degeneration or with other findings related to coexisting medical problems may be especially useful in following the progress of underlying disease while watching for changes potentially associated with tamoxifen therapy.

In conclusion, despite extensive oncologic experience with tamoxifen in breast cancer management, relatively few case reports of ocular toxicity have appeared in the medical literature. The most striking cases of retinopathy with macular edema have occurred in patients receiving high daily doses ($\geq$ 180 mg/d) and achieving total cumulative doses of greater than 100 g tamoxifen, although refractile retinal crystals have been identified in asymptomatic patients on usual doses of 20 to 40 mg/d. The pathophysiology of retinopathy and keratopathy are unclear. Recent cross-sectional and prospective studies (including large randomized adjuvant therapy clinical trials) suggest that the incidence and prevalence of tamoxifen-related eye disease is low with drug doses in current use and that age-related eye disease and ocular complications of other medical processes may complicate its diagnosis. The visual disturbances and retinal changes associated with tamoxifen toxicity may be subtle, and it is not reasonable to expect a nonophthalmologist to detect early tamoxifen ocular toxicity. All physicians should be aware of the potential for ocular toxicity associated with tamoxifen and encourage baseline ophthalmologic evaluations and follow-up monitoring of any ocular complaints that arise during therapy.

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