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RESEARCH

Amiodarone-induced ocular and extra-ocular toxicity: a retrospective cohort study

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Abstract

Amiodarone (AMD) is a largely employed anti-arrhythmic agent for the treatment of recurrent supraventricular and ventricular tachyarrhythmias. Because of its lipophilic properties, prolonged half-life and prevailing biliary excretion, it is not rarely responsible for potentially severe adverse events that can involve one or more organs with a prevalence ranging from 15% in the first year of drug intake to 50% in patients treated for a longer time. In addition to pro-arrhythmia effects, AMD toxicity may result in a variable combination of clinical manifestations, including visual impairment, thyroid dysfunctions, pulmonary diseases, liver injury, neutropenia or thrombocytopenia. We aimed to describe the AMD-induced ophthalmologic and non-ophthalmologic side effects observed in a longitudinal cohort of patients. Seventeen Caucasian patients, who were on amiodarone therapy for a variable period, were enrolled in this retrospective, cross-sectional, observational study. All of them were referred to the Department of Ophthalmology and Neuroscience of the University of Bari, Italy, because of visual disturbances of variable severity. Three patients were given 3 intravenous boluses of 150 mg AMD followed by progressively decreasing oral doses, whereas 14 patients received a loading daily dose of 600–1200 mg orally, reduced after 2–3 weeks to a maintenance daily dose of 200–400 mg. All patients underwent complete clinical and laboratory assessments, according to a standard protocol. Ophthalmologic examination included intraocular pressure, ocular motility, visual field testing, angiography, optical coherence tomography, best-corrected visual acuity (BCVA) and grading of AMD-induced keratopathy by slit-lamp biomicroscopy. At diagnosis, eye disorders ranging from blurred vision and deterioration of visual acuity to eye redness and progressive glare were reported in 14 patients and lasting photophobia in the remaining 3 patients. Verticillate keratopathy (VK), stage 1–4, was diagnosed in all of them. Following AMD cessation, the patients were checked after a mean of 94 days and clear corneas were found in 12 of them, whereas lower-stage VK persisted in 5 patients. A 20/40 visual outcome or better was detected in 29 of 34 eyes (85.3%). Bilateral optic disk edema was found in 3 patients. Fundoscopic examination performed 23 months after AMD discontinuation showed that optic disk edema was reduced in all 3 patients, though to a variable extent. Optic neuropathy with protracted disk edema was diagnosed in a single patient who complained of progressive visual loss. Almost 2 months after AMD cessation, disk edema was reduced in OD > OS and BCVA partially improved. Extra-ocular manifestations included poorly symptomatic hypothyroidism in 2 patients, and overt myxedema, cholestatic liver injury, pancytopenia and interstitial pneumonitis associated with subclinical hypothyroidism in one patient each. A point stemming from our study and not clearly emphasized in the literature is that while a higher maintenance dose of AMD for a longer time was responsible for the most advanced grade 4 VK, no correlation was found between the occurrence of extra-ocular manifestations and the severity of ophthalmological signs or complaints. Patients assuming AMD should undergo close monitoring by specialist clinicians of a multidisciplinary team with the aim of an early recognition of eye, thyroid, liver and lung toxicities, thus preventing more serious complications.

Keywords Amiodarone · Liver injury · Optic disk edema · Optic neuropathy · Pancytopenia · Pulmonary toxicity · Thyroid dysfunction · Verticillate keratopathy

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Introduction

Amiodarone (AMD) is an iodine-rich benzofuran derivative, class III anti-arrhythmic agent that is largely employed for the prevention and treatment of potentially life-threatening supraventricular and ventricular tachyarrhythmias [1]. It acts by slowing the conduction rate and prolonging the refractory period of the sino-atrial and atrioventricular nodes [2]. Its excretion is mainly via the liver and the bile duct, and its average half-life is 58 days with a range from 25 to 100 days [3]. AMD has a pharmacologic profile characterized by the large volume of distribution and high tissue affinity. Because of its highly lipophilic properties, prolonged half-life and prevalent biliary excretion, several potentially severe AMD-associated side effects have been described [4–6]. They can involve a single organ or two or more organs in variable combinations, their prevalence being approximately 15% in the first year of drug intake but as high as 50% in the aged patients who assume AMD at higher doses (≥ 400 mg daily) and/or for a longer time [1]. However, adverse events have also been reported with maintenance, low-dose regimens [7–9].

Clinical manifestations of toxicity encompass (but are not limited to) pro-arrhythmia effects such as sinus bradycardia below 60 beats per minute and atrioventricular conduction disturbances [10], thyroid dysfunctions such as hypothyroidism and less frequently thyrotoxicosis [11], interstitial pneumonitis, hypersensitivity pneumonitis, organizing pneumonia, or acute respiratory distress syndrome [12], transient elevation of transaminases or severe acute hepatitis [13], blue-gray cutaneous discoloration or photosensitivity [14], neutropenia [15] or thrombocytopenia [16], neuromyopathy [17] and neuropsychiatric disorders [18]. Because AMD distributes pharmacologically to virtually all body organs, it is not surprising that an additional target of its potential multiorgan toxicity is the eye. Overall, subjective visual disorders have been reported to range widely from 2 to 40% of the patients [19], but corneal microdeposits that can be detected in most of them are infrequently associated with visual impairment. Thus, ocular toxicity has been underreported and challenging to diagnose until the visual loss becomes severe and bilateral [20, 21]. In addition, patients on AMD are not commonly advised to undergo regular ophthalmologic check-ups.

In the following, we summarize the AMD-associated ophthalmologic and non-ophthalmologic adverse effects observed in a longitudinal cohort of patients who were diagnosed and followed-up at tertiary referral centers of the University of Bari, Italy, with specific experience in ophthalmology and internal medicine. Furthermore, this study addresses a specific gap in the existing body of evidence, namely to what extent the observed adverse effects were reversible upon discontinuation of AMD.

Material and methods

This was a cross-sectional observational study of 17 Caucasian patients, whose medical records were obtained from a computerized database. Because of its retrospective nature, every efforts were made to minimize bias in patient selection or data interpretation. Inclusion criteria were as follows: (a) patients enrolled from February 2013 to July 2022, hospitalized one or more times in the Arrhythmia Department of the University of Bari with different types of tachyarrhythmias before being admitted to the Department of Internal Medicine of the same University; (b) loading plus maintenance duration of AMD treatment for at least 6 months; (c) independently of the occurrence or the absence of extraocular signs and symptoms, patients complaining of visual disturbances of variable severity, referred to the University's Department of Ophthalmology and Neuroscience. Exclusion criteria were as follows: (a) patients who had previously experienced single-lateral or bilateral ocular trauma or had undergone intraocular surgery; (b) patients with concomitant diseases of the anterior segment, retina or optic nerve; (c) patients taking warfarin or apixaban because AMD has been shown to enhance their anticoagulant effect, that could result in major bleeding and thromboembolic events [22]; (d) patients taking digoxin whose steady-state concentration may be increased by AMD, thus causing digitalis toxicity [23].

At diagnosis, each patient underwent complete clinical and laboratory assessments, performed according to a standard protocol. In particular, the following data were collected: established coronary artery disease, chronic heart failure, arterial hypertension, diabetes mellitus, hyperlipidemia, transient ischemic attack, peripheral and pulmonary thromboembolism, liver function abnormalities, glomerular filtration rate, thyroid function tests (fT4, TSH) as well as previous hospitalizations and medication history. All patients were followed-up every 3–6 months, with a median follow-up time of 43 months (range 297).

A 12-lead electrocardiogram was performed in all patients before starting AMD administration, during the loading phase and approximately every 6 months throughout the maintenance period. In-hospital hemodynamic monitoring was also carried out with variable frequency. The length of AMD administration was established from the date of the first prescription to the end of follow-up. Fourteen patients were given AMD orally, at a loading daily dose of 600–1200 mg in the first 2–3 weeks, followed by a maintenance daily dose ranging from 200 to 400 mg, whereas the remaining 3 patients were initially treated with a loading

dose of three intravenous boluses of 150 mg AMD, followed by oral administration of 500 mg for 2 weeks and then sequential maintenance doses of 400 and 200 mg/day, that were further lowered to 100 mg whenever possible (Table 1).

A comprehensive ophthalmologic examination included intraocular pressure (IOP) by Goldmann applanation tonometry, a complete biomicroscopic assessment, ocular motility, visual field testing by automated, static white-on-white perimetry test, fluorescein or indocyanine green angiography, and optical coherence tomography. Best-corrected visual acuity (BCVA) was measured on the Snellen chart, and the patients were grouped according to the following grading system: grade I, 20/25 or better; grade II, 20/30–20/40; grade III, 20/50–20/160; grade IV, 20/200 or worse [24]. Additional ophthalmological tests were accomplished as required, at the time of diagnosis and at variable intervals during follow-up.

Grading of AMD keratopathy was established by slit-lamp biomicroscopy according to the 4-grade system proposed by Orlando et al., that has largely replaced the 3-stage system described by Kaplan & Cappaert [25] because it better reflects an orderly progression and more suitably correlates with the duration of AMD intake [26]. In grade I, golden-brown corneal microdeposits with a dusting-like appearance are present at the level of the lower pupillary margin. In grade II, the microdeposits show a linear pattern and tend to extend from the lower pupillary margin to the limbus. A verticillate, whorl-like, branching pattern of the golden-brown deposits characterizes grade III keratopathy, that can eventually progress to grade IV when the deposits assume the appearance of irregularly round clumps that may invade the visual axis.

Results

As shown in Table 1, our cohort of 17 patients consisted of 6 females (35.3%) and 11 males (64.7%), with a median age at presentation of 63 (range 34–84) years. The cardiological diagnoses that required the prescription of AMD were non-valvular atrial fibrillation in 10 patients (58.8%), atrial flutter in 3 patients (17.6%), supraventricular tachycardia and ventricular tachycardia in 2 patients each (11.8%). As mentioned above, except for 3 patients (number 5, 6 and 10), who initially received 3 intravenous boluses of AMD 150 mg, the route of administration was oral. The loading

Table 1 Baseline patient characteristics

Patient number	Sex. Age (yrs)	Cardiovascular diagnosis	Amiodarone		
			Loading oral dose (mg/day × 2–3 weeks)	Maintenance oral dose (mg/day)	Total duration of administration (months)
1	F, 61	SVT, arterial hypertension	600	200	15
2	M, 59	NVAF, ischemic heart disease	600	200	7
3	M, 70	NVAF	700	200	22
4	M, 34	NVAF, arterial hypertension	1200 → 800	400 → 200	13
5	F, 69	NVAF, previous myocardial infarction	500*	200 → 100	8
6	M, 77	NVAF	500*	200	33
7	M, 83	AFL, abdominal aortic aneurysm	600	200	26
8	M, 54	SVT, arterial hypertension	600	400 → 200	10
9	F, 58	mVT	600	300	38
10	F, 73	AFL, arterial hypertension	500*	400 → 100 → 200	18
11	M, 50	NVAF, coronary artery bypass	600	300	31
12	M, 84	NVAF, ischemic heart disease	700	200	28
13	M, 55	VT	1200	200	9
14	F, 63	AFL	600	200	19
15	M, 63	NVAF	600	200	27
16	M, 74	NVAF, previous myocardial infarction	500	200 → 100	23
17	F, 55	NVAF	700	300	33

The cohort included 6 females and 11 males with atrial or ventricular arrhythmias and a median age of 63 years (range 34–84). The loading mean daily dose was 647 mg, followed by a maintenance mean daily dose of 276.5 mg for a median total (loading + maintenance) duration of amiodarone intake of 22 months (range 7–38 months)

AFL, atrial flutter; mVT, monomorphic ventricular tachycardia; NVAF, non-valvular atrial fibrillation; SVT, supraventricular tachycardia; VT, ventricular tachycardia

*Preceded by 3 intravenous boluses of amiodarone 150 mg

mean daily dose was 647 mg for 2 or 3 weeks, followed by a maintenance mean daily dose of 276.5 mg for a median total (loading + maintenance) duration of AMD intake of 22 months (range 7–38 months).

At diagnosis, ocular symptomatology was largely variable and included lasting photophobia, colored rings around lights, blurred vision, eye redness and deterioration of visual acuity (Table 2). The BCVA reflecting the severity of the ocular impairment was 20/40 or worse in 28 of 34 eyes (82.3%). Unilateral, mildly increased IOP was detected in 5 patients (numbers 1, 4, 5, 8, 9) who were treated with topical carbonic anhydrase inhibitor brinzolamide for 1–3 weeks, whereas patient number 16 with bilateral increased IOP was given, in addition to topical brinzolamide, oral acetazolamide 250 mg daily for a month.

As expected, AMD keratopathy with the appearance of bilateral verticillate keratopathy (B-VK) was diagnosed by slit-lamp biomicroscopy in all patients, including 2 patients in whom VK was associated with subcapsular cataract (number 4) and dry eye syndrome (number 7). The most advanced grade 4 VK was detected in patients 9, 11 and 17 who, compared with the remaining 14 patients, received a higher maintenance dose of AMD (300 mg daily) for a longer time (38, 31 and 33 months, respectively). Following the cardiological assessment that AMD cessation was not life-threatening, the drug was discontinued, and the patients were checked after a mean of 94 days (range 70–122 days). Slit-lamp biomicroscopy showed clear corneas in 13 patients and persistent, stage 1 or 2

VK in 4 patients. At last follow-up, BCVA was found to be unchanged in 13 eyes (38.2%) and improved in 21 eyes (61.8%). A good visual outcome (20/40 or better) was found in 29 of 34 eyes (85.3%).

B-VK associated with bilateral optic disk edema was diagnosed in 3 patients (17.6%) (Table 2). Patient number 1 complained of fleeting vision changes and a single episode of bilateral superior visual field amaurosis, protracted for a few minutes. The optic disk edema was mostly nasal and associated with splinter hemorrhages on the disk margin. Despite AMD cessation, the edema was reduced but still detectable 3 months later, leaving a BCVA of 20/30 OD and 20/40 OS at last follow-up. Patient number 8, who had only taken AMD for 10 months, underwent repeated ophthalmologic checks because of decreased vision and persistent

Table 2 Amiodarone-induced ocular adverse events in the patients being studied

Patient number	Subjective ocular symptoms	Ophthalmological diagnosis	IOP OD-OS (mmHg)	BCVA At diagnosis		BCVA At last follow-up	
				OD	OS	OD	OS
1	Fleeting vision changes	B-VK stage 2 and B-ODE	18–22	20/40	20/50	20/30	20/40
2	Mild, though lasting photophobia	B-VK stage 2	14–13	20/40	20/40	20/40	20/40
3	Slight visual deficit	B-VK stage 2 (OD), stage 1 (OS)	13–14	20/60	20/40	20/30	20/20
4	Blurred vision and progressive glare	B-VK and anterior subcapsular cataract	19–23	20/40	20/80	20/20	20/40
5	Blurred vision	B-VK stage 2	22–20	20/40	20/40	20/30	20/30
6	Blurred vision, halos	B-VK stage 2	14–18	20/80	20/80	20/40	20/60
7	Glare and dryness of OU	B-VK stage 2 and dry eye syndrome	15–15	20/30	20/25	20/30	20/25
8	Persistent photophobia	B-VK stage 3 and B-ODE	13–22	20/70	20/50	20/40	20/30
9	Photophobia, blue halos surrounding lights	B-VK stage 4	23–19	20/80	20/60	20/40	20/40
10	Eye redness	B-VK stage 3	14–14	20/80	20/50	20/80	20/50
11	Persistent glare	B-VK stage 3 (OD), stage 4 (OS)	16–14	20/40	20/40	20/30	20/30
12	Colored rings around lights	B-VK stage 2	12–13	20/30	20/30	20/30	20/30
13	Haloes around lights	B-VK stage 1	18–14	20/20	20/25	20/20	20/25
14	Remarkable photosensitivity	B-VK stage 2	15–18	20/60	20/40	20/40	20/40
15	Moderate visual deficit	B-VK stage 2; B-ODE OS > OD	13–14	20/40	20/60	20/25	20/40
16	Bilateral, insidious onset, progressive visual loss	B-VK stage 3; optic neuropathy with protracted B-ODE	23–25	20/80	CF	20/50	20/400
17	Minimal, persistent glare	B-VK stage 4	15–15	20/40	20/40	20/40	20/40

Bilateral verticillate keratopathy, diagnosed in all patients, was associated with optic disk edema in 3 patients, and both optic neuropathy and optic disk edema in 1 patient. Unilateral or bilateral, mildly increased IOP was detected in 6 patients. At diagnosis, the BCVA was 20/40 or worse in 28 of 34 eyes, whereas at last follow-up, it was unchanged in 13 eyes and improved in 21 eyes, with a good visual outcome (20/40 or better) in 29 of 34 eyes

BCVA, best corrected visual acuity (Snellen eye chart); B-ODE, bilateral optic disk edema; B-VK, bilateral verticillate keratopathy; CF, counting fingers; IOP, intraocular pressure (normal values: 10–21 mmHg); OD, right eye; OS, left eye; OU, both eyes

photophobia. Fundoscopy showed mild vitreous haze, pale optic disk and macular edema. AMD discontinuation resulted in a remarkable reduction of the optic disk edema and slow improvement of the visual acuity from 20/70 OD and 20/50 OS at diagnosis to 20/40 OD and 20/30 OS at last follow-up. Patient number 15 was assessed because of a gradual vision loss with flickering sight. The left eye showed moderate optic disk swelling and a faint optic disk hemorrhage, whereas fundus examination of the fellow eye was unremarkable. However, almost two months later the loss of vision extended to the right eye. A thorough ophthalmologic examination revealed a moderate optic disk swelling in both eyes, a centro-cecal scotoma of the visual field in OS, and a BCVA of 20/40 OD and 20/60 OS. AMD was discontinued and replaced with flecainide. At last follow-up, optic disk edema had largely subsided, and an improvement of the visual acuity was recorded (20/25 OD and 20/40 OS).

In addition to B-VK stage 3, optic neuropathy with protracted disk edema was diagnosed in patient number 16 (5.9%) who reported bilateral, insidious onset and progressive visual loss that occurred 23 months after starting AMD therapy. His visual acuity was 20/80 OD and counting fingers OS with an altitudinal defect on Goldmann perimetry that was total in OS and limited to the inferior field in OD. Both disks were crowded and lacked the physiological cup. A moderate, bilateral increase in the thickness of optic nerve fibers, prevalent on the left papilla, was detected by spectral domain optic coherence tomography. A clinical diagnosis of AMD-induced optic neuropathy was entertained, and the drug was stopped. When the patient was re-examined 54 days later, disk edema was found to be reduced in both eyes, though to a much lower degree in OS, and BCVA was partially improved to 20/50 OD and 20/400 OS. The altitudinal field defects were considered largely unmodified at last follow-up.

Although the relatively small number of patients enrolled in this study prevented the achievement of statistically significant conclusions, no correlations were found between the overall visual outcome and demographic or comorbidity features.

Additional extra-cardiovascular and extra-ocular manifestations were identified in 11 patients (Table 3). Prior to starting treatment with AMD, patients numbers 3, 6, 13, 14 and 15 were diagnosed with recent-onset type-2 diabetes mellitus, gouty arthritis, class-2 obesity, previous mastectomy for breast cancer and polycystic kidney disease, respectively. On the contrary, the clinical diagnoses for the other 6 patients were made after they received AMD for a variable period, thus suggesting that they could be ascribed to the drug toxicity. Below is a brief overview of their clinical traits.

Patients number 1 and 12 complained of mild weakness, fatigue and persistent feeling of cold. fT4 levels were 0.5 and 0.3 ng/mL, respectively (normal range: 0.7–2.2 ng/mL); conversely TSH levels were 7.2 and 9.2 IU/mL (normal range: 0.5–4 IU/mL). Both patients were diagnosed with subclinical or poorly symptomatic hypothyroidism.

Table 3 Before starting amiodarone, extra-cardiovascular and extra-ocular diseases were diagnosed in 5 patients

Patient number	At diagnosis	During follow-up
1	None	Hypothyroidism
2	None	None
3	Recent-onset type-2 diabetes mellitus	None
4	None	None
5	None	Pancytopenia
6	Gouty arthritis	None
7	None	None
8	None	None
9	None	Cholestatic liver injury
10	None	Myxedema
11	None	None
12	None	Hypothyroidism
13	Class-2 obesity	None
14	Left mastectomy for breast cancer	None
15	Polycystic kidney disease	None
16	None	None
17	None	Interstitial lung disease and subclinical hypothyroidism

At variable time intervals (7–27 months) from the beginning of amiodarone therapy, a thyroid dysfunction was detected in 4 patients, in one of them associated with interstitial lung disease, and pancytopenia and cholestatic liver injury were found in 1 patient each

Patient number 10 showed a similar but more remarkable clinical picture that included weight gain, fatigue, cold intolerance, scanty hair, constipation and non-pitting edema of the lower extremities. fT4 and TSH levels were 0.3 ng/mL and 15.6 IU/mL, respectively. A diagnosis of myxedema was entertained, and the daily dosage of AMD was initially reduced to 100 mg with substantial improvement of the clinical and laboratory features, but 3 months later AMD was discontinued. Anti-thyroglobulin and anti-thyroid peroxidase antibodies tested positive at high titers. In all 3 patients thyroid hormone replacement was started with low daily doses (25–50 µg) of levothyroxine, that were gradually modified with the aim of keeping TSH levels at the upper limit of the normal reference values. The hormonal status was checked every 5–6 months and the dosage of levothyroxine properly adjusted. An isolated, slight increase of TSH levels was repeatedly detected in patient number 17 that will be discussed below.

Patient number 9, a 58-year-old woman with monomorphic ventricular tachycardia, was taking a maintenance oral dose of 300 mg AMD for over 3 years when she was found to have abnormal liver tests compatible with cholestatic liver injury. Alcohol consumption and injection drug abuse were excluded. Vital signs were within the normal range. Physical findings were normal. Laboratory tests showed total bilirubin, 1.9 mg/dL (normal values [nv]: 0.7–1.1 mg/dL); aspartate aminotransferase, 160 U/L (nv: 19–35 U/L); alanine aminotransferase, 174 U/L (nv: 7–45 U/L); γ-glutamyl transpeptidase, 105 U/L (nv: 6–29 U/L) and negative tests for hepatitis A, B and C. Anti-nuclear, anti-liver kidney microsome (LKM) and anti-mitochondrial antibodies were not detected. The serum concentration of AMD was found to be 1012 ng/mL (therapeutic range: 500–1000 ng/mL). The patient was diagnosed with AMD-induced hepatotoxicity and the drug was discontinued. Two weeks later, a liver biopsy showed moderate fibrosis and steatosis as well as several Mallory bodies in the periportal area. The liver enzymes gradually decreased and returned to normal after about three months, but AMD was not resumed.

Patient number 5 with non-valvular atrial fibrillation and previous non-ST-elevation myocardial infarction was found to have a moderate pancytopenia (hemoglobin, 10.1 g/dL with a normal MCV; white blood cells, $3.2 10^9$/L; absolute neutrophils, 1.38 10^9/L; platelets, 6910^9/L) and persistent myalgias associated with a moderate increase in serum creatine kinase. On physical examination, neither splenomegaly nor lymphadenopathy was detected. A peripheral blood smear was negative, and a total body computed tomography (CT) was unremarkable. In addition to normal trilineage hematopoiesis, a bone marrow biopsy unexpectedly revealed multiple non-caseating granulomas. Infectious causes, autoimmune disorders and sarcoidosis were ruled out. Mindful of the possibility that AMD is a possible, though uncommon cause of iatrogenic cytopenia [27–29], the drug (that the patient had taken for 8 months) was discontinued and simvastatin (20 mg daily) was replaced by rosuvastatin (10 mg daily) that is not cleared by the hepatic cytochrome 450 enzyme system. All other medications were unchanged. Two months later, blood cell counts were improved but still partially reduced. At the last outpatient follow-up (133 days after AMD discontinuation) blood cell counts were fully restored (hemoglobin 12.9 g/dL; white blood cells 6.510^9/L; absolute neutrophils, 3.6910^9/L; platelets, 15710^9/L).

Patient number 17, who smoked a pack a day for almost 10 years in her thirties but quit following smoking cessation counseling, complained of non-productive mostly nocturnal cough, shortness of breath and moderate weight loss. Home medications included a combination of perindopril, indapamide and amlodipine to control her refractory arterial hypertension. In addition to non-valvular atrial fibrillation, physical examination revealed scanty bilateral rhonchi, a pulse oximetry of 94% and no malleolar edema. Flexible bronchoscopy showed a mildly inflamed mucosa but bronchoalveolar fluid tested negative for a large spectrum of infectious agents and was found to contain a small number of cytotoxic T-lymphocytes. Several blood and sputum cultures also provided consistently negative results. Following a chest X-ray that revealed micronodular opacities more evident in the lower lobes, a high-resolution CT showed remarkable bilateral ground-glass opacities with honeycombing, typical of interstitial lung disease. AMD-induced interstitial pneumonitis was diagnosed and, following the cardiological consultation, the drug was permanently discontinued. The patient was given oral prednisone at a daily dose of 0.5 mg/kg body weight for 3 weeks, that was then slowly tapered to a maintenance daily dose of 5 mg. Four months later, the patient reported a remarkable improvement of her subjective symptoms and the control high-resolution CT at the same level of the previous lesions revealed the almost total disappearance of the parenchymal abnormalities. This patient also had a subclinical hypothyroidism, suggested by a slight increase of TSH (4.7 and 5.1 IU/mL on 2 occasions 3 months apart).

Discussion

AMD is one of the most effective and most frequently prescribed anti-arrhythmic drugs for the treatment of recurrent and potentially life-threatening atrial and ventricular arrhythmias. However, it may be associated with an array of adverse events, that are often undiagnosed due to their mild nature. Because VK does not usually cause visual loss, most patients do not complain of ophthalmologic symptoms, and this explains why it took 9 years to collect the 17 patients included in the present study. The North American Society

for Pacing and Electrophysiology recommends, in addition to cardiac evaluation, close monitoring of thyroid, liver and respiratory function tests, chest x-ray as well as ophthalmic, neurologic and dermatologic evaluation before and during AMD treatment [30]. Even so, a poor adherence to recommended clinical guidelines for monitoring AMD adverse reactions has been repeatedly reported [31, 32]. None of our 17 patients adhered to these guidelines and the characteristic common to all of them was the onset of ocular disturbances of variable severity associated with the protracted intake of AMD. No additional, potential confounders or underlying conditions that might have influenced the interpretation of adverse effects were detected. The multiorgan toxicity of this medication is usually related to a high cumulative dose as well as to the drug bioavailability, individual predisposition, advanced age and concomitant diseases such as hypertension, diabetes, dyslipidemia and lung function impairment [21, 33, 34].

In accordance with literature data [35–37], corneal microdeposits were the most common sign of ophthalmologic toxicity. They formed golden-brown vortex-like figures invisible to naked eye but easily detectable by slit-lamp biomicroscopy and were responsible for bluish halo symptoms and mildly impaired visual acuity. As expected from the experience described in previous reports [25, 26], the most advanced stage 4 VK was detected in patients 9, 11 and 17 who were given AMD at higher doses and for a longer time (Table 1). But bilateral VK was detected also in our patient 2, who was given a loading oral dose of 600 mg AMD for 3 weeks followed by a maintenance oral dose of 200 mg for a total duration of 7 months. In a systematic review of 25 case reports, ocular adverse effects of variable severity were detected in patients receiving a daily dose of AMD ranging from 200 to 1200 mg for a period of 2 months to 6 years [37]. Drug discontinuation in our patients resulted in disappearance of VK and remarkable improvements of optic disk edema and optic neuropathy at varying times during follow-up.

It is important to emphasize that AMD-induced VK is indistinguishable from that observed in patients with autoimmune diseases who assume hydroxychloroquine [38] or in those with Fabry's disease, an X-linked lysosomal storage disorder characterized by the gradual accumulation of glycosphingolipids in several eye tissues, including the corneal epithelium [39]. Similarly, AMD keratopathy has been defined by D'Amico et al. [40] as a drug-induced lipid storage disease following their observation on the light and transmission electron microscopy of complex lipid deposits within lysosome-like intra-cytoplasmic inclusions in corneal, conjunctival, and lens epithelium of a patient who was treated with 600 mg/day of AMD for 14 weeks.

AMD-induced optic neuropathy has been reported in approximately 1% of the patients [30], but it is still a matter of debate whether this severe complication (diagnosed in our patient number 16) may be caused by a lengthy administration of AMD that would result in retinal toxicity. The major reasons of this uncertainty are: (a) the close similarity of the clinical features between AMD-induced optic neuropathy and non-arteritic anterior ischemic optic neuropathy (AION); (b) the equally similar fundoscopic pictures of AMD neuropathy and AION; (c) the fact that patients in need of AMD therapy are those with severe cardiovascular diseases and/or co-morbidities such as hypertension, diabetes, dyslipidemia and current smokers, who are also at high risk of developing AION [33, 41, 42].

The actual and distinctive characteristics of AMD-induced optic neuropathy have not been clearly established because in a randomized controlled trial it would be ethically unacceptable to deprive the patients assigned to the control arm of the necessary medication. However, slow and insidious onset, progression over months, more frequently bilateral involvement, and protracted disk edema are considered the distinguishing features of AMD-induced optic neuropathy. On the contrary, patients with non-arteritic AION usually show acute or subacute clinical course, unilateral visual loss that is complete at diagnosis and in whom disk edema resolves over weeks [43]. An attempt to overcome these diagnostic difficulties has been made by Chen & Hedges [41], who proposed to classify the patients into three categories: (1) Likely AMD optic neuropathy; (2) likely non-arteritic AION; (3) non-arteritic AION exacerbated by AMD. Based on this classification, our patient number 16 should be best assigned to the category "likely non-arteritic AION". Using a different approach based on temporal features and optic nerve appearance, AMD-induced optic neuropathy has been classified into the following 5 clinical categories with progressively decreasing frequency: insidious onset (43%), acute onset (28%), retrobulbar (13%), increased intracranial pressure (8%) and delayed-progressive onset (8%) [44].

AMD-induced thyroid dysfunction is more frequently diagnosed as hypothyroidism (422%) and less often as thyrotoxicosis (2–12%) [30, 45–47]. Because our patients were all from areas with a normal iodine uptake, subclinical or clinically overt hypothyroidism were the only AMD-induced thyroid dysfunction observed in 4 of our patients (Table 3). AMD was discontinued and the low fT4 levels were easily corrected with a suitable dosage of L-thyroxine. On the contrary, AMD-associated thyrotoxicosis is more commonly diagnosed in areas with low iodine uptake and can be of type-1 when it develops on an underlying and pre-existing nodular or autoimmune thyroid disease, and of type-2 when it affects a previously normal thyroid gland [48]. The high iodine content of AMD, much higher than the daily iodine demand, accounts for the frequent detection of AMD-induced thyroid dysfunction.

Cholestatic liver injury was diagnosed incidentally in patient number 9 who had been taking AMD for 38 months. Although she was asymptomatic, her serum levels of alanine aminotransferase, aspartate aminotransferase and γ-glutamyl transpeptidase were over 3 times the upper limits of the normal range, thus requiring drug cessation. Previous studies have consistently shown that AMD-induced hepatotoxicity can be detected in a largely variable percentage of asymptomatic patients ranging from 14 to 82%, whereas a symptomatic, hepatitis-like clinical picture has been reported in 1–3% of patients [19, 49, 50]. The possible cause of liver involvement is the lipophilic property of AMD, that can enhance its tendency to accumulate in organs rich in adipose tissue such as the liver [19]. When a liver biopsy was performed, as happened in our patient, hepatic phospholipidosis, bridging fibrosis, steatosis and pseudo-alcoholic liver changes were observed, including the presence of Mallory bodies and ballooning of hepatocytes [49, 51]. The presence of lamellar lysosomal inclusion bodies representing phospholipidosis have also been described on electron microscopy [52].

Clinically overt hematologic adverse events induced by AMD have been rarely reported. In addition to selective, though transient neutropenia [15], a higher risk of agranulocytosis has been observed in patients with AMD-induced thyrotoxicosis receiving methimazole and propylthiouracil as compared with patients with thyrotoxicosis related to other causes and treated with the same anti-thyroid drugs [29]. Thrombocytopenia has also been described as hematologic complication of AMD and its pathogenesis has been ascribed to immune-mediated platelet destruction following the occurrence of drug-induced antibodies to platelet glycoproteins [16]. Our patient number 5 developed moderate pancytopenia after 8 months of AMD intake. When a bone marrow biopsy was performed, multiple non-caseating granulomas were detected. After excluding other possible causes, AMD was withdrawn, and this resulted in improvement of the blood cell count that slowly returned to normal over a period of 4 months. A similar observation of AMD-induced bone marrow granulomas with secondary pancytopenia was reported by Erie et al. [28].

An additional, potentially severe and frequently missed complication of AMD is pulmonary toxicity, that has been diagnosed with a frequency largely variable from 2 [30] to 5–15% of patients [12], depending on the drug daily dose, the length of time the drug is taken, the patient's age, and the possible occurrence of pre-existing lung diseases. Like in our patient number 17, ground-glass infiltrates can be detected by CT, although other manifestations of pulmonary involvement such as interstitial pneumonitis, neoplastic-like nodules and fibrosis of variable extent have also been described [53, 54]. In addition to AMD discontinuation, corticosteroid treatment is required in more severe cases. A careful and timely assessment of clinical, biochemical, and radiographic features as well as function testing (spirometry, diffusing capacity measurement) is usually performed to exclude alternative diagnoses such as lung infections and heart failure.

It has been suggested that interstitial lung disease and possibly additional AMD-induced adverse reactions are immune-mediated, but the exact mechanism(s) underlying the impairment of the target organs is largely unknown. Experimental data support the hypothesis that oxidation of AMD by cytochrome P450 leads to reactive metabolites and production of factors such as heat shock protein-40 (HSP-40) that can activate inflammasomes and the immune system. In a minority of patients, this process would result in immune response and immune-mediate adverse events [55]. Because AMD-induced toxicity is to a large extent the consequence of the daily dose and the cumulative effect of AMD intake over time, prevention strategies include, whenever possible, dose reduction, drug cessation or shift to dronedarone in patients at risk because of pre-existing involvement of the most common target organs.

A comparison of our results with those of the literature should be taken with caution due to the different inclusion and exclusion criteria, the relatively small number of our cohort and the occurrence or absence of confounding factors. For example, the very low incidence (0.6%) of ocular adverse effects that Kim et al. [19] described while retrospectively screening 961 patients treated with AMD for arrhythmia is likely ascribable to its low average maintenance dose (227 mg daily). On the contrary, VK was detected in all our patients (who received a mean daily dose of 276.5 mg for a median total duration of AMD intake of 22 months) along with bilateral optic disk edema in 3 patients and optic neuropathy with protracted optic disk edema, anterior subcapsular cataract and dry eye syndrome in one patient each. These observations indirectly confirm that the dose and duration of AMD intake should be considered independent predictors for side effects. In addition, at variance from previous observations [14, 17, 18], none of our patients were diagnosed with photosensitivity or blue-gray cutaneous discoloration, neuromyopathy and neuropsychiatric disorders.

The following strengths of our study should be mentioned: (a) a comprehensive framing of the patients, jointly provided by the same internists and the same ophthalmologists throughout the study period; (b) the homogeneous collection of data as a consequence of a rewarding collaboration between the tertiary eye care and internal medicine centers of the same university hospital. However, the following limitations should also be acknowledged: (a) the small size of our cohort of patients, with consequent reduced power of the study and the impossibility to establish the actual prevalence of the different adverse events of AMD; (b) the retrospective nature and selection bias of a single-center study, which

inevitably resulted in insufficient control of all variables; (c) the balk to generalize our findings because of the small sample size and single-center design; (d) the relative shortness of follow-up after discontinuation of AMD, ranging from 3 to 11 months (median 7 months) that, keeping in mind the lipophilic nature of AMD and its long half-life, prevented a thorough assessment of the long-term evolution of ocular and extra-ocular involvement.

Conclusion

Patients treated with AMD should be fully aware of the risks related to its potential multiorgan toxicity and should undergo a multispecialty clinical surveillance and regular laboratory testing throughout the treatment period and for a few months after drug discontinuation. Each specialist clinician of the multidisciplinary team should provide a periodic (six-monthly) monitoring for the medical area of one's own competence, with a focus on a timely detection of the drug toxicity that would prevent the occurrence of more severe outcomes. Additional prospective studies are required to extend our findings and make recommendations for clinical practice.

Author contributions R.D. and F.D. conceived and designed the study, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the analysis. A.V., G.A., S.G., G.C. contributed to data collection, assembly, analysis and interpretation, and critically revised the manuscript for important intellectual content. All authors reviewed the manuscript, approved the draft submission, and accept responsibility for all aspects of this study.

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Data availability All the relevant data have been provided in the manuscript. Supplementary datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The corresponding author is Editor-in-Chief of this journal.

Ethics approval and informed consent statement All procedures were carried out in compliance with the ethical standards of the University of Bari and in accordance with the tenets of the 1964 Declaration of Helsinki and its later amendments. The ethical approval for the study was given by the ethics committee of the University of Bari Medical School. The need for written informed consent was waived by the ethics committee because of the retrospective nature of the study. No animal experiments were included in the study.

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