REVIEW ARTICLE

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Amiodarone
Review of Pulmonary Effects and Toxicity

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Abstract

Amiodarone, a bi-iodinated benzofuran derivative, is, because of its high effectiveness, one of the most widely used antiarrhythmic agents. However, adverse effects, especially potentially fatal and non-reversible acute and chronic pulmonary toxicity, continue to be observed. This review provides an update of the epidemiology, pathophysiology, clinical presentation, treatment and outcome of amiodarone pulmonary effects and toxicity. Lung adverse effects occur in approximately 5% of treated patients. The development of lung complications appears to be associated with older age, duration of treatment and cumulative dosage, high levels of its desethyl metabolite, history of cardiothoracic surgery and/or use of high oxygen mixtures, use of iodinated contrast media, and probably pre-existing lung disease as well as co-existing respiratory infections. Amiodarone-related adverse pulmonary effects may develop as early as from the first few days of treatment to several years later. The onset of pulmonary toxicity may be either insidious or rapidly progressive. Cough, new chest infiltrates in imaging studies and reduced lung diffusing capacity in the appropriate clinical setting of amiodarone use, after the meticulous exclusion of infection, malignancy and pulmonary oedema, are the cardinal clinical and laboratory elements for diagnosis. Pulmonary

involvement falls into two categories of different grades of clinical significance: (i) the ubiquitous 'lipoid pneumonia', the so-called 'amiodarone effect', which is usually asymptomatic; and (ii) the more appropriately named 'amiodarone toxicity', which includes several distinct clinical entities related to the differing patterns of lung inflammatory reaction, such as eosinophilic pneumonia, chronic organizing pneumonia, acute fibrinous organizing pneumonia, nodules or mass-like lesions, nonspecific interstitial pneumonia-like and idiopathic pulmonary fibrosis-like interstitial pneumonia, desquamative interstitial pneumonia, acute lung injury/acute respiratory distress syndrome (ARDS) and diffuse alveolar haemorrhage. Pleural/pericardial involvement may be observed. Three different and intertwined mechanisms of lung toxicity have been suggested: (i) a direct toxic effect; (ii) an immune-mediated mechanism; and (iii) the angiotensin enzyme system activation. Mortality ranges from 9% for those who develop chronic pneumonia to 50% for those who develop ARDS. Discontinuation of the drug, control of risk factors and, in the more severe cases, corticosteroids may be of therapeutic value. Supportive measures for supervening ARDS in the intensive care setting may become necessary.

1. Introduction and Historical Perspective

Amiodarone, because of its high level of effectiveness, is one of the most widely used antiarrhythmic agents, although amiodarone-related adverse effects, especially acute and chronic pulmonary drug toxicity, continue to be observed.[1] This review provides a thorough update of the epidemiology, risk factors, pharmacokinetics and pathophysiology of lung damage related to amiodarone use. It further describes the range of clinical manifestations as well as the role of the laboratory, imaging, pulmonary function tests, bronchoalveolar lavage (BAL) and biopsy in the documentation of the disease. Principles of treatment and clinical follow-up are discussed based on recent data concerning the prognosis and outcome of amiodarone pulmonary toxicity.

Amiodarone-related adverse pulmonary effects may develop as early as from the first 2 days of the initiation of treatment to several years after. Cough, new infiltrates in the chest radiographs and reduced lung diffusing capacity of carbon monoxide (DLCO) in the appropriate clinical setting of amiodarone use after the meticulous exclusion of infection, malignancy and pulmonary oedema are the cardinal clinical and laboratory elements for diagnosis. Reported pulmonary toxicities range from mild subacute airway, lung or pleural illness to rapidly progressive and fatal acute respiratory distress syndrome (ARDS) [table I].

Amiodarone, a bi-iodinated benzofuran derivative (contains 37% of iodine by weight) [figure 1] was introduced into clinical practice as an antianginal agent in 1962, and in 1967 was developed for the treatment of ventricular and supraventricular tachyarrhythmias, and proved highly effective.[2,3] Amiodarone is categorized as a class III antiarrhythmic agent (Vaughan-Williams classification), as it prolongs myocardial repolarization via potassium channel blockade. However, amiodarone also has numerous other effects, including actions that are similar to those of antiarrhythmic classes I, II and IV.[4] Specifically, amiodarone decreases conduction velocity by blocking sodium channels (class I effect), it antagonizes non-competitively α- and β-adrenergic receptors (class II effect), but also exerts a class IV antiarrhythmic effect by acting as a calcium channel blocker.[5] Amiodarone is currently approved for the treatment of life-threatening, recurrent ventricular arrhythmias, such as ventricular fibrillation or ventricular

Table I. Amiodarone-induced lung effects and toxicity

Acute airways and lung disease	Subacute/chronic lung disease	Pleural disease
Reversible narrowing of airways (bronchospasm)	Lipoid pneumonia	Pleural effusion (±pericardial effusion)
Bronchial asthma exacerbation	Chronic eosinophilic pneumonia (CEP)	Pleural thickening (±pericardial thickening)
Acute desquamative interstitial pneumonia (DIP)	Chronic organizing pneumonia (COP)	Drug-induced lupus (pleuropericarditis)
Acute lung injury (ALI)-acute respiratory distress syndrome (ARDS)	Acute fibrinous and organizing pneumonia (AFOP)	
Diffuse alveolar haemorrhage (DAH)	Pulmonary nodules or masses	
	Non-specific interstitial pneumonia (NSIP)-like	
	Interstitial pulmonary fibrosis (IPF)-like	

tachycardia, when these have not responded to documented adequate doses of other available antiarrhythmic drugs or when alternative agents could not be tolerated. Although amiodarone is not the drug of choice in the treatment of atrial fibrillation, it is the most commonly used drug for this purpose because of its superior efficacy over other agents for maintaining sinus rhythm.[6] Amiodarone prescriptions doubled between 1989 and 1994, and its use further increased subsequently.[7]

A decade after the first use of amiodarone in medicine, it became apparent that, apart from its therapeutic properties, the drug causes toxicity to organs such as the lungs,[8] gastrointestinal tract and liver, eyes, thyroid gland, skin, neuromuscular system and genitourinary tract, as well as the heart itself.[9-11] Amiodarone pneumonitis was described first in the early 1980s in the US,[8] although similar cases were also observed in Europe.[12] Complications of the respiratory system are currently identified as one of the most common forms of toxicity, and represent one of the leading reasons for discontinuation of the drug. Fatal complications of amiodarone include ARDS, pulmonary fibrosis, cirrhosis and bradycardia leading to cardiac arrest.

2. Epidemiology and Risk Factors

Amiodarone thyroid and ophthalmic adverse effects occur more often than lung toxicity. However, the latter is considered the most preoccupying adverse effect because of its non-reversible potential and fatal consequences.[5] The incidence of amiodarone lung toxicity varies greatly, based on the design of the studies describing it and the criteria used for its definition. Lung toxicity is mostly reported in adult populations worldwide.[7,13-16] In one of the few double-blind, placebo-controlled trials examining the efficacy of amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias, severe pulmonary fibrosis was encountered in 1.2% of patients receiving amiodarone in dosages of 300–800 mg/day compared with 0.9% in the control group.[17] The incidence of lung toxicity increases in other studies when it is defined as the development of cough, fever, dyspnoea and/or pleuritic chest pain in combination with new radiographic findings in patients without evidence of congestive heart failure, infectious disease or malignancy that subside with drug withdrawal, and ranges from 4.2% to 17%.[7,13,18,19]

Age is one of the most important risk factors for amiodarone-induced pulmonary side effects,

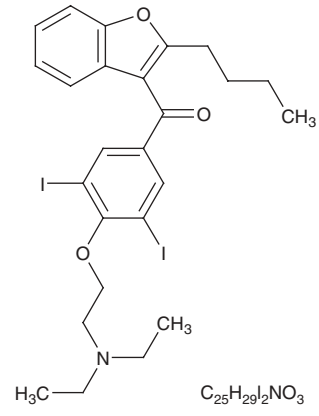

Fig. 1. Chemical structure and molecular formula of amiodarone.

with older patients being more susceptible.[13,18,20] Indeed, amiodarone pulmonary toxicity increases 3-fold for every 10 years of age in patients aged >60 years compared with those aged <60 years.[7] More specifically, lung function changes, especially DLCO, are shown to have a significantly accelerated decline in elderly patients.[21]

Other significant risk factors for amiodarone lung toxicity are related to duration and intensity of amiodarone treatment. More specifically, patients who receive amiodarone for 6–12 months present the highest risk.[7,18] According to recent data, the cumulative incidence of amiodarone lung toxicity increases from 4.2% to 7.8% and 10.6% at 1, 3 and 5 years of use, respectively.[13] The maintenance and cumulative doses of amiodarone are considered independent risk factors for lung toxicity. It is shown that amiodarone maintenance dosages higher than 500 mg/day are more toxic than dosages lower than 300 mg/day, although pulmonary toxicity may develop even at 200 mg/day.[13,22] A cumulative dose above 10 g up to 150 g increases *per se* the risk for pulmonary toxicity,[7,23,24] as well as plasma levels of its desethyl metabolite during maintenance therapy.[13,18]

In the 1990s, cardiothoracic surgery and high concentrations of oxygen (high inspiratory fraction of inhaled oxygen [FiO_2]) delivered to patients under amiodarone treatment perioperatively emerged as potent risk factors for acute amiodarone lung toxicity. ARDS developed with significant related morbidity and mortality in certain cases.[23] Based on these observations, the cautious use of amiodarone was established in the intensive care unit.[23,25-28] A critical question in amiodarone use is whether pre-existing lung disease is an independent risk factor for lung toxicity. This issue has not been clearly addressed until now, with large prospective trials showing that in survivors at 1 year of amiodarone treatment there is a slight but significant difference in DLCO measurements between all patients and patients with a history of chronic obstructive pulmonary disease (COPD). However, no difference between the two groups is encountered for noncardiac mortality, and an abnormal baseline DLCO (<60% of predicted) with or without an initial abnormal chest radiograph does not seem to predispose to pulmonary toxicity.[15,18,19] These findings are in accordance with more recent observations that pretreatment DLCO is not an independent risk factor for amiodarone lung toxicity, at least for DLCO levels >45%. Patients with DLCO levels lower than these values are excluded from the studies, therefore firm conclusions cannot be reached.[13] In the AFFIRM (Atrial Fibrillation Follow-up of Rhythm Management) study, pre-existing pulmonary disease was associated with a higher risk of diagnosed amiodarone pulmonary toxicity but did not increase pulmonary death and all-cause mortality rates. Therefore, cautious use of amiodarone to treat atrial fibrillation is considered acceptable in elderly patients with atrial fibrillation, even if pre-existing pulmonary disease is present.[29]

Although amiodarone lung toxicity-related mortality causes great concern in everyday clinical practice, it is rarely reported in prospective trials, ranging from 9%[18] to up to 50%[23] when ARDS develops. Despite the efforts to uncover the mechanisms of amiodarone-induced lung toxicity, no drugs that could prevent its development have been described. The only encouraging results, based on previous experimental observations,[30-32] are those of two study groups examining retrospectively the role of ACE inhibitors and angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) in patients receiving amiodarone treatment. Both concluded that angiotensin II induced by chronic heart failure seems to increase the risk of amiodarone lung toxicity and that amiodarone lung toxicity is less common in patients treated with either ACE inhibitors or ARBs.[13,33,34]

3. Pharmacokinetics and Pathophysiology of Lung Damage

Through its lipophilic moiety, amiodarone (figure 1) concentrates in organs with high lipid content such as adipose tissue, thyroid, liver and lungs.[35] However, at the other end of the molecule is a slightly cationic *N*-diethyl amino side chain (hydrophilic end), which confers amphiphilic

properties. Furthermore, amiodarone is metabolized to N-desethylamiodarone, an even more polar compound, by two cytochrome P450 (CYP) enzymes; CYP2C8 in the liver and CYP3A4 isoenzyme in the liver and intestines. The metabolite penetrates into tissues, including the lungs, approximately five times more than the original molecule, acting as a sustained release reservoir, and may unpredictably increase serum concentrations. Lung parenchymal concentrations of amiodarone may significantly exceed even those of the heart, especially if administered intravenously.[36] The extensive tissue binding of amiodarone results in a pharmacokinetic profile with a high volume of drug distribution ($V_d = 5000$ L) and an extremely long elimination half-life ($t_{½} = 30–108$ days). These characteristics explain why both the therapeutic and toxic effects of the drug do not remit immediately after discontinuation of treatment, and why complications involving any organ, including the lungs, resulting from amiodarone administration may occur days to months after initiation of treatment or at any time during treatment, even months after cessation of drug administration.[37-39] A dose or treatment duration 'threshold' to avoid toxicity from amiodarone has not been established.

Amiodarone, as an amphiphilic cationic compound, interferes with the movement of phospholipids across intracellular membranes and inhibits phospholipid catabolism through its potent inhibitory effect on lysosomal phospholipase.[40] This effect leads to the accumulation of high concentrations of phospholipid-bound drug in membrane-rich structures such as macrophage lysosomes (lamellar inclusions on electron microscope) [figure 2a].[41] Similar laminated ultrastructural inclusions are found in phospholipidosis induced by other amphiphilic drugs[42] and in hereditary lysosomal storage disease, including Niemann-Pick disease and Fabry disease.[43] Drug-induced phospholipidosis assumes the form of a 'foamy cell' response, e.g. lipid accumulation mainly in histiocytic cell lines (lipid-laden macrophages and related cells) in various organs. In the lungs, structural cells such as type II pneumocytes (figure 2b) and endothelial cells as well as other interstitial and intra-alveolar inflammatory cells can be involved; this constitutes a type of storage lung disorder referred to as 'lipoid pneumonia'.[44]

In the lungs this phospholipidosis may produce two effects of different grades of physiological and clinical significance. First, the above-mentioned lipoid pneumonia – where the foamy cells by occupying space both intra-alveolarly and interstitially may solely reduce effective surface for gas exchange – does not usually cause symptoms in the patient with high-reserve normal lungs and can be detected only by a moderate and progressive reduction of DLCO. This represents the so-called 'amiodarone effect' on the lungs (table I; figure 3).[45] The second effect includes several distinct clinical entities related to the differing patterns of inflammatory lung reaction (tissue damage) to its presence, appropriately called 'amiodarone toxicity', which may be clinically expressed as chronic eosinophilic pneumonia (CEP), chronic organizing pneumonia (COP) [formerly called bronchiolitis obliterans organizing pneumonia (BOOP)], acute fibrinous and organizing pneumonia (AFOP), nodules or mass-like lesions (amiodaronoma), non-specific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis (IPF)-like interstitial pneumonia, desquamative interstitial pneumonia (DIP), acute lung injury (ALI)/ARDS and diffuse alveolar haemorrhage (DAH) [table I]. Rarely, pleural/pericardial disease may be observed (table I). Other furan derivatives such as nitrofurantoin and bleomycin may induce similar patterns of lung tissue damage.[46-48]

Amiodarone toxicity is probably related to a combination of different mechanisms: (i) a 'cytotoxic' effect to type II pneumocytes, as well as other cells of the lung parenchyma, such as inflammatory cells, endothelial cells and fibroblasts; (ii) an 'immune'-mediated mechanism in genetically predisposed patients;[49] and (iii) the activation of the angiotensin enzyme system.[31-34] The toxic mechanism leads to the disruption of the lysosomal membranes by amiodarone molecules through protein C activation and the subsequent release of toxic oxygen radicals, which may induce activation of the pathways of

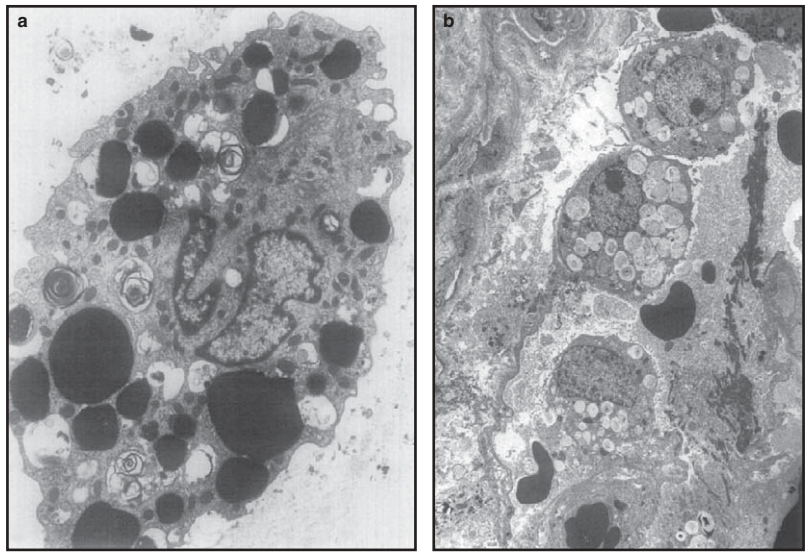

Fig. 2. (**a**) Ultrastructural features of macrophage recovered from bronchoalveolar lavage fluid. The cytoplasm contains abundant lipid and occasionally lamellated inclusions (Electron Microscope [EM] ×8000). (**b**) Distal air space in amiodarone toxicity. The cytoplasm of type II pneumocyte contains myelinoid inclusions difficult to distinguish from its proper lamellar bodies. Note hyaline membrane alongside the alveolar wall (EM ×6600) [reproduced from Bedrossian et al.,[44] with permission from Elsevier].

caspase and lead to the apoptosis of lung epithelial cells.[50] An additional mechanism relates to the reduced deactivation of toxic metabolites of the drug.[51,52] Furthermore, *in vitro* studies of the last decade both in primary cultures of rat type II pneumocytes and in the human A549 alveolar epithelial cell line have shown that amiodarone induces alveolar epithelial cell (AEC) apoptosis abrogated by antagonists of angiotensin II. Amiodarone is found to upregulate angiotensinogen messenger RNA and protein in primary cell cultures mediated by activation protein-1 family transcription factors.[30-32] Angiotensin II is generally increased in chronic heart failure patients. A number of experiments have shown that angiotensin II enhances amiodarone-induced apoptosis of AECs.[33] In a rat bleomycin-induced model of pulmonary fibrosis, angiotensin II is shown to promote fibrosis through stimulation of angiotensin II type 1 receptor and transforming growth factor-β_1.[53] Apoptosis of AECs plays an important role in the development of acute lung injury and fibrosis characteristic of cryptogenic organizing pneumonia, acute respiratory distress syndrome and other pulmonary inflammatory and fibrotic syndromes.[54] Furthermore, epithelial cell apoptosis is a common event and probably an essential feature of idiopathic pulmonary fibrosis. Several mechanisms appear to be implicated in this process, including upregulation of the release of angiotensin peptides that induce epithelial apoptosis by fibroblasts/myofibroblasts.[55] Based on these observations, one could speculate that the synergistic effect of amiodarone and angiotensin II on AECs apoptosis could be a significant pathway of amiodarone-related lung damage.

Regarding the immunological perspective, some authors advocate an imbalance between T helper (Th) type 1 and Th type 2 lymphocyte subpopulations and production of cytokines,[56] such as tumour necrosis factor-α and transforming growth factor-β, both released by the alveolar macrophages in an animal model of amiodarone toxicity.[57] Both the 'cytotoxic' and the 'immune' mechanism of action could lead independently or in combination in the tissue expression of different forms of lung injury (figure 3).

4. Clinical Picture

4.1 Acute Lung and Airway Disease

The recognition and treatment of amiodarone-induced acute pulmonary toxicity in the intensive care unit setting is challenging. It may occur as early as the second day of treatment and for cumulative doses as low as 1000–1500 mg intravenously.[58,59] Risk factors associated with acute amiodarone-induced pulmonary toxicity include pulmonary angiography, cardiothoracic surgery and high FiO_2.[23,25] Acute amiodarone-induced lung disease has also been described in the setting of sudden withdrawal of corticosteroids.[60] Acute amiodarone-induced lung disease appears rarely and is reported in occasional case reports, although some authors suggest that amiodarone has a potentially important, but largely under-recognized, role in inducing ALI/ARDS in some patients, especially those undergoing cardiac surgery.[23]

Acute pulmonary toxicity related to amiodarone was first described in 1985 in two patients who developed fulminant and fatal respiratory insufficiency after pulmonary angiography.[61] Few distinct types of acute lung tissue damage have been attributed to amiodarone toxicity. The ARDS pattern, with or without alveolar bleeding, belong in the more acute type of amiodarone toxicity presentation, characterized by an abrupt onset, rapid progression and high mortality.[28,62] The chest radiograph usually demonstrates patchy or diffuse infiltrates bilaterally, in an interstitial and/or alveolar confluent pattern (figure 4a) confirmed by the chest CT scan (figure 4b).[63]

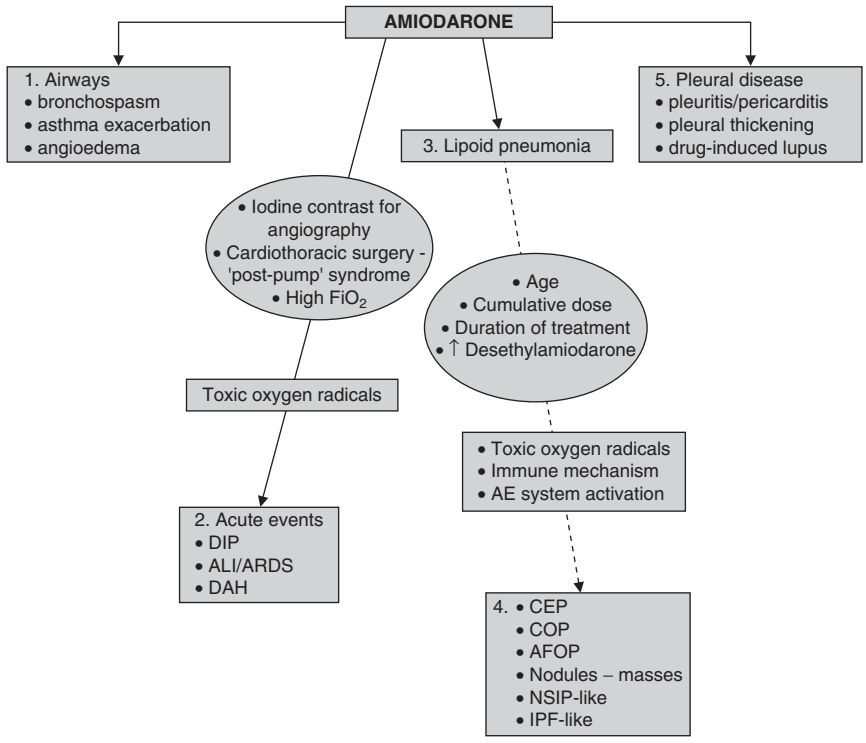

Fig. 3. Schematic representation of amiodarone-induced pulmonary effects and toxicity including hypothetical pathogenetic mechanisms involved. **AE** = angiotensin enzyme; **AFOP** = acute fibrinous organizing pneumonia; **ALI**/**ARDS** = acute lung injury/acute respiratory distress syndrome; **CEP** = chronic eosinophilic pneumonia; **COP** = chronic organizing pneumonia; **DAH** = diffuse alveolar haemorrhage; **DIP** = desquamative interstitial pneumonia; **FiO_2** = inspiratory fraction of inhaled oxygen; **IPF** = idiopathic pulmonary fibrosis; **NSIP** = non-specific interstitial pneumonia; ↑ indicates high levels. The dotted lines indicate occasional progression.

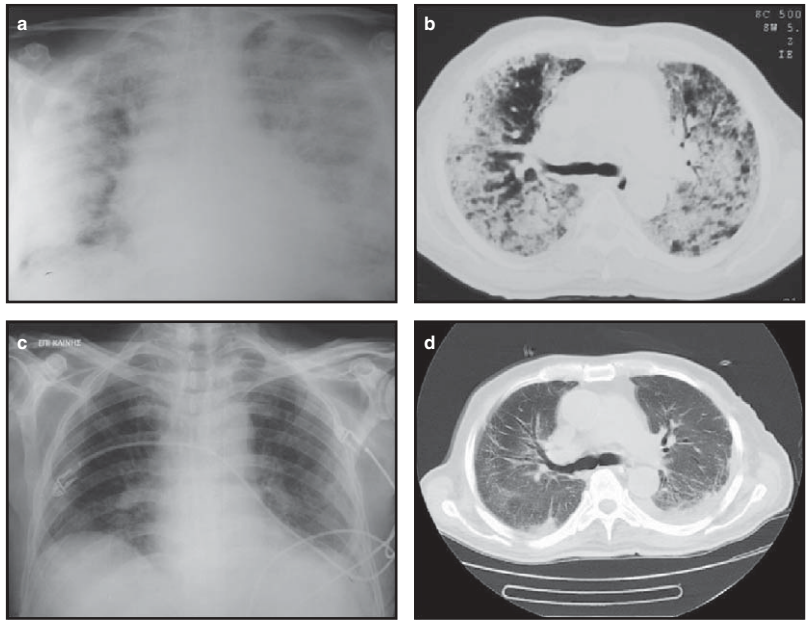

Fig. 4. This 69-year-old man was under treatment with amiodarone 200 mg/day for the previous 4 months because of several episodes of sustained ventricular tachycardia post-acute myocardial infarction. The patient developed fever, dry cough, haemoptysis and progressive dyspnoea with severe respiratory insufficiency that required mechanical ventilation. (**a**) The posteroanterior chest radiograph disclosed diffuse bilateral confluent air-space infiltrates. (**b**) Conventional 10 mm collimation CT scan of the chest confirms the presence of a diffuse air-space filling process consistent with acute respiratory distress syndrome. Amiodarone was withdrawn. A surgical lung biopsy disclosed overlapping features of chronic organizing pneumonia and diffuse alveolar damage (acute fibrinous and organizing pneumonia type) compatible with amiodarone-induced acute lung toxicity. High-dose corticosteroids were added and after a complicated clinical course, the patient recovered and was extubated. (**c**) Resolution of pulmonary opacities 45 days after discontinuation of amiodarone and corticosteroid treatment. (**d**) A synchronous CT of the chest demonstrates minimal left pleural effusion and residual patchy parenchymal changes in the right lung (reproduced by courtesy of Dr K. Pontikis and Dr M. Theodorakopoulou, 2nd Department of Critical Care, National and Kapodistrian University of Athens, Greece).

In this acute onset of amiodarone pulmonary toxicity, fever, cough, dyspnoea and pleuritic chest pain may dominate, while in the already intubated postsurgical patient, alveolar or ground glass opacities depicted on chest radiographs or CT scan and rapid deterioration of the respiratory status constitute the only evidence of the supervening acute lung injury.[64] Differential diagnosis from infectious pneumonia, gastric aspiration and other aetiologies of ALI/ARDS and pulmonary embolism is essential, though difficult.[28,65] Haemoptysis is rare, even in cases of alveolar haemorrhage.[62] There is some evidence that in the short-term context of surgery (particularly cardiac surgery) factors such as high-FiO_2 administration, lung damage of intubation/ventilation, chest surgical damage, the systemic inflammatory response induced by cardiopulmonary bypass ('post-pump' syndrome) and eventually the use of iodine contrast for angiography – through a toxic mechanism of high superoxide radicals production and release of active iodide species – may induce ARDS.[23,25,41,61] Early onset of acute diffuse interstitial pneumonitis with accompanying respiratory failure may also occur with histopathological features of diffuse acute DIP.[66] DAH with orthodeoxia and frank haemoptysis constitute a rare event in amiodarone toxicity patterns.[58,67] Scarce reports exist in the literature concerning the pathogenetic mechanisms of DAH related to amiodarone toxicity.[68] DAH is usually related to mechanisms associated with the presence of either antiglomerular membrane antibodies, antineutrophil cytoplasm antibodies or to immunocomplexes.[69] In the case of amiodarone toxicity,

the detection of antiglomerular basement membrane antibodies has been reported once in the literature without further documentation of this observation.[67,70] Suggestive of the vasculitis hypothesis is the fact that skin biopsies of patients with amiodarone lung toxicity and macular erythema-like skin lesions have been shown to disclose a lymphocytic vasculitis of the small capillaries.[71,72]

Finally, a completely different presentation of acute amiodarone-related adverse effect is bronchospasm, asthma exacerbation and angioedema. All these manifestations develop as anaphylactic-type reactions to amiodarone and are fully reversible with appropriate treatment (figure 3).[73]

4.2 Subacute/Chronic Lung Disease

The ubiquitously present lipoid pneumonia – where, by occupying space both intra-alveolarly and interstitially, the foamy cells may solely reduce effective surface for gas exchange – usually remains asymptomatic in the patient with high-reserve normal lungs and denotes its presence only by a moderate and progressive reduction of DLCO. This presentation represents the so-called 'amiodarone effect' on the lungs (table I; figure 3).[28] Exogenous and endogenous forms of lipoid pneumonia may occur in different clinical settings. The exogenous lipoid pneumonia is an uncommon pneumonitis resulting from the aspiration or inhalation of mineral oil or related substances, such as the prolonged ingestion and inadvertent aspiration of mineral oil-based laxatives, oily nasal or eye drops and liquid hydrocarbon mixture inhaled by fire eaters. Endogenous lipoid pneumonia consists of a chronic mildly inflammatory process, where fat is derived from destroyed parenchymal lung cells as in bronchial obstruction or chronic suppuration.[74-76] The most common cause of endogenous lipoid pneumonia is obstructing bronchogenic lung cancers, while less common causes include connective tissue disease involving the lungs by bronchiolar obstruction, benign bronchial obstructing neoplasms, chronic infections and lung storage disease such as Niemann-Pick disease and others.[77,78] The diagnosis of lipoid pneumonia in the above-reported clinical conditions requires a high degree of clinical suspicion and should be considered in cases of non-resolving pneumonia. Symptoms may be absent or non-specific, and the radiographic findings may reveal linear or nodular consolidations with low attenuation, ground-glass infiltrates or a crazy-paving pattern.[79-81] Magnetic resonance imaging (MRI) may help for the diagnosis, showing high intensity on T1 and T2 sequence.[82] In the case of amiodarone-induced lipoid pneumonia, no imaging studies have been reported.

The most common clinical presentation of amiodarone-induced chronic pulmonary toxicity is a subacute illness characterized by non-productive cough, progressive dyspnoea on exertion and occasionally low-grade fever, malaise and weight loss, in a patient with underlying heart disease receiving amiodarone.[18] Occasionally, orthodeoxia-platypnoea may be observed.[83] The chest radiograph and the CT scans in the majority of patients disclose bilateral patchy, peripheral or diffuse interstitial infiltrates (figures 5a and b and figures 6a–c).[84,85] Physical examination usually reveals bilateral rales. This most appropriately named 'amiodarone subacute-chronic lung toxicity' includes several distinct clinical entities related to the differing patterns of lung chronic inflammatory reaction to its presence, such as eosinophilic pneumonia, chronic organizing pneumonia, acute fibrinous organizing pneumonia, nodules or mass-like lesions, and NSIP and IPF-like interstitial pneumonias. This form of lung disease usually requires months from the initiation of amiodarone administration to become clinically manifest.[7]

Eosinophilic pneumonias comprise a wide spectrum of lung diseases often characterized by peripheral blood eosinophilia ($>1 \times 10^9$ eosinophils/L) and/or alveolar eosinophilia (>25%). Blood eosinophilia may be lacking, as in the early phase of idiopathic acute eosinophilic pneumonia, or in patients already taking oral corticosteroids.[86] Amiodarone is rarely reported to cause eosinophilic pneumonia.[87] Drug-induced eosinophilic pneumonias usually develop insidiously, resembling chronic eosinophilic pneumonia. Alternatively, it

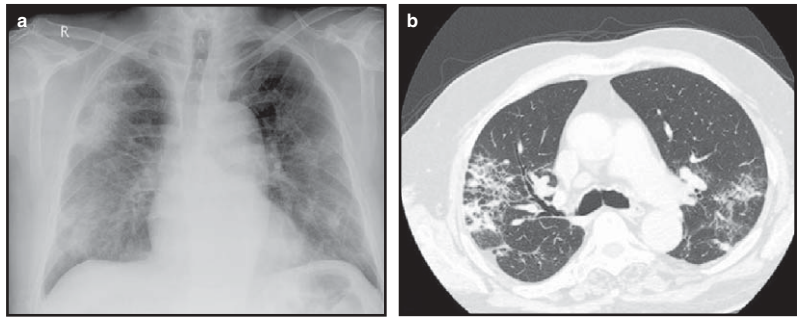

Fig. 5. This 63-year-old man with hypertension was receiving treatment with amiodarone 400 mg/day for the last 14 months for atrial fibrillation. He presented with progressive dyspnoea on exertion, fever, tremor and proximal weakness of the lower extremities. (**a**) The posteroanterior chest radiograph revealed focal areas of consolidation in the right upper and in the lower lobes. Irregular bilateral linear opacities are also noted. (**b**) Conventional 10 mm collimation CT scans of the chest shows bilateral areas of focal consolidation, more extensive in the right lung of increased density (95 Hounsfield Units), areas of ground-glass attenuation and linear opacities in the middle lobe and the lower lobes bilaterally. The clinical and laboratory findings were consistent with amiodarone-induced multi-organ toxicity (chronic organizing pneumonia, thyrotoxicosis and myopathy) [reproduced by courtesy of Dr S. Argentos and Associate Professor N. Kelekis, 2nd Department of Radiology, National and Kapodistrian University of Athens, Greece].

may present as transient pulmonary infiltrates in asymptomatic patients or even with its acute form often requiring mechanical ventilation. A diagnosis of drug-induced eosinophilic pneumonia is based upon a careful review of the drug side effects and exclusion of other possible aetiologies.[88] Eosinophil counts may be found increased in both peripheral blood and BAL in patients with amiodarone pulmonary toxicity, although not high enough to fulfil the above-mentioned criteria for establishing the diagnosis of eosinophilic pneumonia.[89]

COP is a is a predominantly airspace-filling inflammatory and fibrosing active disease where polypoid loose connective tissue and inflammatory cells involve terminal bronchioles, alveolar bronchioles, bronchiolar ducts and acinar spaces.[76] COP may be idiopathic or may occur as a secondary process to a specific injury (infection, drug reaction, radiation), a non-specific reactive change (cancer, vasculitis), or may serve as a minor component of other interstitial pneumonias such as NSIP, eosinophilic pneumonia or hypersensitivity pneumonitis.[90,91] A diagnosis of

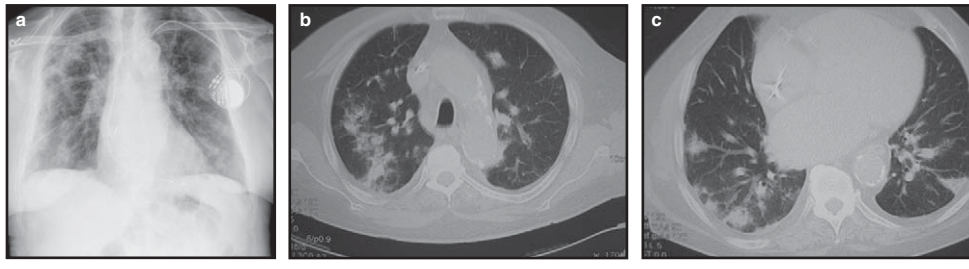

Fig. 6. A 78-year-old man, with a history of coronary artery disease, arterial hypertension, diabetes mellitus, atrial fibrillation and implantation of a pacemaker, was receiving treatment with amiodarone 600 mg/day for the last 4 months. He complained of fever, dry cough and dyspnoea and was admitted to the hospital with the working diagnosis of community-acquired pneumonia. (**a**) The posteroanterior chest radiograph obtained on admission revealed bilateral focal areas of consolidation more extensive on the right lung plus irregular bilateral linear opacities. (**b, c)** The conventional 10 mm collimation CT scans of the chest showed bilateral nodular opacities, more extensive in the right lung and a peripheral wedge-shaped opacity in the left lower lobe, plus areas of ground-glass attenuation. As no improvement was noted, amiodarone was withdrawn. Bronchoscopy failed to disclose microbial pathogens or lipoid pneumonia. The patient gradually improved without corticosteroids and was discharged with the presumptive diagnosis of amiodarone-induced chronic pneumonia (reproduced by courtesy of Dr S. Argentos and Associate Professor N. Kelekis, 2nd Department of Radiology, National and Kapodistrian University of Athens, Greece).

COP secondary to amiodarone may be hard to make as it is indistinguishable from other forms of this disease and must be based on the clinico-radiographic similarities with other forms of COP, and history of amiodarone exposure after the exclusion of other possible causes. Furthermore, it is very difficult to describe the exact prevalence of this type of amiodarone-lung toxicity since definite diagnosis necessitates at least thoracoscopic lung biopsy, which is not encouraged in this group of patients. Therefore, the clinician should base their diagnosis on clinical and radiographic findings.[22,92-95] The chest CT scan usually shows bilateral areas of consolidation and ground glass opacities, often with a peripheral location. Infiltrates may be localized or migratory, while rounded or linear opacities may occasionally represent areas of COP. The clinical presentation of amiodarone-induced COP is similar to that of the idiopathic disease and includes shortness of breath, cough, malaise, low-grade fever and pleuritic chest pain.[96-99]

Irreversible pulmonary fibrosis and ARDS are the most serious manifestations of amiodarone-induced lung toxicity. The exact prevalence as well as the histopathological features of amiodarone-related pulmonary fibrosis are difficult to describe because of the rarity of the presentation and the lack of open lung biopsies, for fear of perioperative complications.[88,100] A variety of reports from patients with the non-specific term of 'amiodarone pneumonitis' reveal septal thickening, non-specific inflammation and interstitial fibrosis in combination with the presence of lipids within interstitial, endothelial and alveolar cells.[44,49] Following the criteria of classification of the most recent Consensus on the Classification of Idiopathic Interstitial Pneumonias, the histological pattern of amiodarone-induced lung pulmonary fibrosis is mostly classified as subacute interstitial lung disease of the NSIP type.[44,49,88,101] The patient usually presents with dyspnoea on exertion, cough, hypoxaemia and desaturation during exercise, while physical examination reveals crackles at auscultation of the chest. Interstitial reticular opacities, traction bronchiectasis and honeycombing at the lung bases are depicted on CT in cases of pulmonary fibrosis.[64] However, it is not clear in every case whether pulmonary fibrosis is due to amiodarone or represents a new case of idiopathic pulmonary fibrosis, but it seems that fibrosis as a result of amiodarone toxicity is a milder, slowly progressive disease.[102,103] The natural history of amiodarone-related pulmonary fibrosis is unknown and response to corticosteroid treatment cannot be predicted.[64]

A thorough review of the literature that we carried out depicts a case of amiodarone lung toxicity presented with the histopathological features of acute fibrinous and organizing pneumonia (AFOP), a variant of interstitial lung disease that does not meet the classic histological criteria for diffuse alveolar damage (DAD), COP or eosinophilic pneumonia and may have a fulminant presentation and a poor prognosis as in DAD patterns of lung disease. In that case a histological pattern of intra-alveolar fibrin and organizing pneumonia with type 2 pneumocyte hyperplasia, oedema, acute and chronic inflammation, and interstitial widening is seen.[104]

In a minority of amiodarone-related abnormalities, the patient may present with nodular lung disease. The clinical picture may vary from a poorly symptomatic patient to a patient with symptoms such as cough, dyspnoea, weight loss and malaise.[105,106] Amiodarone pulmonary toxicity can rarely manifest as a localized lung lesion that is mass-like or nodular, or in the form of multiple pulmonary nodules, sometimes surrounded by a halo or even cavitated.[107-109] Furthermore, a pulmonary mass with associated multiple lung nodules mimicking lung cancer has been reported in the literature.[110] These masses, often called 'amiodaronoma', can localize anywhere, but interestingly, the majority of reported cases describe masses in the upper lobes, particularly in the right upper lobe.[75] Nodules and masses due to amiodarone are usually positive on positron emission tomography scan, leading to an initial deceptive diagnosis of malignancy.[106]

4.3 Pleural Disease

Thickening of the pleura or pericardium, pleural and/or pericardial effusion, and very

rarely drug-induced lupus with pleuropericarditis in association with antinuclear and antihistone antibodies (the serum marker of this subset) may occur as a complication of amiodarone.[111] Patients usually present with pleuritic chest pain and a pleuritic rub on chest auscultation. Pleural effusions are considered rare, may be unilateral or bilateral, and of small or moderate volume.[112-114] The presence of an isolated pleural effusion without the development of other parenchymal abnormalities related to amiodarone is extremely unusual. One case has been reported of amiodarone-induced pneumonitis occurring after the onset of pleural effusion.[115] Diagnostic thoracentesis discloses a paucicellular exudate with lymphocytic or neutrophilic predominance.[116] In another case, foamy cells were described in the cytological examination of pleural fluid.[96] Thickening of the pleura is a common finding, particularly in regions where the peripheral parenchymal lesions are in contact with the pleura.[117] Pericarditis has also been described in association with pleural effusion and pneumonitis.[118] In the case of any amiodarone-induced pleural and or pericardial effusion, detection of antinuclear and antihistone antibodies is required in order to diagnose drug-induced lupus. Pleural effusions usually resolve after discontinuation of amiodarone.

5. The Role of Laboratory Tests and Imaging in the Diagnosis of Lung Toxicity

Laboratory tests are not specific for the diagnosis of pulmonary toxicity due to amiodarone. They may show increased erythrocyte sedimentation rate and lactate dehydrogenase, leukocytosis and rarely eosinophilia. Positive antinuclear antibodies and antihistone antibodies are detected in rare cases of drug-induced lupus due to amiodarone.[111,119] When thyroid and liver amiodarone-related toxicity are also present, thyroid hormones are disturbed and liver enzymes increased.[5,120] Serum brain natriuretic peptide (BNP) levels indicate left ventricular failure. Increased levels of BNP do not exclude amiodarone lung toxicity, since these clinical entities may co-exist.[64] The mucinous high molecular weight glycoprotein KL-6, expressed on type II pneumocytes and bronchiolar cells, has been reported useful as a marker for the detection and evaluation of amiodarone-induced pulmonary toxicity.[121] However, serum KL-6 can be detected in high concentrations in a variety of other interstitial pneumonias and sarcoidosis as well.[122,123] In a recent study that assessed KL-6 above 500 U/mL as a screening tool for the diagnosis of amiodarone lung toxicity in patients taking low doses of the drug, it was shown that KL-6 had a sensitivity, specificity, positive and negative predictive value of 25%, 91%, 22% and 92%, respectively, and that no patient should discontinue amiodarone based on elevated values of KL-6 alone.[13] Apart from blood tests, initial work-up should always include an ECG checking for bradycardia and atrioventricular block.

The chest radiograph may reveal diffuse scattered infiltrates (figures 4a, 5a, 6a), thickening of the interstitial tissue, nodules or mass-like type consolidations with or without cavities, pleural effusion or thickening of the pleura and/or pericardium. These abnormalities can be detected even in mildly symptomatic patients and may take up to 18 months to subside after discontinuation of the drug (figures 4c, 5c). According to guidelines, a chest radiograph should always be performed at initiation of amiodarone treatment and yearly thereafter unless symptoms such as cough or dyspnoea and fever develop.[6,18,124] The chest CT scan is more sensitive than the chest radiographs and may reveal bilateral disease even in cases with unilateral lesions on plain films.[125] The most common findings on CT scans include parenchymal wedge-shaped consolidations (figures 6b and c) or patchy alveolar opacities (figures 4b, 5b, 6b and c), usually located at the periphery of the lung at the lung bases and/or in the upper lobes, areas of focal atelectasis, ground glass opacities mainly in the lower pulmonary fields, reticular opacities, nodules or masses, thickening of the pleura and/or the pericardium, and pleural effusion mainly in regions where the peripheral parenchymal lesions are in contact with the pleura (figures 4d, 6c).[126,127] These lesions are often depicted as very dense on CT because of the sequestration of iodine within the lung tissue,

which although non-metallic is an extremely dense element.[126,128] Density of tissues on the CT scan is expressed by a CT number described in Hounsfield Units (HU), a measure of radiographic attenuation by tissue. The values for air, fat, water and bones are −1024, −150, 0 and >200 HU, respectively. It is shown that lesions >70 HU may be related to amiodarone toxicity.[126] However, serious pulmonary toxicity may occur even in the presence of CT lung lesions with density lower than this cut-off point. The absence of high-density lesions in amiodarone lung toxicity has been described in 27–55% of patients.[117,127,129] On the other hand, high attenuation findings on chest CT are also described in cases of metastatic pulmonary calcification, pulmonary alveolar microlithiasis, talcosis, iodinated oil embolism, tuberculosis, silicoproteinosis and amyloidosis.[130] Therefore, they should always be interpreted with caution in the appropriate clinical setting in association with the complete work-up of the patient so that amiodarone is not interrupted without reason. The concomitant presence of similar findings of very high attenuation in the liver and spleen are indicative of amiodarone-related lesions without necessarily implying toxicity.[131-133] Amiodarone deposition within the myocardium can also be recognized on CT due to the increased attenuation of the cardiac muscle.[127]

Intravenously administered radioactive ^{67}Gallium (^{67}Ga) was introduced in the evaluation of amiodarone pulmonary toxicity in 1984. Since this form of lung damage is also a form of inflammatory alveolitis and interstitial lung disease, a ^{67}Ga scan was thought to be useful in the early detection of this pulmonary complication.[134] A ^{67}Ga scan is usually abnormal in patients suspected of suffering from amiodarone toxicity, showing focal, patchy or diffuse activity. The exact mechanisms of abnormal uptake of ^{67}Ga are not definitely known, but several interpretations have been suggested: an affinity of ^{67}Ga for lactoferrin; a possible leakage of ^{67}Ga at the site of lung damage as a result of increased permeability of cell membranes or blood vessels; and the accumulation of ^{67}Ga in inflammatory cells.[135] Nevertheless, ^{67}Ga scans have no specificity in amiodarone pulmonary toxicity and may be helpful only in distinguishing it from pulmonary oedema and in monitoring progress.[136] Nowadays, they have a minimal use in the evaluation and follow-up of patients with pulmonary complications from amiodarone.

6. The Role of Pulmonary Functional Tests in the Diagnosis of Lung Toxicity

According to the most recent practical guide for clinicians who treat patients with amiodarone, pulmonary function tests (PFTs) including DLCO should be performed at baseline and then regularly or for unexpected cough or dyspnoea, especially in patients with underlying lung disease, if there are suggestive chest radiographic abnormalities and if there is clinical suspicion of pulmonary toxicity.[6] This recommendation is based on several studies showing that PFTs in the majority of patterns of amiodarone pulmonary toxicity may reveal a restrictive pattern of abnormality, with decreased values of DLCO. The decrease seems to be significantly greater in patients with pre-existing pulmonary disease such as COPD.[15,19,137] Even more importantly, a reduction in DLCO of 15% is a strong indicator for the diagnosis of pulmonary toxicity due to amiodarone, with a sensitivity of 68–100% and a specificity of 69–95%.[13,19,21] However, discontinuation of the drug should never rely solely on this finding. On the contrary, an unchanged DLCO value in successive measurements excludes clinically significant pulmonary toxicity from the drug.[19,21,137]

7. The Role of Bronchoalveolar Lavage and Lung Biopsy in the Diagnosis of Lung Toxicity

After excluding cardiogenic pulmonary oedema and other emergencies such as pulmonary embolism, the patient with suspected amiodarone lung toxicity should undergo bronchoscopy in order to exclude infections and malignancy as far as possible.[138] BAL may provide evidence of amiodarone exposure but has no specificity for the diagnosis of amiodarone toxicity.[64] More

precisely, the total cell count is significantly elevated in amiodarone-treated patients compared with normal controls.[44] The BAL pattern displays a great variability in such patients and may be lymphocytic (21%), neutrophilic (26%), mixed (33%) and normal (20%). Eosinophils are increased in almost half of patients with either cellular profile.[89,139] The CD4/CD8 ratio average, in the majority of cases, below 1 and increase after discontinuation of the drug.[117,140,141] The discrepancies observed in the BAL pattern in patients with amiodarone pulmonary toxicity are partly explained by temporal differences in the traffic of inflammatory cells related to the pathogenesis of the disease and the timepoint in the natural history of the disease that BAL is performed.[139,142,143] None of the cellular BAL patterns encountered in patients with amiodarone lung toxicity is found to be predictive of a detrimental outcome or of the development of irreversible pulmonary fibrosis.[89] The most characteristic finding in BAL of patients with amiodarone exposure is the marked morphological abnormalities observed in BAL macrophages. These include the presence of two types of abnormal vacuoles when examination is performed under electron microscopy: (i) small optically empty vacuoles; and (ii) larger phagolysosomes containing phospholipidic material organized in lamellar structures. Due to their appearance, these macrophages are called 'foamy' (figure 2a). Similar inclusions are also found in reactive type II pneumocytes (figure 2b). Neither the number nor the appearance of 'foamy' macrophages is a predictor of amiodarone lung toxicity. However, since they are rarely found in normal subjects, their presence is considered indicative of exposure to amiodarone and their total absence in BAL makes the diagnosis of amiodarone toxicity less probable.[44,139,144] Haemosiderin-laden macrophages can also be found in BAL from patients with amiodarone-induced pneumonitis, probably related to the coexistent chronic left-sided heart failure, lung damage due to amiodarone or, less commonly, alveolar haemorrhage – a very rare complication of amiodarone.[76,145]

Foamy macrophages, reactive type II pneumocytes, as well as endothelial cells with cytoplasmic lamellar inclusions containing phospholipids, are also found on histopathological examination of lung tissues from patients with amiodarone exposure obtained either by transbronchial or by open lung biopsy. This pattern of lung damage is called phospholipidosis and is a characteristic amiodarone lung effect encountered even in non-toxic patients.[22,44,49] In cases of diffuse interstitial pulmonary disease, lung biopsy reveals interstitial inflammation, fibrosis and hyperplasia of type II pneumocytes. Foamy alveolar macrophages are always present. Hyaline membranes and organizing pneumonia may be occasionally present.[44,49,125,146] Severe interstitial fibrosis and 'honeycomb' appearance resembling IPF-like lesions are extremely rare.[44,106,147] In cases of masses or nodules, pathological examination reveals chronic interstitial inflammation, myofibroblasts and foamy macrophages.[41] In acute fulminant cases, diffuse alveolar damage with hyaline membranes with or without diffuse alveolar haemorrhage may be seen.[23,49,148] In cases of amiodarone lung toxicity developed in the form of pleural disease, histopathological examination usually reveals organizing fibrinous pleuritis with a light diffuse infiltrate of lymphocytes, plasma cells and monocytes, some vacuolated, with fibrin plaques near the pleural surface.[44,113] However, the risk of ARDS after surgical lung biopsy for patients with toxicity from amiodarone is high and is accompanied by rapid progress and high mortality.[27] Therefore, according to the most recent practical guide for clinicians who treat patients with amiodarone, surgical lung biopsy should generally be avoided. Diagnosis is often one of exclusion and is based on strong clinical suspicion, consistent history, radiological and clinical findings, as well as rigorous exclusion of alternative aetiologies. Improvement after discontinuation of the drug and response to corticosteroids advocates diagnosis.[6,45]

8. Principles of Treatment

When pulmonary toxicity due to amiodarone is suspected it is prudent to stop treatment

immediately, as the continuation of the drug increases the risk of complications, and to proceed to the work-up needed for the safe documentation of amiodarone lung toxicity.[6,64,89] The substitution of amiodarone by another antiarrhythmic agent or the insertion of an automatic defibrillator in collaboration with a cardiologist in order to prevent the recurrence of life-threatening arrhythmias should be the second major concern.[64,120,149,150] After discontinuation of the drug, most patients will experience gradual improvement if the disease is limited. In more advanced cases the addition of corticosteroids is advised, despite the lack of controlled trials.[6,60,151,152] An exact dose or duration of treatment has not been established. Regimens of 0.5–1 mg/kg of prednisolone with gradual tapering are usually prescribed for months, often for a period of 1 year. Tapering of corticosteroids depends on the response time of each patient, since there is evidence that amiodarone remains in lung tissue even 1 year after discontinuation of the drug.[151] Caution is needed in the gradual reduction of corticosteroids. Cases of aggressive disease relapse have been described after reducing the dose of prednisolone by over 5 mg daily or even 8 months after complete cessation of treatment.[153] In cases where amiodarone is considered absolutely essential for its antiarrhythmic properties, regimens with the lowest possible dose of amiodarone in combination with corticosteroids have been successfully used.[154] Despite treatment, disease may progress to irreversible pulmonary fibrosis and/or death in certain refractory or fulminant cases.[39,89,155] In respiratory failure, oxygen therapy or even mechanical ventilation are applied as necessary. Furthermore, the administration of a wide spectrum antimicrobial therapy initially is required until respiratory infection is reliably excluded. Experimental reports demonstrate the effectiveness of vitamin E in the attenuation of amiodarone-induced pulmonary fibrosis, but this regimen is not included in the standard of care of these patients.[64,156,157] Along with the treatment of pulmonary toxicity, clinicians should always examine the patient for clinical or laboratory evidence of toxicity from other systems (e.g. hyperthyroidism or hypothyroidism, ocular manifestations) and treat them appropriately in collaboration with a team of specialists.[6] Regular follow-up is mandatory with PFTs to check for disease progression, with thyroid hormones for monitoring of thyroid dysfunction and with ECG for evaluation of rhythm status after amiodarone interruption or the need for further cardiological intervention.[60]

9. Prognosis and Outcome

Patients put on treatment with amiodarone must have an initial chest radiograph and PFTs including DLCO for comparison with subsequent tests over time.[14] The chest radiograph should be repeated annually unless indicated earlier, and DLCO should be conducted for unexplained cough or dyspnoea, especially in patients with underlying lung disease or in cases of suggestive radiographic abnormalities, and if there is a clinical suspicion of pulmonary toxicity.[6] The follow-up evaluation should also include, at a minimum, a yearly ECG and, semi-annually, a thyroid profile (thyroid-stimulating hormone, free T4) and liver enzyme profile. Patients must also undergo an ophthalmological evaluation at baseline if visual impairment exists or whenever symptoms occur, in accordance with guidelines.[6]

Respiratory complications from amiodarone toxicity are not easy to estimate. The disease is usually diagnosed approximately 2 months after the first appearance of symptoms.[64,87,155] Mortality is difficult to assess because it differs widely in published series, and in a lot of cases it is not clear whether death has occurred due to toxicity of amiodarone or the underlying cardiac disease. Mortality is approximately calculated at 10% for those who develop pneumonitis, at 20–30% for those admitted to hospital, and 50% for those who develop ARDS.[25,39,158-162] These rates increase even more in elderly patients.[1] The disease usually responds to drug discontinuation and/or corticosteroid administration within a period of 1–6 months.[163,164] Imaging studies have shown the quite complete resolution of the infiltrates, as >85% of them decline. In the

remaining cases, residual elements persist or pulmonary fibrosis develops.[117,127,165] In any case, patient education of the risk of developing toxicity from amiodarone is considered essential. Early diagnosis and treatment have been clearly shown to improve the outcome of the disease.[1,6]

10. Conclusions

The toxicity of amiodarone remains an important clinical entity even with the reduced dose of <200 mg daily. Amiodarone-induced lung disease can be fatal, so early diagnosis and treatment is essential. The symptoms are not specific, and diagnosis is based on a combination of epidemiological, clinical, radiographic and laboratory data. Pulmonary toxicity from amiodarone consists of many different clinical entities, which clinicians should be aware of. A consensus approach to the management of patients receiving amiodarone and their complications would be useful.

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