The changing spectrum of drug-induced myopathies

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Drug-induced myopathies are a group of disorders whose importance lies in the fact that they are potentially treatable and usually reversible if the causative agent is identified and withdrawn. A wide variety of medications used in many different branches of medicine have been recognised as causing muscle adverse effects, ranging from myalgia and asymptomatic hyperCKaemia to severe weakness and at times fatal rhabdomyolysis. There has been increased awareness of these complications since the introduction of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor group of drugs (statins) in the 1980s, and their subsequent association with a range of necrotising and immune-mediated inflammatory myopathies and muscle symptoms. More recently, since the introduction of the immune checkpoint inhibitors for the treatment of advanced malignancies, it has been increasingly recognised that these drugs also have a propensity to induce or exacerbate a variety of immune-mediated myopathies, neuropathies, myasthenic disorders and atypical overlap syndromes, and it is anticipated that these complications will become even more prevalent with increasing use of these medications in the future. This review focusses mainly on these two groups of drugs, and on cytokine-based therapies and VEGF inhibitors which have also been implicated in the induction of immune-mediated inflammatory myopathies.

Key words: drug-induced myopathies, statins, checkpoint inhibitors, immune-mediated

Introduction

Drug-induced myopathies are an important group of iatrogenic disorders that may present in various ways, and are potentially reversible if the causative agent is identified and withdrawn. Many drugs used in different branches of medicine are known to have adverse effects on the skeletal muscles. These vary in severity, ranging from mild myalgia, cramps, and asymptomatic serum CK elevation, to a severe disabling myopathy with associated muscle pain, progressive muscle weakness and atrophy. While severe forms of drug-induced myopathy are uncommon, milder forms are probably more frequent than is appreciated. Some of the earliest drugs recognised to cause myopathy included corticosteroids, emetine, clofibrate, chloroquine, D-penicillamine, ε-aminocaproic acid and heroin [1]. With the continued expansion in the range of therapeutic agents, new myotoxic drug effects were recognised and the spectrum of drug-induced myopathies has continued to expand. Following the introduction of the first statin, lovastatin, in 1987, the myotoxic potential of this group of drugs was soon recognised, particularly after the introduction of cerivastatin in the late 1990s which caused over 100 fatal cases of acute rhabdomyolysis, leading to its withdrawal from the market in 2001. With the introduction of new statins, and their use by many millions of people for the primary and secondary prevention of vascular disease, the range of recognised myopathic effects associated with these drugs has grown, and they are now recognised as be-

ing the pre-eminent therapeutics associated with drug-induced myopathies in the modern era. More recently, other new groups of drugs have also been implicated, including cytokine-based therapies and anti-neoplastic therapies, in particular the group of immune checkpoint inhibitors which have been introduced for the immunotherapy of advanced malignancies.

Pathological mechanisms of drug-induced myopathies

As shown in Table I, the spectrum of pathological reactions induced by drugs in skeletal muscle is very broad, encompassing necrotising, inflammatory, mitochondrial, autophagic, myofibrillar and microtubular myopathies. The most basic reaction is myonecrosis, which typically occurs in statin myopathy, and less frequently with a variety of other therapeutic agents, as well as alcohol and drugs of addiction, and which in its most extreme form results in the syndrome of acute rhabdomyolysis. The underlying molecular mechanisms which lead to myonecrosis have yet to be fully investigated, but are thought to involve effects on the sarcolemma, intracellular calcium kinetics, mitochondrial function and muscle fibre bioenergetics [2,3]. Over the past two decades there has been increasing recognition of the potential of certain drug classes, in particular statins and a number of immune therapies to induce a necrotising autoimmune myopathy (NAM), as well as other types of inflammatory myopathy.

Statin-associated myopathies

Statins have been associated with a wide range of muscle disorders, as shown in Table II. The mildest symptoms include myalgia and muscle cramps, which have variably been reported to occur in as many as 10% of individuals taking a statin. However, because of the nonspecific nature of these symptoms, the frequency of a causative link with the statin has probably been over-estimated in many surveys. The incidence of severe necrotising myopathy and rhabdomyolysis requiring hospital admission is generally agreed to be very low (~1 in10,000

treated individuals) [4], and varies with different classes of statin drug. Risk factors for developing a myopathy include the type of statin, with the lipophilic drugs such as atorvastatin, lovastatin and simvastatin having a higher risk of myopathy than the hydrophilic compounds pravastatin and fluvastatin. Other risk factors include high drug doses, physical exercise, major surgery, co-administration of interacting drugs such as CYP3A4 enzyme inhibitors and fibrates, and other co-morbidities [2]. There is also evidence of a genetic predisposition to statin toxicity, with polymorphisms in the *SLCO1B1* and *COQ2* genes, and variants in the CYP enzyme system being associated with an increased risk of developing myopathy [2,5]. Asymptomatic carriers of mutations in the myophosphorylase, α-glucosidase, carnitine palmitoyltransferase-2, myoadenylate deaminase genes, and MELAS mutations, also have an increased risk of developing a myopathy when taking statins [2].

Statin myopathy is generally self-limiting if the causative drug is withdrawn as soon as possible after the onset of symptoms. The natural history of the myopathy is of improvement over a period of several weeks to months, depending on the initial severity of the muscle symptoms. However, recovery of full muscle strength is usually slow in cases of severe rhabdomyolysis and may take several months. When the symptoms fail to improve or continue to progress after withdrawal of the statin, the possibility of an immune-mediated myopathy initiated by the statin, or of an undiagnosed pre-existing myopathy need to be considered, and further investigations including a myositis autoantibody screen and a muscle biopsy are required.

Immune-mediated myopathies

A shown in Table III, a number of therapeutic agents have been associated with the development of an immune-mediated inflammatory myopathy. In particular, statins and more recently the immune checkpoint inhibitors have been implicated in causing multiple cases of necrotising autoimmune myopathy (NAM), as well as polymyositis and dermatomyositis and other autoimmune diseases. The underlying immunopathological mechanisms in such cases have yet to be fully elucidated, but

Table I. Pathological mechanisms of drug-induced myopathy.

• Necrotising myopathy/rhabdomyolysis (statins, fibrates, alcohol, heroin)
• Immune-inflammatory myopathies (statins, α-interferon, TNFα inhibitors, check-point inhibitors, bevacizumab)
• Mitochondrial myopathy (antiretrovirals, statins, clevudine)
• Lysosomal/autophagic myopathies (chloroquine, hydroxychloroquine, amiodarone)
• Microtubular myopathies (colchicine, vincristine)
• Myofibrillar myopathies (emetine, acute quadriplegic myopathy)
• Catabolic myopathy with type 2 fibre atrophy (corticosteroids)

Table II. Spectrum of statin-induced neuromuscular disorders.

• Necrotising myopathy/rhabdomyolysis
• Immune-inflammatory myopathies – Necrotising autoimmune myopathy (NAM) – Polymyositis/dermatomyositis
• Mitochondrial myopathy
• Unmasking of pre-existing metabolic myopathy
• Myasthenia gravis
• Axonal polyneuropathy

Table III. Drugs associated with induction of immune-mediated myopathies.

• HMGCR-inhibitors (statins)
• Immune checkpoint inhibitors
• Cytokine therapies (interferon-α/β. TNFα blockers)
• Bevacizumab
• D-penicillamine
• Others: tryptophan, procainamide, leflunomide

are thought to involve both humoral complement-dependent antibody mechanisms on the one hand, and T-cell mechanisms on the other.

Statin-associated necrotising autoimmune myopathy (NAM)

Necrotising autoimmune myopathy (NAM) is one of the most common forms of immune-mediated inflammatory myopathy and has multiple causative associations (Tab. IV). Statin-associated NAM is well-documented and is characterised clinically by progressive subacute muscle weakness, very high serum CK levels (> x10), and the presence of circulating autoantibodies to 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CR), which is the pharmacological target of the statin drugs [4]. Symptoms may develop shortly after commencement of a statin drug, but more often develop in patients who have been on a statin for a number of years. Muscle pathology studies usually show evidence of disseminated polyphasic myonecrosis and regeneration, with an absent

Table IV. Associations of necrotising autoimmune myopathy (NAM).

• Anti-HMGCR antibodies – Statin therapy – Statin-naïve
• Anti-signal recognition antibodies
• Anti-synthetase antibodies
• Malignancy
• Viral infections

or sparse inflammatory infiltrate, comprising predominantly macrophages and small numbers of CD4 and CD8 T-cells. Immunohistochemistry shows diffuse expression of MHC-I antigen in muscle fibres (Fig. 1), together with sarcolemmal deposition of the complement membrane-attack complex (C5b-9) on non-necrotic muscle fibres, in keeping with a complement-dependent antibody mediated mechanism of muscle injury [4,6].

The condition is estimated to affect ~2-3 per 1000 individuals taking statins, but it is also recognised that about one-third of cases of NAM with anti-HMGCR antibodies have not had previous exposure to a statin [7]. Because of this, and because of the large number of individuals over the age of 50-65 years who are taking statins, some doubt has therefore been cast on the causative role of statins in NAM, and it has been suggested that the association could be coincidental [8]. The possibility that individuals affected by NAM may have a genetic predisposition is suggested by the finding that the Class II HLA allele DRB1*11:01 is strongly associated with the development of anti-HMGCR autoantibodies, even in the absence of previous statin exposure [4]. Further confirmation is required to support the hypothesis that statins can initiate an autoimmune myopathy in genetically susceptible individuals, by leading to over-expression of HMGCR in muscle fibres, and loss of immune tolerance [4].

The natural history of anti-HMGCR associated NAM is of continued progression even after withdrawal of the statin, although some milder cases may improve spontaneously. In the majority of cases, however, aggressive treatment with prednisone in combination with an immunosuppressive agent such as azathioprine, methotrexate or mycophenolate is required, and is often effective in controlling the disease. However, in cases with more severe weakness, or who are not responsive to corticosteroids and immunosuppressants, a third-line agent such as intravenous immunoglobulin or rituximab may need to be added to achieve control of the myopathy.

Immune checkpoint inhibitors

During the past 6 years there have been increasing reports of a spectrum of neuromuscular and other neurological complications of treatment with immune checkpoint inhibitors (ICPIs) in patients with advanced malignancies such as metastatic melanoma, non-small cell lung cancer, genitourinary and gastrointestinal malignancies, and Hodgkin's lymphoma [9-11]. These drugs work by blocking the co-stimulatory molecules on T cells (CTLA-4 and PD-1, or its ligand PD-L1), thereby allowing them to exert their cytotoxic effects on tumour cells. However, the resulting upregulation of the immune response can result in initiation of a variety of autoimmune disorders, or aggravation of pre-existing disorders such as myasthenia gravis or multiple sclerosis, which
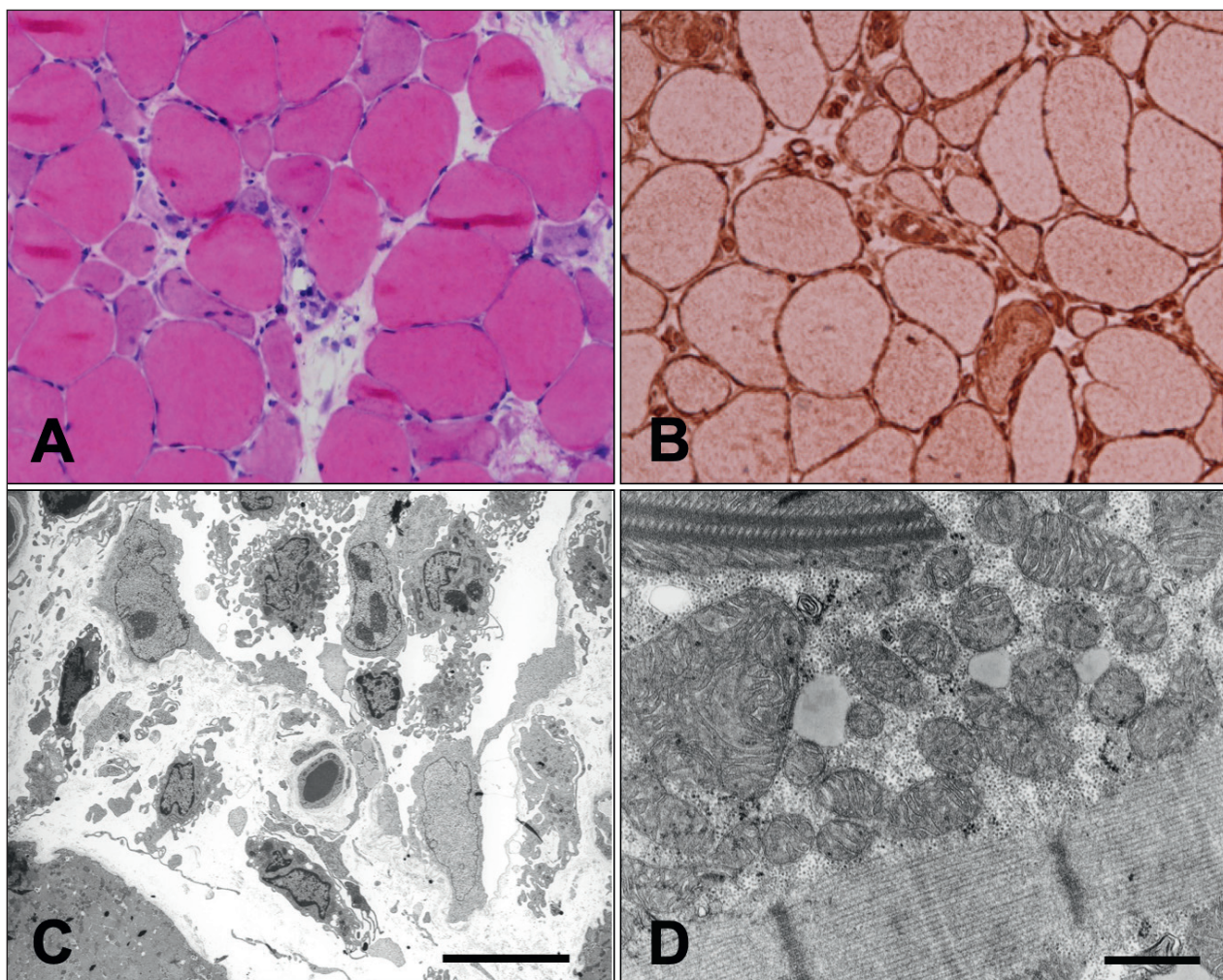
Figure 1. A) Statin-induced necrotising myopathy (H&E x40); B) Widespread sarcolemmal and sarcoplasmic MHC-I expression in case of statin-induced NAM (x40); C) Electron micrograph showing interstitial mononuclear cellular infiltrate in a case of statin-induced NAM (Bar 10 μm); D) Electron micrograph showing mitochondrial pleomorphism and paracrystalline inclusions in a case of statin-induced myalgia and exercise intolerance (Bar 1μm).

may previously have been subclinical and undiagnosed. A variety of ICPIs are now available to treat different malignancies, and include ipilimumab, which targets CTLA-4; pembrolizumab, novolumab and cemiplimab that block PD-1; and atezolizumab, avelumab and durvalumab that are PD-L1 inhibitors [11]. These drugs can be used either on an individual basis, or in combination to improve the chances of an effective response to the tumour.

The range of neuromuscular disorders which have been reported in patients treated with ICPIs is shown in Table V, and include myasthenia gravis, immune-mediated necrotising and inflammatory myopathies and polyneuropathies, as well as radiculopathies and mononeuropathies. The overall incidence of these complications is

thought to be less than 1% with the ICPs in current use, and is higher when CTLA-4 and PD-1/PD-L1 inhibitors are administered in combination. Although the incidence of these disorders is low, it is still much higher than in the general population, and it is predicted that it will continue to rise with increasing use of ICPs for different types of malignancy [9].

A review of 22 reported cases of ICPI-associated myopathies by Puwanant and colleagues [10] in 2019, revealed that the onset was usually within the first 2-3 months after commencement of treatment, and that the clinical phenotype was quite variable. While the phenotype may resemble classical presentations such as NAM, polymyositis or dermatomyositis, atypical features such as oculo-bulbar

symptoms and co-existing myocarditis were quite common. In addition, overlap syndromes including myopathy with associated myasthenia or neuropathic features were also not uncommon. Orbital myositis has also been reported [12]. Over 50% of cases improved following discontinuation of ICPIs and treatment with varying combinations of corticosteroids, immunosuppressive agents, IVIG and plasma exchange, but there was a 27% mortality [10].

The immunopathological mechanisms which underlie these diverse autoimmune complications of ICPI therapy remain to be investigated, but are presumed to involve induction of autoreactive T-cells and stimulation of autoantibody production as a result of removal of co-stimulatory molecule control over the immune response. These effects are likely to be further enhanced in individuals with a pre-existing autoimmune disorder, with resulting deterioration or unmasking of the underlying condition. ICPIs are thought to enhance Th1 and Th17 cell responses and have effects on regulatory T-cell function, resulting in a shift in the T-reg/Th17 balance, favouring the development of autoimmunity [9]. The possibility that genetic variants in CTLA-4 may predispose certain individuals to develop autoimmune disorders when treated with an ICPI has also been suggested [9].

Cytokine-based therapies

It is important to be aware of the possibility that Type 1 interferons may induce an inflammatory myopathy or other autoimmune conditions when they are used therapeutically for the treatment of immune disorders, malignancies or chronic infections although this occurs only rarely [13]. There have been a number of reports of the onset of polymyositis or dermatomyositis, as well as other autoimmune disorders, in patients treated with interferon-α2 for hepatitis C or certain malignancies [12]. Moreover, the onset of severe dermatomyositis has been reported in a patient with multiple sclerosis who had been treated with interferon-β for 5 years [14].

A number of TNFα-blockers have also been associated rarely with the development of dermatomyositis or polymyositis when used for the treatment of rheumatoid arthritis or other types of arthropathy, or inflammatory bowel disease. In a review of 24 such cases by Zengin and colleagues [15], there were 12 cases of polymyositis and 12 of dermatomyositis, and the drugs implicated included etanercept (10), infliximab (5), adalimumab (5) and lenercept (2). In the majority of these patients the myositis developed in spite of the fact that they were on methotrexate as a disease-modifying therapy, and improved with immunotherapy.

VEGF inhibitors

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits angiogenesis by binding circulating vascular endothelial growth factor (VEGF), thereby inhibiting its binding to cellular receptors, and is used in the treatment of non-small cell lung cancer, colon and renal cancer, glioblastoma multiforme and other malignancies. Although not identified in RCTs, there have been occasional reports of rhabdomyolysis developing after commencement of treatment with the drug [16], as well as reports of inflammatory myopathy [17] (Oflazer P, personal communication). There have also been reports of rhabdomyolysis associated with administration of sunitinib and erlotinib which are also VEGF inhibitors [18]. The mechanism of the myopathy with these drugs has not been investigated and it remains to be determined what role immune-mechanisms play.

Conclusions

The spectrum of drug-induced myopathies has changed quite markedly over the past 30 years, and is continuing to change with the introduction of newer therapeutic agents, particularly for the treatment of malignant disorders. It is likely that with the increasing use of ICPIs for the treatment of an increasing range of advanced malignancies, the prevalence of immune-mediated myopathies and other neuromuscular complications will continue to increase, and that, together with statins, ICPIs will become one of the major causes of drug-induced necrotising and immune-inflammatory myopathies and neuromyopathies. The underlying pathophysiology of these drug-induced disorders is still poorly understood, and further investigation is needed of the immunopathogenesis and mechanisms leading to the loss of immune tolerance.

Table V. Neuromuscular complications of immune checkpoint inhibitors.

•   Myopathies
    – Necrotising myopathy
    – Polymyositis
    – Dermatomyositis
    – Nonspecific myopathy
    – Orbital myositis

•   Myasthenia gravis

•   Neuropathies
    – Guillain-Barré syndrome
    – Chronic inflammatory demyelinating polyneuropathy
    – Polyradiculopathy
    – Vasculitic neuropathy
    – Cranial neuropathies

•   Overlap syndromes

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