4-1-2022

Complement in autoimmune inflammatory myopathies, the role of myositis-associated antibodies, COVID-19 associations, and muscle amyloid deposits.

Marinos Dalakas
Thomas Jefferson University; University of Athens Medical School

Taylor & Francis
Taylor & Francis Group

Expert Review of Clinical Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierm20

Complement in autoimmune inflammatory myopathies, the role of myositis-associated antibodies, COVID-19 associations, and muscle amyloid deposits

Marinos C. Dalakas

To cite this article: Marinos C. Dalakas (2022) Complement in autoimmune inflammatory myopathies, the role of myositis-associated antibodies, COVID-19 associations, and muscle amyloid deposits, Expert Review of Clinical Immunology, 18:4, 413-423, DOI: 10.1080/1744666X.2022.2054803

To link to this article: https://doi.org/10.1080/1744666X.2022.2054803

Published online: 27 Mar 2022.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
2022, VOL. 18, NO. 4, 413–423
https://doi.org/10.1080/1744666X.2022.2054803

Taylor & Francis
Taylor & Francis Group

REVIEW

Complement in autoimmune inflammatory myopathies, the role of myositis-associated antibodies, COVID-19 associations, and muscle amyloid deposits

Marinos C. Dalakas[a,b]

[a]Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA; [b]University of Athens Medical School, Neuroimmunology Unit, National and Kapodistrian University, Athens, Greece

ABSTRACT

Introduction: The inflammatory myopathies (IM) have now evolved into distinct subsets requiring clarification about their immunopathogenesis to guide applications of targeted therapies

Areas covered: Immunohistopathologic criteria of IM with a focus on complement, anti-complement therapeutics, and other biologic immunotherapies. The COVID19-triggered muscle autoimmunity along with the correct interpretation of muscle amyloid deposits is discussed.

Expert opinion: The IM, unjustifiably referred as idiopathic, comprise *Dermatomyositis (DM), Necrotizing Autoimmune Myositis (NAM), Anti-synthetase syndrome-overlap myositis (Anti-SS-OM), and Inclusion-Body-Myositis (IBM)*. In DM, complement activation with MAC-mediated endomysial microvascular destruction and perifascicular atrophy is the fundamental process, while innate immunity activation factors, INF1 and MxA, sense and secondarily enhance inflammation. Complement participates in muscle fiber necrosis from any cause and may facilitate muscle-fiber necrosis in NAM but seems unlikely that myositis-associated antibodies participate in complement-fixing. Accordingly, anti-complement therapeutics should be prioritized for DM. SARS-CoV-2 can potentially trigger muscle autoimmunity, but systematic studies are needed as the reported autopsy findings are not clinically relevant. In IBM, tiny amyloid deposits within muscle fibers are enhanced by inflammatory mediators contributing to myodegeneration; in contrast, spotty amyloid deposits in the endomysial connective tissue do not represent 'amyloid myopathy' but only have diagnostic value for amyloidosis due to any cause.

ARTICLE HISTORY
Received 20 January 2022
Accepted 15 March 2022

KEYWORDS
Inflammatory myopathies; complement; muscle amyloid; SARS-CoV -2-myopathy

1. Introduction

Inflammatory myopathies (IM) are a heterogeneous group of acquired myopathies, which, based on distinct clinical, histological, and immunopathological features as well as association with certain autoantibodies, have evolved into four distinct subsets: *Dermatomyositis (DM), Necrotizing Autoimmune Myositis (NAM), or Immune-Mediated Necrotizing Myopathy (IMNM), Anti-synthetase syndrome-overlap myositis (Anti-SS-OM), and Inclusion-Body-Myositis (IBM)* [1,2]. As recently stated by Tanboon et al., the clinicopathological classification of IM, as first introduced 30 years ago [3,4], had also included Polymyositis (PM), even if we have repeatedly stated for many years that it is a very rare disease subtype. It has now become more clear that PM is not only rare but may not exist as an isolated entity; because it may very rarely seen in association with another autoimmune systemic or viral disease it has been included in the classification of IM mostly for historical reasons [1]. As continuously witnessed by many authors in the last 15 years, patients referred to experienced centers for PM they either have IBM, NAM, or an inflammatory dystrophy [1–7]. Each of the four IM subsets has distinct clinical features, pathomechanisms, prognosis, and response to therapies, requiring careful clinicopathologic correlations with expertise not only in clinical neuromuscular diseases but concurrently in muscle histopathology and immunopathology to exclude disease mimics.

This article briefly describes the main clinicopathologic and immune features of each IM subtype, but it is mostly focused on the role of complement in facilitating necrosis within the muscle tissue, predominantly in DM and NAM. The main reason for such a focus is to stimulate interest considering the exciting success of anti-complement therapeutics in other autoimmune neurological diseases where complement plays a role such as Myasthenia gravis and Neuromyelitis (NMO-SD). Within the pathogenetic mechanisms of all IMs, reference is made on the significance of amyloid muscle deposits and on COVID19-triggered immunopathology. These are discussed because amyloid is seen within the muscle fibers in IBM and viruses have been implicated as triggering factors in IM, but both issues need clarification due to recent rather confusing reports to avoid misinterpretations in reference to their significance in the field of IM. Further, anti-complement therapeutics may have a beneficial effect on COVID-associated conditions, as discussed later, hence their relevance in the treatment of IM during the COVID19 pandemic.

CONTACT Marinos C. Dalakas marinos.dalakas@jefferson.edu; mdalakas@med.uoa.gr Department of Neurology, Thomas Jefferson University, Philadelphia, PA USA

Article highlights

- The inflammatory myopathies are not "idiopathic" as unjustifiably have been currently referred. They comprise four distinct subsets: *Dermatomyositis (DM), Necrotizing Autoimmune Myositis (NAM), Anti-synthetase syndrome-overlap myositis (Anti-SS-OM), and Inclusion-Body-Myositis (IBM)*.
- The fundamental mechanism in DM is complement activation and MAC-mediated microvasculopathy that lead to ischemia and perifascicular atrophy, and not interferon os secondary elements of innate immunity as some believe. Anti-complement agents targeting C3-C5 may lead to sustained clinical remission and should be explored in controlled trials.
- There is strong evidence that SARS-CoV-2 does not infect muscle fibers but, like any other virus, has the potential to trigger muscle autoimmunity but this remains to be explored as findings from autopsy cases are unconvincing and clinically irrelevant. Prospective studies with clinicopathologic correlations are needed.
- Spotty amyloid deposits in the endomysial connective tissue do not represent 'amyloid myopathy' as recently stated, but they only have diagnostic value to detect amyloidosis due to any cause, neuropathic, systemic, or hereditary.
- Biologic agents targeting FcRn should be explored as potential therapeutic agents in DM, NAM, and anti-SS-OM

2. Clinicopathologic characteristics, immunopathology, and role of complement

2.1. General clinical principles

Patients with all IM subtypes experience slow, subacute, and rarely acute-onset of muscle weakness mostly in proximal muscles, such as climbing steps, getting up from a chair or raising arms, as seen in all subtypes except for IBM which may often present first with distal muscle weakness in hands and feet with difficulties making a grip, typing, or raising the feet and legs [1–9]. Weakness in the neck-extensor muscles can be prominent, resulting in head drop or difficulty holding up the head; dysphagia can be seen in all IM subsets. In some clinically advanced cases, respiratory muscles are also affected. Myalgia and muscle tenderness are features in all IM subsets, but they are especially prominent in anti-SS-OM. Extramuscular manifestations such as arthralgia, Raynaud's phenomenon, and pulmonary complications due to interstitial lung disease are frequent in anti-SS-OM and amyopathic DM with anti-MDA-5 [Melanoma Differentiation-Associated protein-5] antibodies [1–7,9,10]. Up to 75% of all IM patients have various autoantibodies directed against nuclear RNAs or cytoplasmic antigens, which although nonpathogenic, can be associated with distinct clinical phenotypes aiding in the classification or diagnosis. The clinico-immuopathology of each of the four main IM subsets and the role of complement is as follows:

2.2. Dermatomyositis (DM)

2.2.1. Clinicopathology

Patients with DM manifest characteristic skin changes consisting of periorbital blue-purple discoloration, an erythematous

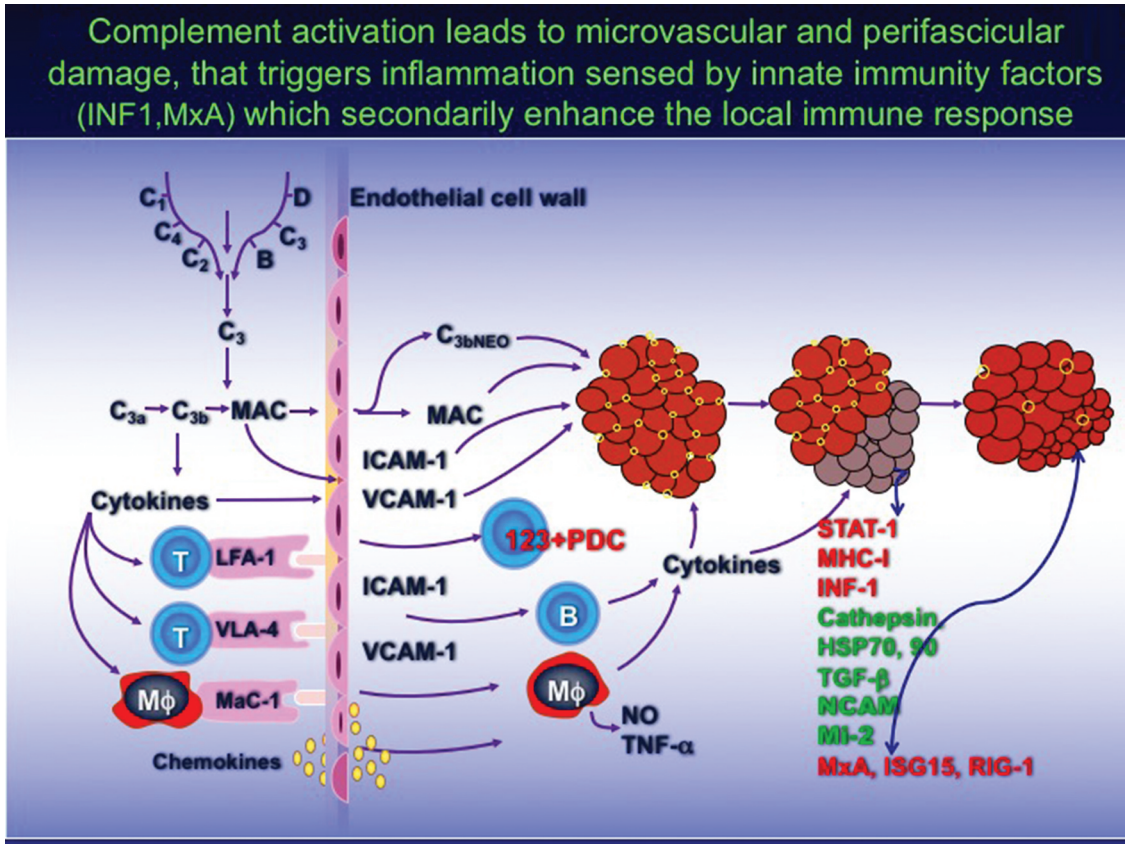

Figure 1. Complement activation leads to microvascular and perifascicular damage, that triggers inflammation sensed by innate immunity factors (INF1, MxA) which secondarily enhance the local immune response [modified from [1,7]].

rash on the face but also on the neck, anterior chest, and shoulders, and a violaceous eruption (Gottron's rash) at the knuckles. Skin changes precede or accompany proximal muscle weakness. In a small patient subset, the disease is clinically limited to the skin, referred to as 'amyopathic dermatomyositis,' because they have normal strength [11]; their muscle biopsies, however, always show subclinical inflammatory myopathic features [1,7]. Cracked palmar fingertips ('mechanic's hands') are characteristic along with dilation of the capillary loops at the base of the fingernails. The symptoms of Dermatomyositis may overlap with mixed connective tissue disease, systemic sclerosis, and with the anti-synthetase syndrome-overlap myositis (anti-SS-OM) [1,2,7]. The muscle biopsy shows inflammation, predominantly around the blood vessels (perivascularly) or in the interfascicular septae and the periphery of the fascicles, with necrosis and phagocytosis due to microinfarcts that lead to hypoperfusion and layers of atrophic fibers at the periphery of the fascicle referred to as perifascicular atrophy [1–7] **[**Figure 1**, as modified from** [1,7]**]** In patients with active disease, the serum Creatine Kinase is elevated but it may at times be normal reflecting the predominance of the pathology in the interstitial connective tissue. In 15% of adults with DM, there is a malignancy risk the first 3–5 years from disease onset [1,12]. Certain *Dermatomyositis-associated antibodies* may be connected with a specific DM subtype. Specifically, antibodies against (a) Mi-2, highlight typical skin lesions; (b) melanoma differentiation–associated protein-5 (MDA-5) are mostly connected with amyopathic DM or with interstitial lung disease; and (c) transcriptional intermediary factor-1 (TIF-1) and nuclear matrix protein NXP-2, are likely connected with cancer-associated DM [1,2,6,13].

2.2.2. Role of complement in the immunopathology of Dermatomyositis

In DM, the endothelium of the capillaries is primarily targeted by C5b-9 Membranolytic Attack Complex (MAC) which is deposited on the endothelial cells early in the disease and before any evident muscle fiber destruction [1–7,14–16]. The complement deposits cause endothelial cell necrosis and reduction of the endomysial capillaries leading to ischemia and micro infarcts especially at the periphery of the fascicles explaining the noted perifascicular atrophy; the remaining capillaries have dilated lumens probably in an effort to compensate for the ischemic process [1–7] (Figure 1). The MAC activation triggers the release of proinflammatory cytokines, up-regulation of adhesion molecules on endothelial cells and migration into the endomysium of activated CD4 + T-cells, macrophages, B cells, and CD123+ plasmacytoid dendritic cells [1].

How does the activation of the lytic complement pathway takes place remains unclear. Evidence suggests a direct C1q-mediated CP (Classical Pathway) activation process by the diseased endothelium because C1q and C4 are deposited early in the disease in the proximity to C5b-9 without concurrent Immunoglobulin IgG deposits [16–19]. Whether MAC deposition on the endomysial capillaries is the consequence of low CD59 expression or low levels of circulating vitronectin and clusterin enabling an innocent bystander process, remains

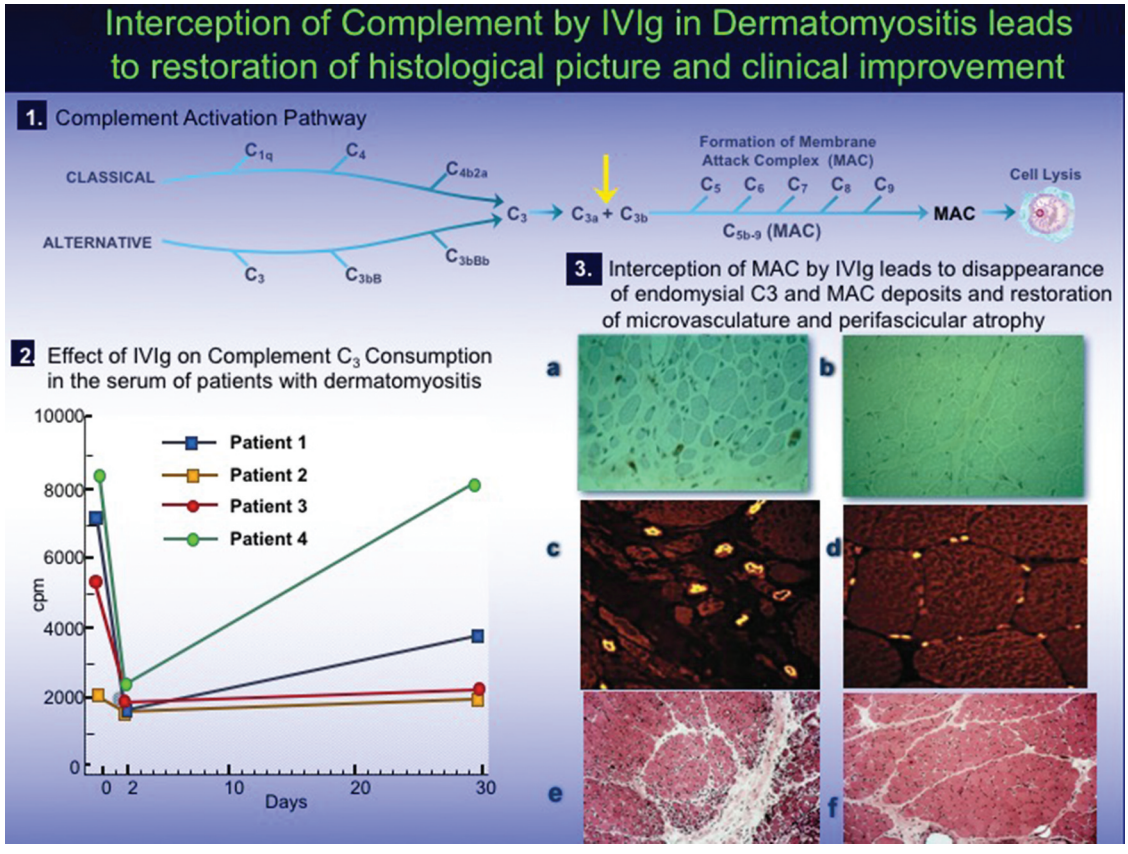

Figure 2. Interception of complement by IVIg in Dermatomyositis leads to restoration of histological picture and clinical improvement [modified from [23,24]].

a theoretical but never explored possibility [17–19]. Innate immunity also plays a secondary role, as evidenced by the increased expression of type-I interferon-inducible proteins in the perifascicular regions [20]; such an effect is, however, secondary to inflammatory ischemic damage, which is sensed by the retinoic acid-inducible gene-1 signaling leading to auto-amplification of local inflammation by activating β-interferon and MHC-1, as discussed [21], enhancing further the local complement-triggered inflammation.

In spite of the uncertain events that trigger complement activation, the primary event in DM is unambiguously a complement – mediated microangiopathy because inhibition of C3b by IVIg results not only in interception of MAC assembly in the patients' tissues but also in significant clinical improvement, resolution of histopathological changes and disappearance of MAC from the muscle fibers (1,3,7), as clearly depicted in Figure 2 and explained below.

2.2.3. Key observations on complement and inflammatory molecules in DM based on the effects of IVIg

IVIg, comprised of IgG immunoglobulin molecules from a pool of thousand donors, binds C1q effectively preventing pathogenic antibodies from triggering the complement cascade; it also binds activated C3 and C4 inhibiting their tissue deposition [22,23] **[#1 in Figure 2 as modified from [23,24]]**. The most convincing *in vivo* and *in vitro* example of the efficacy of IVIg via complement inhibition is the double-blind, placebo-controlled study in patients with treatment-resistant dermatomyositis, which has clearly shown that IVIg is clinically effective by inhibiting complement at the C3 level [24]. Based on this pivotal study conducted 30 years ago, IVIg rapidly forms complexes with C3b, inhibits C3 consumption as early as 2 days after infusion, and intercepts MAC formation in the patients' muscles by reducing the assembly of C5 convertase [19,23] **[#2 in Figure 2, as modified from [23,24]]**. These effects were shown in the serum of DM patients randomized to IVIg and their repeated muscle biopsies in correlation with the clinical improvement [23,24]. IVIg exerted an impressive and statistically significant clinical benefit compared to placebo-randomized patients, leading after three monthly infusions to normalization of their muscle strength and elimination not only of the active violaceous skin rash but also of the chronic scaly skin eruptions [24]. Based on repeated muscle biopsies from the improved patients, IVIg inhibited MAC deposits from the endomysial capillaries by intercepting the incorporation of C3 into the C5 convertase assembly resulting in resolution of the destructive histological changes with reversal of the atrophic muscle fibers and improved microvasulatute due to neovascularization [23] **[#3 in Figure 2: a,c,e before therapy compared, respectively, with b,d,f, as modified from [23,24]]**. By inhibiting complement, IVIg also eliminated the endomysial inflammatory cells and downregulated key cytokines and adhesion molecules including the overexpression of the intercellular adhesion molecule (ICAM-I) on the endomysial capillaries, the major histocompatibility complex class I (MHC-I) antigen on muscle fibers, and the TGF-β_1 in the connective tissue, both at the protein and mRNA level [25]. IVIg also modified certain immunoregulatory and structural genes based on gene array studies in the repeated muscles of DM patients who improved after IVIg therapy, with upregulation of the expression of the chemokine Mig/CXCL9 gene and reduction of anosmin-1/KAL-1 gene, which encodes a protein involved in fibrosis or tissue remodeling clinically correlating with reduced of long-standing fibrosis in the muscle and the skin lesions [26].

2.3. Necrotizing autoimmune myositis (NAM) or immune-mediated necrotizing myopathy (IMNM)

2.3.1. Clinicopathology

NAM—a term more preferable and euphonic than the commonly used IMNM—has now evolved as one of the most common IM subtype [1,2,7]. It may have an acute onset, reaching its peak over days or weeks or a steadily progressive course over weeks or months causing severe weakness and very high creatine kinase (CK) levels. NAM may also occur after viral infections and in association with cancer or immune check point inhibitors [1,2,27]; it has been, however, often, although non-convincingly, attributed to statins or overdiagnosed as a 'statin-myopathy' in patients on chronic statin administration [28], even though the evidence has been peripheral [29,30]. Acute rhabdomyolysis, as prominently seen in

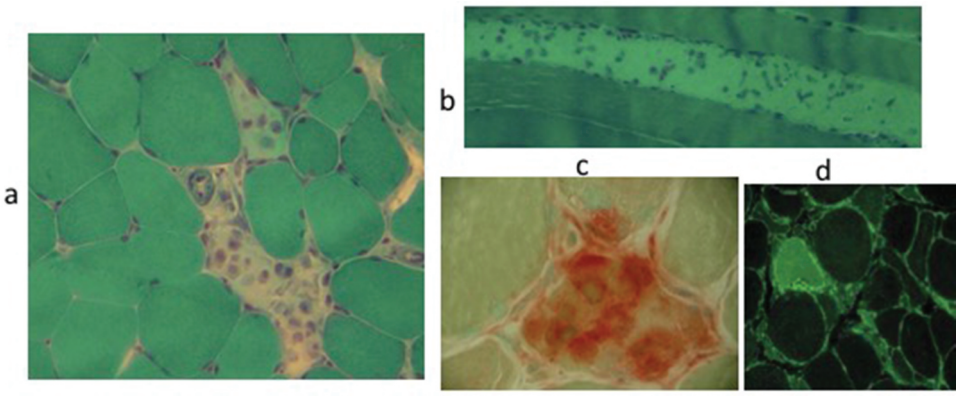

Figure 3. Main histopathological features of Necrotizing Autoimmune Myositis characterized by necrotic fibers (a, b) invaded by macrophages (c), that exhibit spotty MHC-I expression (d) [modified from [1]].

NAM, can very rarely coincide with the initiation of statin therapy, which is implicated as the causative factor in rare cases of acute-onset NAM, but there is no direct and convincing evidence supporting the view that statins play a role in suddenly triggering NAM or worsening a preexisting myopathy in patients who have been taking statins for years [1,29–33]. The most characteristic histological finding in NAM is the abundance of necrotic fibers invaded or surrounded by macrophages; MHC-I upregulation mostly in the necrotic fibers is common but lymphocytic infiltrates are sparse [1,2,7], **as depicted in** Figure 3 **[modified from** [1]**]**. In a number of muscle biopsies there is deposition of complement on the necrotic muscle fibers and occasionally on some blood vessels [1,2,9,28,29].

2.3.2. Necrotizing autoimmune myositis-specific antibodies and role of statins

Two antibodies, one directed against the translational transport protein SRP (Signal Recognition Particle) and another against a 100-kd autoantigen identified as HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) are seen in up to 65% of NAM patients [1,2,9,28–31]. These are important disease markers, but whether they are pathogenic, as proposed [28,32], remains unclear. Since HMGCR is the pharmacological target of statins which can upregulate HMGCR in myotubular cells in tissue cultures [28], anti- HMGCR antibodies have been considered associated with prior statin use. Although this is a very logical hypothesis, in reality these antibodies have been most often observed in statin-naive patients and more commonly in patients with malignancies rather than those taking statins [9,27,33,34]. Arguably, a very small number of patients early on when statins are initiated may experience transient myalgia, and others transient CK elevation but no overt muscle weakness. If myalgia persists, it is a sign of statin intolerance as seen in some patients. The implication, however, that *chronic* statin administration can, all of a sudden, trigger what is labeled as 'statin-myopathy' in the form of NAM with antibodies against HMGCR, a ubiquitous and non-muscle-specific antigen, has not been substantiated [33,34]. Since NAM is now the commonest inflammatory myopathy and more than 25% of Americans above the age of 40 are prescribed statins, the noted association between statins and NAM is likely a chance phenomenon [1,34]

2.3.3. Role of complement in NAM

Because in NAM, in addition to the antibodies, there are necrotic fibers, CD68+ macrophages in the endomysium, and spotty MHC-I expression with complement deposition as depicted in Figure 3, a complement-mediated cytotoxicity with the recruited macrophages representing an antibody-dependent cell-mediated cytotoxicity (ADCC) has been proposed [32]. Although this may seem a reasonable hypothesis, the evidence implicating the complement-dependent pathogenic role of these antibodies via an ADCC mechanism is very weak and unconvincing. Both, SRP and HMGCR, are antibodies directed against non-muscle-specific antigens localized in the endoplasmic reticulum and are highly unlikely immunopathlogically that antibodies against such ubiquitous cytoplasmic antigens can selectively target muscle fibers and cause cell necrosis [31,33,34]. Most importantly, classic muscle immunopathology studies have shown that the expression of MHC-1 and the deposits of C5b-9 complement are *always* observed in necrotic and regenerating fibers due to any cause including nonimmune myopathies [35,36]; in muscular dystrophies for example, the necrotic fibers unambiguously activate complement, which in turn stimulates cellular infiltrates and macrophages [35,36]. Further, the argument that the anti-SRP and HMGCR antibodies can cause atrophy in myotubular cultures [37] is irrelevant to the pathogenesis of NAM, which is characterized by abundant muscle fiber necrosis and devastating muscle fiber destruction, not by nonspecific muscle fiber atrophy. The observations that C1q can be present in the proximity to the sarcolemma alongside IgG deposits and that some scattered necrotic muscle fibers show C5b-9 sarcolemmal deposits [32] may seem compelling regarding involvement of the CP pathway in myofiber necrosis; we need, however, to be cognizant and objectively recognize that such complement activation is inherently associated with muscle fiber necrosis from any cause and do not denote specificity in the immunopathogenesis of NAM. Our concerns and reservations that we have repeatedly expressed since 4 years ago [31,33,34] about the pathogenicity of complement interpretation in NAM proposed by Allenbach et al. [32] are now justified. In a phase 2, randomized, placebo-controlled clinical trial, zilucoplan, a monoclonal antibody against complement C5, did not have significant clinical effects in patients with NAM, and the study was prematurely terminated [ClinicalTrials.gov identifier: NCT04025632]. Patients with NAM based on small open-label series but also in our experience respond very well to IVIg, but this benefit is likely unrelated to complement inhibition but likely due to other immunomodulatory effects exerted by IVIg.

2.4. Anti-synthetase syndrome-overlap myositis (Anti-SS-OM)

These patients present with systemic sclerosis-like lesions, mild-to-moderate proximal muscle weakness, interstitial lung disease, arthritic changes in the form of subluxation of the interphalangeal joints and 'mechanic's hands' [1,2,7]. The anti-SS-OM syndrome is characterized by the presence of antibodies against anti-synthetase, primarily anti-Jo-1; hence, the naming *'anti-Jo-1 syndrome'* that dates back to 30 years ago [38]. These patients seem to also have necrotizing features including CD68+ cells in the perimysium and perifascicular muscle fibers [2,39] but also CD3+ lymphocytes, with the histological signs overlapping those of DM; whether anti-SS-OM is a histologically distinct entity with necrotizing features in the perimysial and perifascicular areas different from the perifascicular lesions seen in DM, as suggested based in small series [2], remains a reasonable possibility that requires careful clinicohistologic confirmation. Antibodies against *aminoacyl-tRNA synthetases*, are detected in 20–30% of these patients [1,2,5,7], with most common the one directed against the histidyl-transfer RNA synthetase (*anti-Jo-1*) which accounts for 75% of all the anti-synthetases and defines the 'anti-synthetase- syndrome.' The pathogenic role of these antibodies, which are directed against ubiquitous cytoplasmic antigens, remains uncertain. Because in anti-SS-OM there is

necrosis in the perifascicular areas that presumably implicate complement activation, this subset may theoretically be amenable to anti-C3 or C5 anti-complement therapeutics.

2.5. Inclusion body myositis (IBM)

IBM is the most common inflammatory myopathy in patients above the age of 50. It is also the most disabling because it responds poorly to all available therapies and experimentally performed clinical trials [1–7]. The disease starts slowly, over years, rather insidiously and often asymmetrically with weakness and atrophy, either in distal upper extremity muscles, such as finger flexors with forearm atrophy, or the lower extremities with quadriceps muscle weakness and frequent falls due buckling of the knees; mild facial muscle weakness and dysphagia are also seen in more than 50% of the patients [1,3–7,40,41].

Inclusion-body myositis is a complex disorder because autoimmunity co-exists with myodegeneration [1,7,41,42]. $CD8^{+}$cytotoxic T-cells not only surround but also invade healthy, non-necrotic muscle fibers, which aberrantly express MHC-I, probably induced by T-cell-activated cytokines; the CD8/MHC-I complex is characteristic of IBM aiding in the histological diagnosis [1,3–7,41–44]. Plasma cells and myeloid dendritic cells are also seen among the endomysial infiltrates, while nonspecific a*nti-cytosolic 5′-nucleotidase- 1A (cN1A*), detected in 33–51% of IBM patients, highlight the immune dysregulation and B-cell activation [1,3–7,41–45]. The evidence of degeneration is highlighted by the presence of autophagic vacuoles with bluish-red material, proteinacious aggregates positive for ubiquitin, tau and TDP43 and congophilic amyloid deposits within the muscle fibers next to the vacuoles, visualized best with crystal violet or fluorescent optics as shown in Figure 4(a) **[as modified from** [1]**];** chronic myopathic changes with atrophy and increased connective tissue as well as 'ragged-red' or cytochrome oxidase–negative fibers due to abnormal mitochondria, are also frequent [1,3–7,41–46]. The co-existence of degeneration and autoimmunity has been the impetus to study their interrelationship. MHC-1 or nitric oxide-induced cell stress along with long-standing proinflammatory cytokines, like interferon-γ and IL1-β, can cumulatively enhance degeneration with further accumulation of stressor molecules, misfolded proteins, and amyloid deposits leading to further disease progression with muscle atrophy and myofiber loss [1,7,10,42–48].

2.5.1. Muscle Amyloid and Neuroinflammation in IBM with comments on the recent label 'Amyloid-Myopathy'

In IBM, bAPP amyloid is deposited within the muscle fibers along with other misfolded protein aggregates; their accumulation along with autophagy seem enhanced by chronic T-cell-mediated cytotoxicity molecules and pro-inflammatory cytokines, such as IFN and IL1b [47–50]. On this basis, immunosuppressive agents have been tried in IBM but all failed probably because the degenerative cascade starts insidiously very early in the disease process, being already advanced when patients seek medical advice [1,7,10,47–52]. More specifically, the pivotal controlled studies with IVIg and steroids were statistically negative [53,54], while the highly scholarly trial with Alemtuzumab targeting activated T cells but also B cells showed clear but small benefits [55] requiting a larger trial.

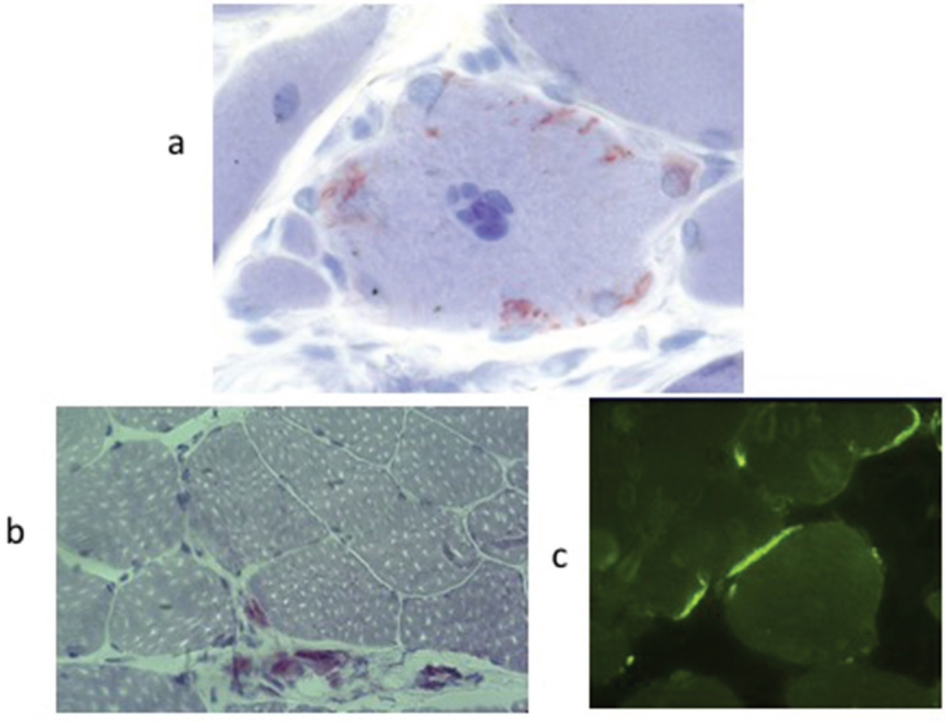

Figure 4. Amyloid deposits within muscle fibers in IBM (a) [modified from [1]]. Amyloid in the connective muscle tissue (b,c) is seen in all kinds of amyloidosis, from neuropathies (b) to systemic (c) and only has diagnostic value [modified from [51,60,61]].

Amyloid can be seen *within* the muscle fibers not only in IBM, as depicted in Figure 4a, but also in several chronic vacuolar myopathies, dystrophies, even in chronic neurogenic conditions, like post-polio syndrome [56]; it does not however denote 'amyloid myopathy' as recently suggested even stating 'unmasking the master of disguise' [57–59]. Apart from such amyloid deposits inside the muscle fibers connected to disease chronicity or neuroinflammation, small or spotty amyloid deposits outside the muscle fibers in the interstitial connective muscle tissue, the perimysium, or around muscle fibers have been repeatedly observed in the patients with amyloid neuropathies, either TTR (Figure 4(b)) or plasma cell dyscrasia (Figure 4 (c)) **[modified from** [51,60,61]**]**, more than 30 years ago [60–62]. In pivotal studies on a large number of amyloid neuropathy patients, such connective tissue amyloid deposits were of diagnostic, but not of pathogenic significance, and clearly not constituting 'amyloid myopathy' as recently proposed [57–59,63]. In a large number of patients with polyneuropathies, the muscle biopsy had a high diagnostic yield for detecting amyloidosis, even more than a nerve biopsy or the abdominal fat [60–62]. In these studies, among patients with various neuropathies, amyloid was detected in the endomysial connective tissue in at least 39 studied patients, concluding that the muscle is not only an excellent tissue to search for generalized amyloidosis due to any cause, such as kidney, heart, plasma-cell dyscrasia, and genetic (TTR) or sporadic amyloid neuropathies but also a useful source to identify, extract and characterize the type of amyloid with biochemistry and immunocytochemistry using antibodies against light chains, AA, or transthyretin as previously done [60,61]. These amyloid deposits have the same diagnostic value, as very recently shown for the skin in amyloid neuropathies [64] The mere presence of amyloid speckles in the connective tissue or decorating the periphery of muscle fibers, as depicted in Figure 4(b,c), does not by any means fulfill clinicopathologic criteria of myopathy and does not clearly represent myopathy; naming them recently as 'amyloid myopathy' based on very few specimens [57–59,63] is not correct.

Amyloid deposits are also unrelated to complement. In IBM, there may be areas of complement deposits in rare necrotic muscle fibers associated with the necrotic process as discussed earlier, but not within the vacuolated or amyloid-positive fibers to justify consideration for anti-complement therapies.

3. SARS-CoV-2 as a potential trigger of IM and role of anti-Complement immunotherapies

The connection of viruses as possible triggers of IM-known for many years [65]- has become timely during the COVID19 pandemic. Because viruses have the potential to break tolerance, they can trigger an immune inflammatory myopathy during or after the infection [1,7,65]. Several attempts, however, to amplify a variety of common viruses, including paramyxoviruses, mumps, coxsackieviruses, influenza, cytomegalovirus, and Epstein–Barr virus, from the muscles of patients with IM have all failed [65]. Perhaps, the best studied viral connection has been with retroviruses in patients infected with HIV or Human-T–cell-lymphotropic Virus-I who developed IM including IBM [1,7,66–69]. In a number of such specimens, retroviral antigens were detected not within the muscle parenchyma but only within some endomysial macrophages (Trojan-horse mode); further, several autoinvasive T cells were clonally driven or retroviral-specific [68]. During the COVID19 pandemic, there has been evidence that some COVID19-infected patients develop multifactorial myalgia and weakness even elevated CK suggestive of an inflammatory myopathy similar to HIV-assocted cases [69]; there has not yet been, however, a convincing clinicopathological series of IM in COVID19-infected patients except of rare case reports [70,71].

Two large series entirely on muscle-autopsied specimens from ICU-hospitalized patients who died from SARS-CoV-2, have now reported lymphocytic infiltrates and a few scattered MHC-1-positive muscle fibers in up to 55% of the examined specimens [72,73]. Other histological but nonspecific features included capillary expression of human myxovirus resistance protein MxA, some NK cells and occasional MAC deposits which however were also seen in SARS-CoV -2-negative ICU controls. Although there was absolutely no clinical information to support myositis, these nonspecific autopsy histological observations were interpreted as COVID-19-postinfectious-immune-mediated myositis [72]. MHC-1 upregulation can be seen in necrotic or regenerating muscle fibers from any cause, including muscular dystrophies [74]; further, active viruses, like HIV/HTLV-1, strongly upregulate MHC-I even on normal muscle fibers in asymptomatic individuals [69]. In an aggressive viral disease like SARS-CoV -2, where cytokines and inflammatory mediators are abundant, scarcely observed lymphoid cells are non-muscle-specific and can be seen in any tissue, as observed in autopsied hearts, nerves, and muscles without clinical myocarditis, neuritis, or myositis [75]. Like any other virus, SARS-CoV-2 has however the potential to trigger myositis, as some rare anecdotal cases suggest [71], but we still need to identify it and define the inflammatory myopathy subtype, along with its frequency and mechanism [75]. The reports from autopsy patients with long-standing weakness due to critical illness neuromyopathy do not provide direct evidence of viral-related myositis; a SARS-CoV-2-myositis should be investigated in infected patients who present with muscle weakness and elevated CK. Although these autopsy series, in spite of the reported claims, did not show myositis in people who have died from COVID19 [75], they did show that nonspecific inflammatory cells can be seen in any tissue of SARS-CoV-2 patients early in the disease due to abundant cytokines and inflammatory mediators. Physicians should be therefore careful not to overdiagnose them as tissue-specific inflammatory or autoimmune disease processes [75]. These autopsy series did convincingly, however, show that SARS-CoV-2, although detectable in the lung tissue, was not found in muscle and did not infect muscle fibers [72,73], which was not- unexpected because no viruses, temporally implicated in viral-triggered myositis, have been up to now detected in muscle or have been shown to infect muscle tissue based on detailed molecular studies [65–69]. Instead, viruses, as convincingly shown with HIV early in that epidemic, can induce

T-cell mediated-cytotoxicity or viral-specific T cells and macrophages that invade muscle fibers without infecting the muscle [1–4,7,66–69,75]. Reports claiming immunohistochemical viral stains or viral-like particles in muscles from ICU patients with severe histological myopathic changes should be viewed with caution.

3.1. Complement and COVID19

Since complement is an integral component of the innate immune response to common viruses, activation of C3 can worsen the COVID-19- associated acute respiratory distress syndrome; as a result, abundant complement deposits can be seen in the lung biopsies of SARS-CoV-2-infected patients [76,77]. On this basis, anti-complement therapies are considered as having potential beneficial effects in COVID-19-infected patients and trials with ravulizumab and eculizumab are currently ongoing [78–80]. In relevance to IM, the clinical importance of this concept applies to patients with DM or NAM where complement plays a role in their pathomechanism. If such patients are infected with COVID-19, very appropriate questions have been raised as to whether anti-complement therapeutics, like a trial with eculizumab, have the potential to exert a protective effect against severe disease worsening or even being a preferable means in treating such rare events [19].

4. Present treatment algorithm for DM, NAM, anti-SS-OM

For patients with DM, NAM and anti-SS-OM, prednisone remains the first-line drug based on experience but not controlled studies. As steroid-sparing agents, mycophenolate is our preferred agent, but others choose Azathioprine or Methotrexate. If frequent relapses occur or the response to steroids is not satisfactory or not well tolerated, IVIg is the best choice, especially in DM based on the strongly positive controlled study [24]; further, IVIg is now FDA-approved for DM. If steroids and IVIg are insufficiently effective, proceed to biologics with the primary one rituximab which, in our experience, has been very helpful in many of our tested patients. Among new agents, the biologics against complement (i.e. Eculizumab), IL-6 (Tocilizumab), CD20/CD19 monoclonals, or FcRn inhibitors like *Efgartigimod* should be investigated in controlled studies [81,82]

5. Expert opinion

The field of Inflammatory myopathies, comprised of disorders originally described by neurologists, has tremendously advanced for 3 decades, from 1980 to 2010, thanks to enormous contributions of Neuromuscular Neurology scholars who, by combining clinical expertise with neuromuscular pathology and immunopathology, recognized distinct disease subtypes, precisely defined their clinicopathological criteria, and performed pivotal clinical trials, such as the successful IVIg trial in Dermatomyositis [24]. Over the last decade, the field is gradually changing hands and direction. Neurologists with muscle pathology and immunopathology training become increasingly scarce with exceptionally few still performing or processing their own patients' muscle biopsies in their own muscle enzyme histochemistry laboratories, as their former scholars and mentors did. Today most clinicians involved in the diagnosis and care of IM patients have different training backgrounds, comprised mostly by rheumatologists, internists, neurorheumatologists, or neurologists/elctromyographers; muscle biopsies are now performed by surgeons, read by pathologists on paraffin sections or with elementary enzyme histochemistry and immunopathology stains and without clinicopathologic assessments or correlations. This disconnection has changed the philosophy of the IM field; the former neuromuscular scholars when looking at their patients' muscle biopsies had the patient's symptoms in mind, thinking of the diagnostic possibilities and therapies, like looking their muscles *in vivo*. The focus has now steadily shifted; muscle-associated antibodies (called 'myositis-specific, ' even if nonpathogenic), muscle imaging, and new clinical phenomenology are leading the way in establishing new diagnostic and classification criteria among same-minded groups. There has even been a change in the name to '*Idiopathic* Inflammatory Myopathies' although it is unclear what idiopathic refers to. We do not call the rheumatoid arthritis, scleroderma, Sjogren's syndrome or multiple sclerosis 'idiopathic' although the knowledge of inflammation and autoimmunity in IM is comparable to the other common autoimmune diseases.

The impact of not relying anymore on clinico-immunopathologic correlations is highlighted in the present review by three issues, the role of complement and autoantibodies, viruses and specifically COVID19 in triggering IM, and the role of muscle amyloid deposits. Complement plays a major role in muscle fiber necrosis due to any cause including muscular dystrophies, as highlighted in the classic studies of Dr Andrew Engel, who convincingly concluded more than 25 years ago that 'there is no evidence to support a role of antibody-dependent complement-mediated muscle fiber injury in the major inflammatory muscle diseases' [35,36]. These studies have clearly shown that the ingress of specific C5b9 complement components into muscle fibers activates the lytic pathway that assembles the MAC, while the chemotactic C5a molecule recruits macrophages to the necrotic fibers. Unfortunately, these classic observations, which are quite valid today, have been forgotten; a series of recent studies repeatedly conclude that nonspecific antibodies against cytoplasmic and ubiquitous antigens are 'complement-fixing' because they were found deposited on complement-bearing necrotic fibers [37], not taking into account that the complement was already there due to ongoing necrosis and had nothing to do with these antibodies, as now supported by a negative anti-complement study. On the other hand, the fundamental role of complement in causing microangiopathy in dermatomyosits, described by three different scholarly groups more than 20 years ago [14–19,23,24] is now viewed as a secondary event because DM is now fancifully labeled as interferonapathy [reviewed in [2]]. I wonder who will prefer to treat DM with anti-interferon type-1 agents (if

exist) instead of IVIg, anti-B cell-targeted therapies, or anti-complement agents, a question especially relevant to DM, which I strongly consider as the main candidate among all IM for anti-complement therapies [19]. The lack of clinico-pathological correlations is best exemplified by the interpretation of COVID19-triggered IM. Based only on autopsy samples from comatose patients who died from a systemic COVID-disease, pathologists have interpreted nonspecific histological muscle findings, such as spotty MHC-1 expression and a few scattered lymphocytic cells, as 'clinically significant' [72], an obvious misinterpretation; it cannot be clinically significant myopathological findings in comatose patients that died from a systemic disease without ever having, when alive, clinical myopathy. During an active viral infection or an aggressive viral systemic disease, nonspecific inflammatory cells or MHC-expression can be seen in any tissue due to release of cytokines and inflammatory mediators, as classically described in other viral infections even without clinical signs of myopathy [67–69]. What was reported in these autopsied muscles has been a rather misleading overinterpretation of the classic immunopathological features described 40 years ago by the legends in the field such as George Karpati and Andrew Engel [43,74]. Another also surprising interpretation is the tiny amyloid deposits seen in the muscle connective tissue. For years, it is known that such amyloid spots in the connective tissue are only of diagnostic significance, similar to the abdominal fat biopsy, seen in all types of amyloidosis, from plasma cell dyscrasic to genetic amyloid neuropathies [57–59]. These tiny amyloid deposits do not represent 'amyloid myopathy' as recently overinterpreted [54–56]; it is not pathologically possible that these connective tissue amyloid dots can cause histological signs of myopathy in patients who clinically have neuropathy.

This personal view, although critical, is aiming to pinpoint how the field of IM is now changing and highlight that a comprehensive expertise and unbiased interpretation of clinicopathological findings still remains the best means to advance the field and capitalize on new therapies. The IM experts should be open-minded to work together with previous leaders in the field and focus on combining excellence in the clinic, being able to distinguish functional weakness or fatigue from true myopathic weakness caused either by an IM subtype or inflammatory dystrophy; correctly interpret the biopsies in conjunction with the clinical features; and appreciate immunology and molecular immunopathology to apply target-specific immunotherapies. One cannot envision how a clinician who is not a neurologist can confidently distinguish muscle weakness due to IM from myasthenia, muscular dystrophy, neuropathy or neuronopathy and interpret the electromyographic findings; or how an electromyographer can judge the significance of the circulating antibodies and express a scholarly and critical opinion in interpreting the immunology and immunopathology; and still how a general pathologist can appreciate the clinical phenomena seen in various IM subtypes or offer an opinion in applying target-specific immunotherapies. The field on immunotherapeutics in IM, such as anti-complement therapeutics highlighted in this review, or against FcRn and B cells [80,81] requires such a combined expertise to select the most suitable targeted therapy in this arguably complex and heterogeneous group of IM.

Disclosure of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

The author(s) reported that there is no funding associated with the work featured in this article.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Dalakas MC, Longo DL. Inflammatory muscle diseases. N Engl J Med. 2015;372:1734–1747.
•• **An important, objective and comprehensive review**
2. Tanboon J, Uruha A, Stenzel W, et al. Where are we moving in the classification of idiopathic inflammatory myopathies? Curr Opin Neurol. 2020;33:590–603.
3. Dalakas MC. Polymyositis, dermatomyositis and inclusion-body myositis. N Engl J Med. 1991;325:1487–1498.
4. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. Lancet. 2003;362:971–982.
5. Pestronk A. Acquired immune and inflammatory myopathies: pathologic classification. Curr Opin Rheumatol. 2011;23 (6):595–604.
6. Needham M, Mastaglia FL. Inclusion body myositis: current pathogenic concepts and diagnostic and therapeutic approaches. Lancet Neurol. 2007;6:620.
7. Dalakas MC. Therapeutic Targets in patients with inflammatory myopathies: present approaches and a look to the future. Neuromuscul Disord. 2006 Apr;16(4):223–236.
8. Cox FM, Titulaer MJ, Sont JK, et al. A 12-year follow-up in sporadic inclusion body myositis: an end stage with major disabilities. Brain. 2011;134(11):3167–3175.
9. Watanabe Y, Uruha, A., Suzuki, S., Nakahara, J., Hamanaka, K., Takayama, K., and Nishino, I. Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry. 2016;87(10):1038–1044.
10. Fiorentino DF1, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. Arthritis Rheum. 2013;65(11):2954–2962.
11. Femia AN1, Vleugels RA, Callen JP. Cutaneous dermatomyositis: an updated review of treatment options and internal associations. Am J Clin Dermatol. 2013;4:291–313.
12. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001;357(9250):96–100.
13. Casiola-Rosen L, Mammen AL. Myositis autoantibodies. Curr Opin Rheumatol. 2012;24(6):602–608.
14. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. Ann Neurol. 1990;27:343–356.
15. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med. 1986;314:329–334.

16. Lahoria R, Selcen D, Engel AG. Microvascular alterations and the role of complement in dermatomyositis. Brain. 2016;139:1891–1903.
• **An important validation about the role of complement in dermatomyositis**
17. Nauta AJ, Trouw LA, Daha M, et al. Direct binding of C1q to apoptotic cells and cell blebs induces complement activation. Eur J Immunol. 2002;32:1726–1736.
18. Sakuta R, Murakami N, Jin Y, et al. Diagnostic significance of membrane attack complex and vitronectin in childhood dermatomyositis. J Child Neurol. 2005;20:597–602.
19. Dalakas MC, Alexopoulos H, Spaeth PJ. Complement in neurological disorders and emerging complement-targeted therapeutics. Nature Rev Neurol. 2020;16(11):601–617.
•• **An excellent and comprehensive review on complement and its role in autoimmune neurological diseases**
20. Greenberg SA, Pinkus JL, Pinkus GS, et al. Interferon-α/β-mediated innate immune mechanisms in dermatomyositis. Ann Neurol. 2005;57:664–678.
21. Suárez-Calvet X, Gallardo E, Nogales-Gadea G, et al. Altered RIG-I/DDX58-mediated innate immunity in dermatomyositis. J Pathol. 2014;233(3):258–268.
22. Basta M, Illa I, Dalakas MC. Increased in vitro uptake of the complement C3b in the serum of patients with Guillain-Barré syndrome, myasthenia gravis and dermatomyositis. J Neuroimmunol. 1996;71:227–229.
23. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J. Clin. Inves. 1994;94:1729–1735.
•• **A fundamental study demonstrating the effect of IVIg on complement**
24. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immunoglobulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329:1993–2000.
•• **A first and the pivotal double-blind study demonstrating the effect of IVIg in dermatomyositis**
25. Amemiya K, Semino-Mora C, Granger RP, et al. Downregulation of TGF-β1 mRNA and protein in the muscles of patients with inflammatory myopathies after treatment with high-dose intravenous immunoglobulin. Clin Immunol. 2000;94:99–104.
26. Raju R, Dalakas MC. Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIg and biological validation of clinically relevant genes. Brain. 2005;128:1887–1896.
27. Allenbach Y1, Drouot L, Rigolet A, et al. Anti-HMGCR autoantibodies in European patients with autoimmune necrotizing myopathies: inconstant exposure to statin. Medicine (Baltimore). 2014;93(3):150–157.
28. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 2011;63(3):713–721.
29. Alshehri A, Choksi R, Bucelli R, et al. Myopathy with anti-HMGCR antibodies: perimysium and myofiber pathology. Neurol Neuroimmunol Neuroinflamm. 2015 Jun 4; 2(4):e124.
30. Dalakas MC. Necrotising autoimmune myopathy (NAM): antibodies seem to be specific markers in aiding diagnosis. J Neurol Neurosurg Psychiatry. 2016;87:1037.
31. Dalakas MC. Inflammatory myopathies: update on diagnosis, pathogenesis and therapies, and COVID-19-related implications. Acta Myologica. 2020;39:289–301. cCollection 2020.
32. Allenbach Y, Arouche-Delaperche L, Preusse C, et al. Necrosis in anti-SRP + and anti-HMGCR + myopathies. Neurology. 2018;6: e507–e517.
33. Dalakas MC. Are autoantibodies pathogenic in necrotizing myopathy? Nature Rev Rheumatol. 2018 May;14(5):251–252.
34. Dalakas MC. Case 22-2019: a 65-Year-Old Woman with Myopathy. N Engl J Med. 2019;381:1693–1694.
35. Spuler D, Engel AG. Unexpected sarcolemmal complement membrane attack complex deposits on nonnecrotic muscle fibers in muscular dystrophies. Neurology. 1998;50:41–46.
• **Pioneering study demonstrating the role of complement in muscle fiber necrosis**
36. Engel AG, Biesecker G. Complement activation in muscle fiber necrosis: demonstration of the membrane attack complex of complement in necrotic fibers. Ann Neurol. 1982;12:289–296.
•• **Pioneering study demonstrating the role of complement in muscle fiber necrosis**
37. Arouche-Delaperche L, Allenbach Y, Amelin D, et al. Pathogenic role of anti-signal recognition protein and anti-3-hydroxy-3-methylglutaryl-CoA reductase antibodies in necrotizing myopathies: myofiber atrophy and impairment of muscle regeneration in necrotizing autoimmune myopathies. Ann Neurol. 2017;81:538–548.
38. Love LA, Leff RL, Frazer DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore). 1991;70:360–374.
39. Bucelli RC, Pestronk. A Immune myopathies with perimysial pathology. Clinical and laboratory features. Neurol Neuroimmunol Neuroinflamm. 2018 Mar;5:e434.
40. Badrising UA, Maat-Schieman M, van Duinen SG, et al. Epidemiology of inclusion body myositis in the Netherlands: a nationwide study. Neurology. 2000;55(9):1385–1388.
41. Greenberg SA. Inclusion body myositis: clinical features and pathogenesis. Nat Rev Rheumatol. 2019 May;15(5):257–272.
42. Dalakas MC. Molecular links between inflammation and degeneration: lessons on "Neuroinflammation" using IBM as a model. Ann Neurology. 2008;64:1–3.
43. Emslie-Smith AM, Arahata K, Engel AG. Major histocompatibility complex class I antigen expression, immunolocalization of interferon subtypes, and T cell-mediated cytotoxicity in myopathies. Hum Pathol. 1989;20:224–231.
44. Schmidt J, Rakocevic G, Raju R, et al. Upregulated Inducible Costimulator and ICOS-Ligand in inclusion body myositis muscle: significance for $CD8^+$ T cell Cytotoxicity. Brain. 2004;127:1182–1190.
45. Pluk H, van Hoeve Bj P, van Dooren SH, et al. Autoantibodies to cytosolic 5′-nucleotidase 1A in inclusion body myositis. Ann.Neurol. 2013;73(3):397–407.
46. Ivanidze J, Hoffmann R, Lochmüller H, et al. Inclusion body myositis: laser microdissection reveals differential up-regulation of IFN-γ signaling cascade in attacked versus nonattacked myofibers. Am J Pathol. 2011;179(3):1347–1359.
47. Schmid J, Barthel K, Zschüntzsch J, et al. Nitric oxide stress in sIBM muscle fibres: inhibition of iNOS prevents IL-1β-induced accumulation of β-amyloid and cell death. Brain. 2012;135:1102–1114.
48. Schmidt J, Barthel K, Wrede A, et al. Interrelation of inflammation and APP in sIBM: IL-1β induces accumulation of β-amyloid in skeletal muscle. Brain. 2008;131:1228–1240.
49. Lünemann JD, Schmidt J, Schmid D, et al. Beta-amyloid is a substrate of autophagy in sporadic inclusion body myositis. Ann Neurol. 2007 May;61(5):476–483.
50. Schmidt J, Dalakas MC. Inclusion body myositis: from immunopathology and degenerative mechanisms to treatment perspectives. Expert Rev Clin Immunol. 2013 Nov;9(11):1125–1133.
51. Dalakas MC. Sporadic inclusion body myositis: diagnosis, pathogenesis and therapeutic strategies. Nature Rev Rheumatoll Nat Clin Prac Neurol. 2006;2:437–447.
52. Mastaglia FL1, Zilko PJ. Inflammatory myopathies: how to treat the difficult cases. J Clin Neurosci. 2003;10(1):99–101.
53. Dalakas MCIBMIVIG, Dalakas MC, Sonies B, et al. Treatment of inclusion body, myositis with IVIg: a double-blind, placebo-control study. Neurology. 1997;48:712–716.
54. Dalakas MC, Koffman BM, Fujii M, et al. A controlled study of intravenous immunoglobulin combined with prednisone in the treatment of IBM. Neurology. 2001;56:323–327.
55. Dalakas MC, Rakocevic G, Schmidt J, et al. Effect of Alemtuzumab in patients with inclusion body myositis. Brain. 2009;132:1536–1544.
56. Semino-Mora C, Dalakas MC. Rimmed vacuoles with beta-amyloid and ubiquitinated filamentous deposits in the muscles of patients with long-standing denervation (postpoliomyelitis muscular

atrophy): similarities with inclusion body myositis. Hum Pathol. 1998 Oct;29(10):1128–1133.
57. Liewluck T, Milone M. Characterization of isolated amyloid myopathy. Eur J Neurol. 2017;24(12):1437–1445.
58. Pinto MV, Milone M, Mauermann ML, et al. Transthyretin amyloidosis: putting myopathy on the map. Muscle Nerve. 2020;61(1):95–100.
59. Alamr M, Milone M, Naddaf E, et al. Interstitial amyloidosis in sporadicinclusion body myositis. Muscle Nerve. 2021;1–5. https://doi.org/10. 1002/mus.27362
60. Dalakas MC, Engel WK. Amyloid in hereditary amyloid polyneuropathy is related to prealbumin. Arch Neurol. 1981;38(7):420–422.
61. Dalakas MC, Cunningham G. Characterization of amyloid deposits in biopsies of 15 patients with ?sporadic? (non-familial or plasma cell dyscrasic) amyloid polyneuropathy. Acta Neuropathologica. 1986;69(1–2):66–72.
62. Dalakas MC, Fujihara S, Askanas V, et al. Nature of amyloid deposits in hypernephroma. Immunocytochemical studies in 2 cases associated with amyloid polyneuropathy. Am J Pathol. 1984;116(3):447–454.
63. Ono E, Ishii A, Higashi Y, et al. Monoclonal gammopathy of renal significance (MGRS)-related AL amyloidosis complicated by amyloid myopathy: a case report. BMC Nephrology. 2021;22(1). DOI:10.1186/s12882-021-02272-7.
64. Leonardi L, Adam C, Beaudonnet G, et al. Skin amyloid deposits and nerve fiber loss as markers of neuropathy onset and progression in hereditary transthyretin amyloidosis. Eur. J. Neurol. 2022 Jan 31. DOI:10.1111/ene.15268
65. Leff RL, Love LA, Miller FW, et al. Viruses in idiopathic inflammatory myopathies: absence of candidate viral genomes in muscle. Lancet. 1992;339(8803):1192–1195.
66. Dalakas MC. Polymyositis Associated With AIDS Retrovirus. JAMA. 1986;256(17):2381–2383.
67. Cupler EJ, Leon-Monzon M, Miller J, et al. Inclusion body myositis in HIV-1 and HTLV-1 infected patients. Brain. 1996;119(6):1887–1893.
• **First demonstration of HIV with inclusion body myositis providing viral and immunopathological evidence**
68. Dalakas MC, Rakocevic G, Shatunov A, et al. Inclusion body myositis with human immunodeficiency virus infection: four cases with clonal expansion of viral-specific T cells. Ann Neurol. 2007;61(5):466–475.
69. Leon-Monzon M, Illa I, Dalakas MC. Polymyositis inpatients infected with human T-cell leukemia virus type I: the role of the virus in the cause of the disease. Ann Neurol. 1994;36(4):643–649.
70. Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19–triggered autoimmune neurologic disease. Neurol Neuroimmunol Neuroinflamm. 2020;7(5):e781.
71. Pitscheider L, Karolyi, M., Burkert, F. R., Helbok, R., Wanschitz, J. V., Horlings, C.,and Löscher, W. N. Muscle involvement in SARS-CoV-2 infection. Eur. J. Neurol. European. 2021;28(10):3411–3417.
72. Aschman T, Schneider J, Greuel S, et al. Association between SARS-CoV-2 Infection and immune-mediated myopathy in patients who have died. JAMA Neurol. Published online 2021 Jun 11;78 (8):948.
73. Suh J, Mukerji SS, Collens SI, et al. Skeletal muscle and peripheral nerve histopathology in COVID-19. Neurology. 2021;97(8):e849–e858.
74. Karpati G, Pouliot Y, Carpenter S. Expression of immunoreactive major histocompatibility complex products in human skeletal muscles. Ann Neurol. 1988;23(1):64–72.
•• **Fundamental observation about the role of MHC-1 in myositis**
75. Dalakas MC. Non-convincing evidence of SARS-CoV-2-related Myositis in autopsied muscles. JAMA Neurol. [2021 Nov 22]. DOI: 10.1001/jamaneurol.2021.4336
76. Hatzidionysiou K, Svenungsson E, Faustini F. Could severe COVID-19 be considered a complementopathy? Lupus Sci Med. 2020;7(1):e000415.
77. Risitano AM, Mastellos DC, Huber-Lang M, et al. Complement as a target in COVID-19? Nature Reviews Immunology. 2020;20 (6):343–344.
78. Smith K, Pace A, Ortiz S, et al. A Phase 3 Open-label, Randomized, Controlled Study to Evaluate the Efficacy and Safety of Intravenously Administered Ravulizumab Compared with Best Supportive Care in Patients with COVID-19 Severe Pneumonia, Acute Lung Injury, or Acute Respiratory Distress Syndrome: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1):639.
79. Giudice V, Pagliano P, Vatrella A, et al. Combination of ruxolitinib and eculizumab for treatment of severe SARS-CoV-2-related acute respiratory distress syndrome: a controlled study. Frontiers in Pharmacology. 2020;11:857.
80. Mastaglio S, Ruggeri A, Risitano AM, et al. The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. Clinical Immunology. 2020 (Orlando, Fla.);215:108450.
81. Dalakas MC. B cells as therapeutic targets in autoimmune neurological disorders. Nature Clinical Practice Neurology. 2008;4 (10):557–567.
82. Dalakas MC, Spaeth PJ. The importance of FcRn in Neuro-immunotherapies: from IgG catabolism, FCGRT gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. Adv Ther Neurol. 2021 Feb 26;14:17562864219 97381.