Sporadic inclusion body myositis: new insights and potential therapy

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Purpose of the review
To describe new insights and developments in the pathogenesis, diagnosis and treatment of sporadic inclusion body myositis (IBM).

Recent findings
Various hypothesis about the pathogenesis of IBM continue to be investigated, including autoimmune factors, mitochondrial dysfunction, protein dyshomeostasis, altered nucleic acid metabolism, myonuclear degeneration and the role of the myostatin pathway. Serum autoantibodies against cytosolic 5′-nucleotidase 1A have been identified in IBM showing moderate diagnostic performance. The differential diagnostic value of histopathological features, including different protein aggregates, continues to be evaluated. MRI may also be of monitoring value in IBM. New therapeutic strategies are being tested in IBM patients, namely the upregulation of the heat shock response and the antagonism of myostatin.

Summary
Recent important advances have occurred in IBM. These advances, including recent and ongoing clinical trials, may lead to earlier diagnosis and improved understanding and treatment of the disease. Despite improved knowledge, IBM continues to be a puzzling disease and the pathogenesis remains to be clarified. An interdisciplinary, bench to bedside translational research approach is crucial for the successful identification of novel treatments for this debilitating, currently untreatable disorder.

Keywords
inclusion body myositis, myopathies, pathogenesis, treatment

INTRODUCTION

Sporadic inclusion body myositis (IBM) is an acquired muscle disease that predominantly affects individuals older than 45 years of age. The exact prevalence of the disease is uncertain and varies between geographic regions, with prevalence estimates in white populations ranging 1–71 people per million, reaching 139 per million above the age of 50 years [1▪▪]. However, the prevalence of IBM is probably higher as the condition is often undiagnosed or misdiagnosed, which contributes to a diagnostic delay on average of at least 5 years [2,3].

The pathogenesis of IBM is unknown, and despite being classically classified alongside polymyositis, dermatomyositis and immune-mediated necrotizing myopathies as an idiopathic inflammatory myopathy, IBM is a very distinct condition characterized by a slowly progressive course, often with asymmetric weakness, early weakness of the finger flexors and quadriceps muscles, the coexistence of inflammatory and degenerative changes and resistance to immunosuppressive treatment [3–7].

This review focuses on new insights and developments in the pathogenesis, diagnosis and treatment of IBM.

INCLUSION BODY MYOSITIS PATHOGENESIS: NEW INSIGHTS

Multiple hypothesis about the pathogenesis of IBM have been proposed (Fig. 1). Environmental factors (e.g., viral infection), ageing, genetic susceptibility, autoimmunity, accumulation of toxic proteins, myonuclear degeneration, endoplasmic reticulum stress, impairment of autophagy, disruption of the ubiquitin–proteasome system (UPS), myostatin signalling,

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KEY POINTS

- Evidence for the role of autoimmunity, mitochondrial dysfunction, protein dyshomeostasis, altered nucleic acid metabolism and myonuclear degeneration in IBM pathogenesis continues to accumulate.
- In spite of new insights, the primary disease mechanism and the exact interaction between different pathways involved in IBM pathogenesis is yet to be determined.
- The new European Neuromuscular Centre research diagnostic criteria will allow the enrolment of patients at earlier disease stages in future clinical trials.
- MHC class I upregulation, mitochondrial abnormalities and positive immunostaining for p62, TDP-43 and LC3 protein aggregates may have diagnostic potential.
- Autoantibodies against cN1A have moderate diagnostic performance in IBM.
- Targeting protein dyshomeostasis and blocking the myostatin pathway may be promising therapeutic approaches in IBM.

mitochondrial dysfunction and alterations of nucleic acid metabolism have all been proposed to play a role in IBM pathogenesis [8–11]. However, the interplay between these processes and the primary event that leads to the coexistence of autoimmune and degenerative changes remains uncertain.

Regarding the immune mechanisms, the discovery of the first serum autoantibody marker for IBM, targeting cytosolic 5′-nucleotidase 1A (cN1A), represents an important advance [12,13▪▪,14▪▪]. Using a commercial anti-cN1A antibody to stain muscle tissue of IBM patients, it has been shown that cN1A immunoreactivity is predominantly located in rimmed vacuoles and areas of myonuclear degeneration, suggesting a mechanistic link between the inflammatory and degenerative components of IBM [13▪▪]. In another study, the analysis of serum cytokines and the immunophenotyping in peripheral blood and muscle tissue of IBM patients showed that IBM patients had increased levels of T helper 1 cytokines and chemokines, increased levels of $CD8^+CD28^-$ T-cells (interferon-γ producers) and decreased frequency of circulating regulatory T-cells ($CD4^+CD25^+CD127lowFOXP3^+$), compared to healthy controls. The specificity of these findings and the therapeutic potential of modulating the T helper 1 and regulatory T-cell response in IBM remain to be determined [15▪].

Recently, a reduced expression of micro-RNA-1 (miRNA-1), miRNA-133a and miRNA-133b has been reported in IBM (and also in polymyositis and dermatomyositis) muscle tissue versus nonmyositis controls. These miRNAs are critical for muscle differentiation and their reduction correlated with augmented expression of several inflammatory cytokines, namely tumour necrosis factor-α and interleukin-1β [16▪]. In mechanistic experiments, tumour necrosis factor-α inhibited the expression of the above miRNAs and blocked the differentiation of human and mouse myoblasts into myocytes/myotubes in a nuclear factor κB-dependent manner. This inhibition of differentiation was overcome by miRNA-1/133a/133b overexpression. The authors suggest that these results may provide a mechanistic link between the inflammatory and degenerative components of IBM, but this may not be unique to IBM because similar miRNA changes were observed in polymyositis and dermatomyositis [16▪].

Regarding mitochondrial dysfunction, a correlation between the degree of inflammation, degree of mitochondrial changes and atrophy was recently described in IBM muscle biopsies, suggesting a link between these findings [17▪]. The authors hypothesize that in IBM, the ongoing inflammation and cytokine environment, the associated production of reactive oxygen and nitrogen species and the associated endoplasmic reticulum stress have a role in the initiation of mitochondrial DNA damage, leading to the accumulation of clonally expanded mitochondrial DNA deletions and respiratory deficiency, a phenomenon that is not compensated by the malfunctioning cell repair mechanisms. Accumulated mitochondrial mutations could have deleterious effects in the muscle tissue (e.g., atrophy, splitting and breakage), explaining the correlation between respiratory chain deficiency and muscle atrophy [17▪,18,19].

Protein dyshomeostasis continues to prompt great interest as a potential pathogenic mechanism and therapeutic target in IBM. Impaired protein degradation by autophagy and disruption of the UPS may lead to protein accumulation and aggregation and subsequent myofibre injury. Proteins which target ubiquitinated proteins for degradation and autophagy-associated proteins can be found in the sarcoplasm of IBM muscle tissue, for example, valosin-containing protein, Ubiquitin-binding protein p62 (p62), Microtubule-associated proteins 1A/1B light chain 3 (LC3) and neighbour of *BRCA 1* gene 1 (*NBR1*) [20–25]. This suggests either an increased need for protein degradation or impaired UPS and/or autophagy [26]. The colocalization of protein aggregates, immunoproteasomes and major histocompatibility complex (MHC) class I antigens in IBM muscle fibres suggests a possible link between protein degradation and inflammation [27]. One potential therapeutic approach in IBM could therefore be targeting protein dyshomeostasis, for

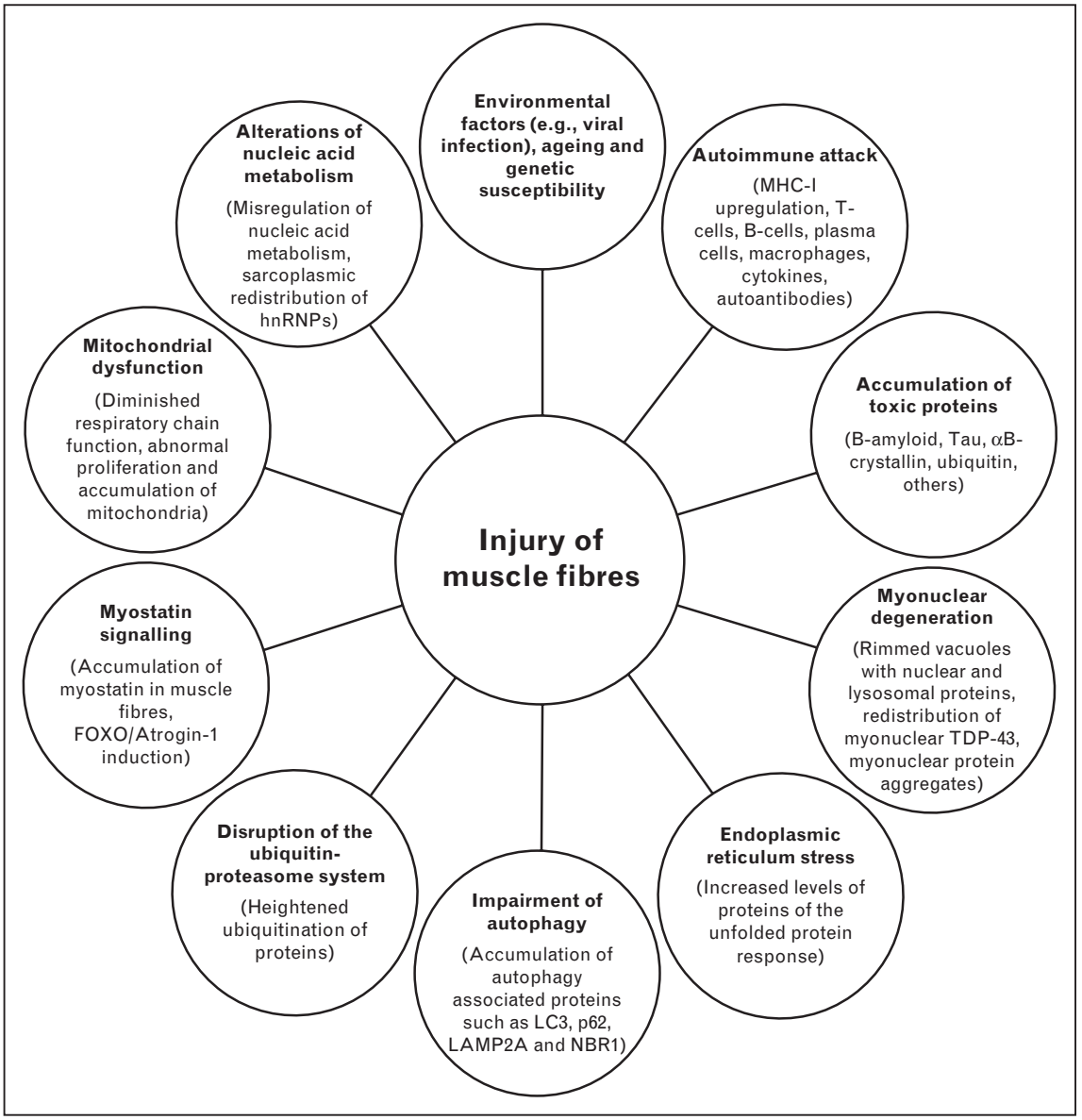

FIGURE 1. Potential pathogenic mechanisms leading to myofibre injury in sporadic inclusion body myositis. FOXO, forkhead box protein; hnRNPs, heterogeneous nuclear ribonucleoproteins; LAMP2A, lysosome-associated membrane protein 2; LC3, microtubule-associated proteins 1A/1B light chain 3; MHC-I, major histocompatibility complex class I; NBR1, next to BRCA1 gene 1 protein; p62, ubiquitin-binding protein p62; TDP-43, TAR DNA-binding protein 43.

example with drugs that are capable of inducing the production of molecular chaperones, such as heat shock proteins, a group of highly conserved molecules involved in preventing the misfolding of proteins and therefore responsible for preventing protein aggregation.

Some of the proteins that accumulate in the sarcoplasm and rimmed vacuoles of IBM muscle tissue are typical of nuclei and lysosomes. One of the most abundant of these proteins seems to be TAR DNA-binding protein 43 (TDP-43) [28]. Along with TDP-43, several heterogeneous nuclear ribonucleoproteins (hnRNPs) such as hnRNPA1, hnRNPA2/B1 and hnRNPC1/C2, have also been shown to accumulate in the sarcoplasm of IBM muscle tissue [29▪▪,30▪▪]. These results support the hypothesis that myonuclei degeneration and RNA metabolism impairment may be also important phenomena in the pathogenesis of IBM [29▪▪,30▪▪, 31–34].

INCLUSION BODY MYOSITIS DIAGNOSIS: NEW INSIGHTS

The muscle biopsy of patients with IBM can show a wide range of changes, including infiltration of the

endomysium by mononuclear cells which may surround and invade non-necrotic muscle fibres (partial invasion), rimmed vacuoles, eosinophilic inclusions, amyloid inclusions, ragged red fibres, cytochrome oxidase negative (COX−) and succinate dehydrogenase positive (SDH+) fibres, sarcolemmal expression of MHC class I, cytoplasmic and/or nuclear tubulofilaments visualized with electron microscopy and various morphological features, such as fibre hypertrophy/atrophy, increased numbers of internal nuclei, split fibres, endomysial fibrosis and necrotic and regenerating fibres. Several immunoreactive protein aggregates have been described, such as p62, phosphorylated tau, TDP-43 and valosin-containing protein. However, none of the protein aggregates is IBM-specific and there is controversy regarding its presence, relative abundance and significance [9,26,35].

The combination of partial invasion, rimmed vacuoles and either amyloid or 15–18 nm tubulofilamentous inclusions visualized with electron microscopy is considered very specific of IBM [36]. However it is now widely recognized that patients with clinically typical IBM may not present this combination of features, which lacks sensitivity, especially in early disease stages [3,37▪]. However, there is still a paucity of data regarding the differential diagnostic performance of pathological findings, both individually and combined.

Over the last few years there has been a shift from a heavily pathologically focused diagnosis of IBM into a more clinically focused diagnosis supported by some but not necessarily all the typical IBM histopathological features. However, it should be noted that despite the existence of an IBM typical early disease pattern characterized by finger flexor and knee extensor weakness, not all patients have this pattern, and the muscle biopsy remains a critical investigation in the differential diagnosis of IBM.

This shift has been reflected in the latest European Neuromuscular Centre diagnostic criteria for IBM (Table 1), which include the following three categories: 'clinico-pathologically defined IBM', 'clinically defined IBM' and 'probable IBM' [38▪▪]. The last two categories are more flexible in terms of the required pathological features, contributing to an increase of the overall sensitivity of the European Neuromuscular Centre criteria and allowing the selection of patients at earlier disease stages, when they may be more amenable to treatment [38▪▪].

Two recent studies assessed the differential diagnostic performance of various pathological features in IBM. Brady *et al.* [39▪▪] investigated markers of protein aggregates, inflammation and

Table 1. European Neuromuscular Centre inclusion body myositis research diagnostic criteria 2011

Diagnostic subgroup	Clinico-pathologically defined IBM	Clinically defined IBM	Probable IBM
Clinical features			
Duration of weakness > 12 months	X	X	X
Age at onset > 45 years	X	X	X
Creatine kinase ≤ 15 times ULN	X	X	X
FF weakness > SA weakness and/or KE weakness ≥ HF weakness	X	–	–
FF weakness > SA weakness; KE weakness ≥ HF weakness	–	X	–
FF weakness > SA weakness or KE weakness ≥ HF weakness	–	–	X
Pathological features			
Endomysial inflammatory infiltrate	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Rimmed vacuoles	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Protein accumulation[a] or 15–18 nm filaments	X	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features
Upregulation of MHC class I	–	At least one, but not all of the four pathological features	At least one, but not all of the four pathological features

FF, finger flexion; HF, hip flexion; IBM, inclusion body myositis; KE, knee extension; MHC class I, major histocompatibility complex class I; SA, shoulder abduction; ULN, upper limit of normal.
[a]Demonstration of amyloid or other protein accumulation by established methods (e.g., for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43).
Adapted with permission from [38▪▪].

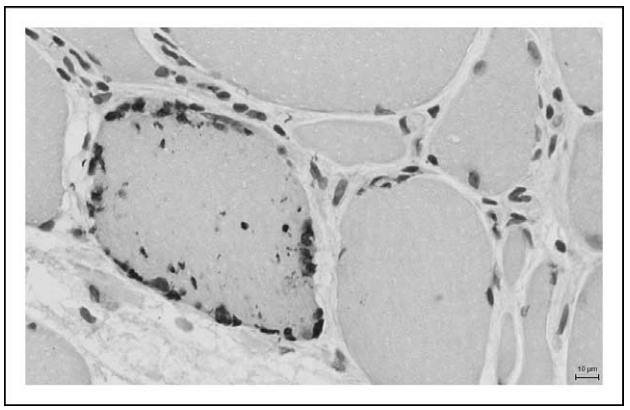

FIGURE 2. Characteristic p62 staining pattern in inclusion body myositis [39▪▪] The following pattern of p62 immunoreactivity is more characteristic of IBM: strongly stained, discreet and clearly delineated, round or angular aggregates, variable in number and size within a muscle fibre but rarely filling it and predominantly located subsarcolemmal, but also perinuclear and adjacent to vacuoles.

mitochondrial changes in IBM. In the presence of rimmed vacuoles, the combination of increased MHC class I (or endomysial T-cells) and a characteristic p62 staining pattern (Fig. 2) distinguished IBM from other myopathies with rimmed vacuoles (93% sensitivity, 100% specificity). In the absence of rimmed vacuoles, and compared with steroid responsive inflammatory myopathies (polymyositis and dermatomyositis), the presence of COX−/SDH+ fibres had excellent sensitivity (100%) and moderate specificity (73%) for IBM, although the above characteristic p62 staining pattern had excellent specificity (100%) but low sensitivity (44%). Therefore, the absence of COX−/SDH+ fibres raises doubt on the diagnosis of IBM, whereas the presence of the characteristic p62 pattern may help to exclude the diagnosis of polymyositis/dermatomyositis when rimmed vacuoles are absent. In another study, Hiniker *et al.* [40▪] evaluated the diagnostic utility of the markers LC3, p62 and TDP-43 in differentiating IBM from possible IBM, polymyositis and polymyositis with COX− fibres. After receiver operating characteristic curve analysis and cut-off determination, the authors suggested that the following thresholds could be of diagnostic value: more than 14% LC3 positive fibres (100% specificity, 83% sensitivity), more than 20% p62 positive fibres (100% specificity, 50% sensitivity) and more than 7% TDP-43 positive fibres (100% specificity, 67% sensitivity) [40▪].

The above mentioned identification of anti-cN1A autoantibodies in IBM represents another important diagnostic advance. High antibody reactivity achieved 96–98% specificity (33–34% sensitivity), whereas moderate reactivity showed 60–70% sensitivity and 89–92% specificity for the diagnosis of IBM in a cohort of patients with neuromuscular diseases, providing a good balance between sensitivity and specificity. When it becomes commercially available, anti-cN1A testing could represent an additional helpful tool to aid in the diagnosis of IBM in clinical practice, particularly at early disease stages [12,13▪▪,14▪▪]. Anti-cN1A antibodies are also good candidates to be incorporated in future IBM diagnostic criteria. In addition to the Immunoglobulin G (IgG) isotype, Immunoglobulin M (IgM) and Immunoglobulin A (IgA) antibodies have also been described [41]. The isotype pattern varies between patients, and it has been proposed that the levels of all three isotypes should be considered to improve diagnostic accuracy. Individually, IgG more than 0.9 absorbance units had 51% sensitivity and 94% specificity, IgA more than 1.2 absorbance units had 49% sensitivity and 95% specificity and IgM more than 1.9 absorbance units had 53% sensitivity and 96% specificity. The combination of isotypes (IgM >1.9, IgA >1.1 or IgG >1.3) increased sensitivity to 76%, retaining a good level of specificity (91%) [41].

Finally, the role of MRI in the diagnosis and monitoring of IBM and muscle diseases in general is increasing [42]. Fatty replacement can be seen on T1-weighted sequences and muscle oedema can be seen on T2-weighted sequences with fat suppression, such as the short tau inversion recovery sequence (Fig. 3). Mimicking the typical clinical presentation, it has been reported that fatty replacement occurs preferentially in the deep finger flexors [43–46] and in the quadriceps femoris muscles [44,45,47]. A relative sparing of the rectus femoris [44,45] and preferential fat accumulation within the medial head of gastrocnemius (in comparison with soleus and lateral gastrocnemius) have also been described [44,45,47]. Bone marrow oedema (interpreted as inflammation) on short tau inversion recovery images can also be seen, but inflammation is usually less prominent than fatty replacement [43,44,46]. Despite being well described, the differential diagnostic performance of the above MRI pattern has not been established and MRI features are not currently included in IBM diagnostic criteria.

INCLUSION BODY MYOSITIS TREATMENT: NEW INSIGHTS

There is no effective treatment for IBM [3,6]. New pathogenesis insights [4,9] have led to the search of alternative therapeutic approaches [6,7].

One of these new approaches is the inhibition of the myostatin pathway. Myostatin belongs to the

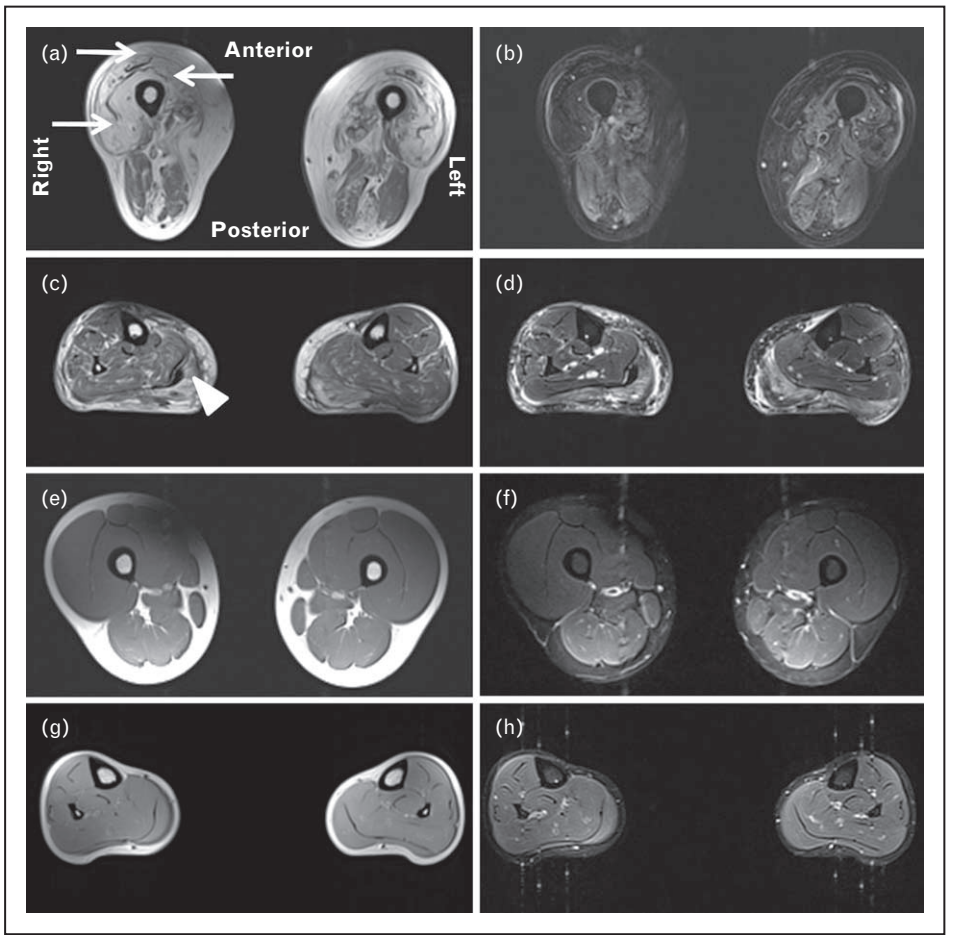

FIGURE 3. Muscle MRI of a patient suffering from sporadic inclusion body myositis and from a healthy control. Axial MRI images of a patient with IBM (a–d) and a healthy control (e–h) with MRI T1-weighted images on the left and the STIR images on the right side. Increased signal within muscles on T1-weighted sequences indicate fatty infiltration whilst on STIR sequences indicate muscle oedema. The patient shows abnormalities typical of IBM with fatty atrophy of the quadriceps muscles in the thigh (a, arrows) and most marked involvement of medical gastrocnemius in the calf (c, arrowhead). Muscle inflammation is evident within many thigh muscles (b) and within gastrocnemius in the calf (d). Corresponding images for a healthy volunteer show homogenous low-signal intensity within muscles. IBM, inclusion body myositis; STIR, short tau inversion recovery.

transforming growth factor-β superfamily and is a negative regulator of skeletal muscle mass. It acts by binding to the activin receptor IIB (ActRIIB)/Alk4/5 receptor complex resulting in activation of the mothers against decapentaplegic homolog 2/3 (SMAD2/3) and mitogen-activated protein kinase intracellular signalling pathways and in inhibition of the phosphoinositide 3-kinase intracellular signalling pathway, leading to changes in gene transcription and effects on protein synthesis that culminate in muscle atrophy [48]. Myostatin accumulation has been shown in IBM muscle fibres [49] and transforming growth factor-β superfamily signalling through the ActRIIB receptor has also been shown to be elevated in IBM muscle tissue (using a SMAD2/3 phosphorylation assay) [50]. Myostatin antagonists can act extracellularly by either binding directly to myostatin (myostatin antibodies, the soluble myostatin receptor ActRIIB-Fc, follistatin, follistatin-related protein 3 (FSTL3), myostatin propeptide, decorin peptides and growth and differentiation factor-associated serum protein 1 (GASP1) or by binding to its receptor complex (ActRIIB antibodies). Some of the myostatin antagonists are naturally occurring molecules (follistatin, FSTL3, myostatin propeptide and GASP1) [48].

Bimagrumab (BYM338), a fully human monoclonal antibody that binds competitively to ActRIIB, was recently tested in a small study enrolling 14 IBM patients (11 Bimagrumab, three Placebo) [50]. A single high dose (30 mg/kg intravenously) of Bimagrumab was administered. After 8 weeks, both MRI thigh muscle volume (right leg +6.5%, $P = 0.024$;

left leg +7.6%, $P=0.009$) and lean body mass (+5.7%, $P=0.014$) increased in the Bimagrumab group versus Placebo. Improvement in the 6-min walking distance test was also observed, peaking at 16 weeks (+14.6%, $P=0.008$, 12/14 patients with follow-up data) [50].

A phase IIb/III randomized, double-blind, placebo-controlled trial is ongoing [51]. The study aims to enrol 240 patients worldwide and will contain four treatment groups in equal proportions as follows: Bimagrumab at 10, 3 and 1 mg/kg and Placebo given intravenously every 4 weeks. Physical function, muscle strength (including knee extension strength), mobility, quality of life and swallowing function, amongst other outcomes, will be assessed at 52 weeks, the primary outcome being change from baseline in the 6-min walking distance test [51]. Myostatin inhibition using Bimagrumab seems a promising approach. However, its long-term safety profile remains to be determined as well as whether the potential to increase muscle volume will actually translate into improved muscle strength and performance. The relationship between changes in muscle mass, muscle strength and physical function is not linear, and it is important to analyse all these outcomes, as they provide complementary information [52].

A gene therapy approach using follistatin to inhibit the myostatin pathway is also being tested. The follistatin gene (*FS344*) is intramuscularly delivered by adeno-associated virus. This open-label trial aims to enrol nine IBM patients, distributed in three groups each with three patients: low dose (2×10^{11} viral genomes (vg)/kg, single leg injection), medium dose (3×10^{11} vg/kg, bilateral quadriceps injection) and high dose (6×10^{11} vg/kg, bilateral quadriceps injection). The primary outcome of the trial is safety; secondary outcomes include changes in muscle function and strength, bilateral MRI and biopsy of quadriceps muscles and thigh circumference measurement [53]. One potential advantage of this approach is that a single administration of adeno-associated virus-FS344 could conceivably lead to long-term expression of the follistatin gene.

Targeting the heat shock response represents another potential therapeutic approach in IBM. This approach is supported by the above described evidence for the role of protein dyshomeostasis in the pathogenesis of IBM. A recent randomized, double-blind, placebo-controlled trial was conducted with Arimoclomol, an orally administered drug that can up-regulate the heat shock response by amplifying heat shock protein expression [54]. The primary outcome of the study was safety and tolerability. Arimoclomol 100 mg three times a day ($n=16$) and Placebo ($n=8$) were administered for 4 months, with a subsequent 8-month blinded follow-up phase. The drug was well tolerated by patients. Furthermore, at 8 months, we detected a trend of slower decline (change) in muscle strength (manual muscle testing and right-hand grip maximum voluntary isometric contraction testing) and physical function (IBM functional rating scale) with Arimoclomol as compared with placebo-treated controls [54]. Targeting protein homeostasis may be a valid therapeutic option in IBM and these data support further research of Arimoclomol in IBM. Because the relationship between physical function and strength is not linear, capturing both provides complementary information [52].

CONCLUSION

The last few years have witnessed important progress in the understanding of IBM. These advances may lead to improved diagnosis and the discovery of effective drug treatments in the future. Nevertheless, the disease-triggering events and exact way how the various disease pathways interact remain to be elucidated. The growing interest of the scientific community and new therapeutic approaches being tested in clinical trials allows us to be hopeful and confident about the future and in the ultimate goal of translating research findings into improved patient care.

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Conflicts of interest

There are no conflicts of interest.

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