



Exploring challenges in the management and treatment of inclusion body myositis

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Purpose of review

This review provides an overview of the management and treatment landscape of inclusion body myositis (IBM), while highlighting the current challenges and future directions.

Recent findings

IBM is a slowly progressive myopathy that predominantly affects patients over the age of 40, leading to increased morbidity and mortality. Unfortunately, a definitive cure for IBM remains elusive. Various clinical trials targeting inflammatory and some of the noninflammatory pathways have failed. The search for effective disease-modifying treatments faces numerous hurdles including variability in presentation, diagnostic challenges, poor understanding of pathogenesis, scarcity of disease models, a lack of validated outcome measures, and challenges related to clinical trial design. Close monitoring of swallowing and respiratory function, adapting an exercise routine, and addressing mobility issues are the mainstay of management at this time.

Summary

Patients with IBM and the medical community face numerous challenges in terms of clinical manifestations, diagnosis, and treatment. Overcoming these challenges necessitates the adoption of innovative research strategies. By understanding and addressing these hurdles, researchers and medical professionals can strive towards improving the management and treatment of IBM enhancing the quality of life for affected individuals.

Keywords

clinical trial design, inclusion body myositis, individualized medicine

INTRODUCTION

Inclusion body myositis (IBM) is the most prevalent muscle disease primarily affecting individuals above the age of 40. The disease has a male predominance occurring nearly twice as frequently in males compared to females [1]. Although variability in presentation exists, IBM most commonly presents with muscle weakness predominantly affecting deep finger flexors and/or knee extensors [2]. IBM is associated with increased morbidity and mortality [3[¶]]. Pharmacologic treatments tried to date have been relatively unsuccessful in modifying disease course without a currently recognized cure [4]. The lack of treatment can be attributed to various challenges spanning from diagnostic challenges to the development of targeted therapies based on a comprehensive understanding of the underlying disease mechanisms. This article examines the diagnostic and management challenges faced by patients with IBM and provides an overview of the current treatment landscape.

CLINICAL PRESENTATION AND ASSOCIATED CHALLENGES

IBM is clinically characterized by chronic, slowly progressive weakness, often asymmetric, presenting with predominant finger flexor and/or knee extensor involvement [2,5–8]. However, less common presentations of this disease can occur in approximately 14% of patients including isolated

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KEY POINTS

- Inclusion body myositis (IBM) is a chronic progressive muscle disease of unclear etiology most commonly presenting with weakness in finger flexion and/or knee extension.
- Variability in clinical presentation and limitations of currently available diagnostic tests often result in delays in diagnosis.
- Current management approach for IBM consists of close monitoring of swallowing and respiratory function, adapting an exercise routine, and addressing mobility issues.
- There is a critical need to develop disease-modifying targeted therapies for IBM able to provide clinically meaningful improvements.

dysphagia, foot drop, proximal upper limb weakness, axial weakness with head drop, and facial diplegia [9[■],10,11]. Furthermore, IBM may be diagnosed even at a preclinical stage manifesting with elevated creatine kinase levels [9[■]]. The lingering course, the variable presentations, and the distal asymmetric weakness, mimicking a mononeuropathy (e.g. ulnar) or a motor neuron disorder, can be challenging for providers to recognize and result in diagnostic delay with time from symptom onset to diagnosis ranging from 4 to 9 years on average [9[■],12].

DIAGNOSIS AND DIAGNOSTIC CHALLENGES

Diagnosis is established based on a combination of clinical features and muscle biopsy findings. Several diagnostic criteria have been published, all requiring a combination of clinical and histopathological features [13–23]. All included diagnostic categories share very high specificity of more than 97% with variable sensitivity ranging from 11% to 84% [23]. The high specificity is in part due to the distinctive histopathological and clinical findings when present. The European Neuromuscular Centre (ENMC) 2013 IBM diagnostic criteria remain one of the most widely used criteria [20]. The mandatory clinical criteria include age of onset later than 45 years, duration of symptoms more than 12 months, and serum creatine kinase levels not more than 15 times the upper limit of normal [20]. Clinical features include weakness of the finger flexors more than shoulder abductors and/or weakness of the quadriceps more than or equal to hip flexors [20]. Figure 1 reveals representative muscle magnetic resonance imaging (MRI) findings of

lower limb involvement in an IBM patient. Although the prominent involvement of deep finger flexors and/or quadriceps are typical in IBM, they are not pathognomonic as other myopathies can have predilection to these muscles (Table 1). Additional challenges are posed in patients with onset of weakness beyond finger flexors and quadriceps as the differential for such presentations is wider.

Pathologic criteria for IBM include endomysial lymphocytic infiltration invading nonnecrotic muscle fibers referred to as autoaggressive inflammation, the presence of rimmed vacuoles, and evidence of protein deposits [20]. A challenge in histopathologic diagnosis is that rimmed vacuoles and congophilic deposits may be absent on muscle biopsy in patients clinically diagnosed with IBM in up to 25% of patients [24]. Selecting the appropriate muscle to biopsy can also be challenging. Choosing a muscle that is only moderately weak is necessary to avoid a false negative result if the muscle is only mildly affected or end-stage (nondiagnostic) muscle changes if the muscle is severely affected [24,25]. Patients may require a repeat muscle biopsy to confirm the diagnosis [9[■]]. Although relatively benign, a muscle biopsy may result in complications such as bleeding or hematoma formation, muscle herniation with activity if the wound is not carefully closed, and/or wound dehiscence [26]. Additionally, other myopathies such as multisystem proteinopathies and myofibrillary myopathies may contain rimmed vacuoles or protein accumulations and can be confused for IBM on pathologic grounds when inflammation is absent or sparse [27,28].

Electrodiagnostic testing through nerve conduction studies and needle electromyography (EMG) is typically performed during diagnostic work up and could help define the nature of the underlying process (neuropathic versus myopathic), rule out disease mimickers, and select a target for biopsy. However, in IBM, long duration high amplitude motor unit potentials (neuropathic) are often present mixed with short duration, low amplitude, complex units (myopathic) [29,30]. This may result in test misinterpretation further delaying the diagnosis.

The utilization of imaging techniques in the diagnosis of myopathies has been on the rise. In IBM, muscle MRI has been proven valuable in supporting the diagnosis due to its ability to detect a characteristic pattern of muscle involvement (Fig. 1) [31,32]. Additionally, muscle MRI can aid in selecting a muscle for biopsy. However, it is important to consider certain limitations, including the time-consuming and expensive nature of MRI, challenges in discerning the pattern at early and advanced stages of the disease, and the need for independent interpretation by neurologists or rheumatologists,

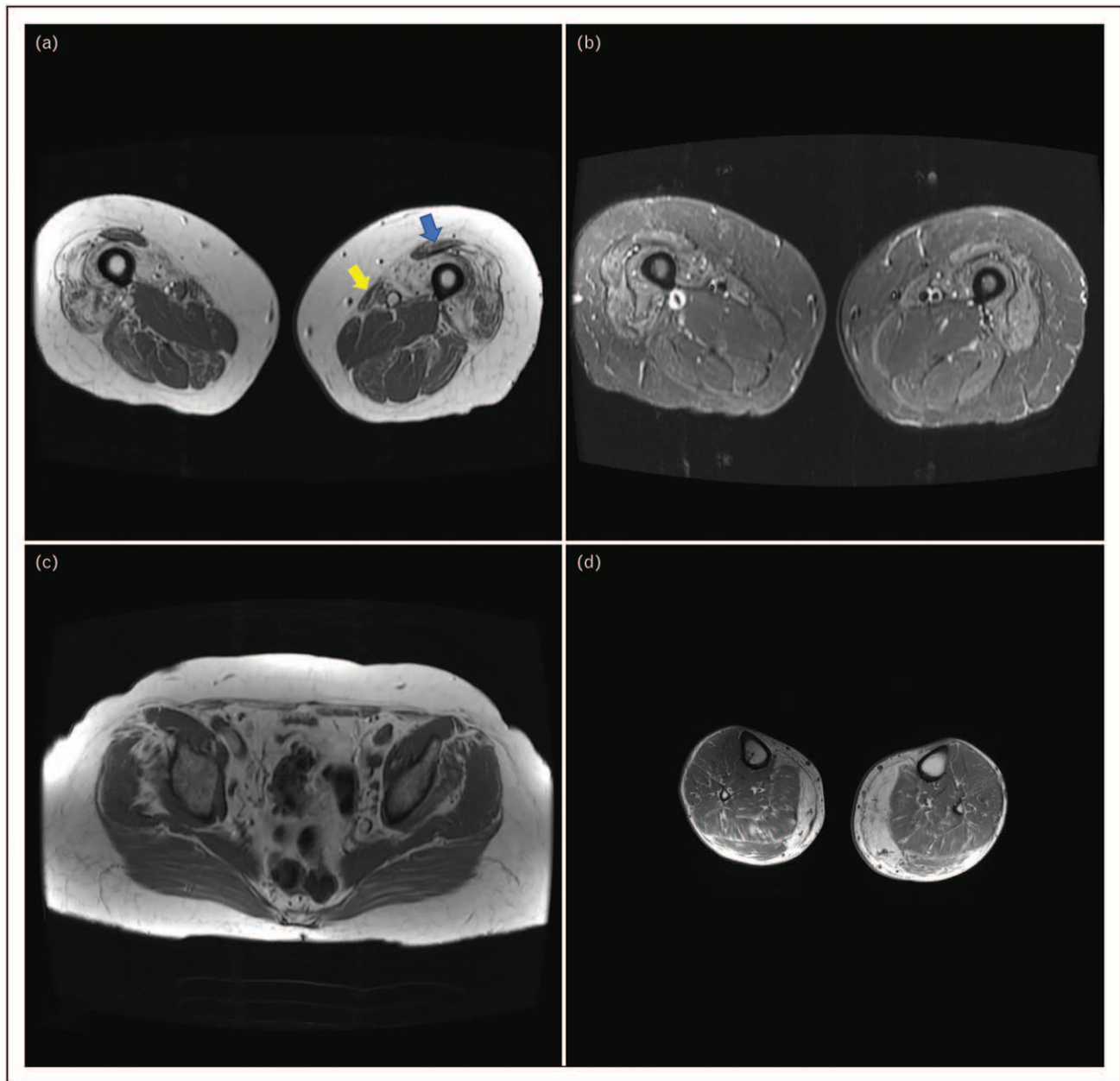


FIGURE 1. MRI findings in inclusion body myositis. Typical muscle MRI findings in IBM: T1 axial images (a, c, d) and FSE-IR sequence (b). (a) Atrophy and fatty replacement of the distal quadriceps, predominantly involving the vastus medialis and lateralis, worse on the right, with sparing of the rectus femoris (blue arrow) and involvement of the sartorius (yellow arrow). In contrast, there is relative sparing of pelvic muscles (c) and more proximal parts of the quadriceps creating a proximal to distal gradient in the quadriceps (not shown). Increased water content in distal quadriceps (b) indicating inflammation (equivalent to a T2 sequence). In the leg compartment, there is prominent involvement of the medial gastrocnemius (d).

as most radiologists may not be well versed in the various patterns associated with myopathies. Moreover, muscle ultrasound is emerging as a promising tool, especially helpful in detecting subclinical muscle involvement of the deep finger flexors, quadriceps, and medial gastrocnemius [33].

Last, the only currently available serum diagnostic biomarker for IBM is cytosolic 5'-nucleotidase 1A (cN-1A) antibody. It has a limited sensitivity

ranging from 30% to 50% [34,35]. Although overall specificity was originally reported to be high (>90%), cN-1A antibodies can also be found also in others diseases such as dermatomyositis, Sjogren's syndrome, antisynthetase syndrome, immune mediated necrotizing myopathy, and systemic lupus erythematosus [36,37]. As a result, the specificity for the antibody currently ranges between 30–80% [38]. Nevertheless, while cN-1A antibody

Table 1. Myopathies that can mimic IBM based on reported patterns of weakness

	Prominent finger flexion weakness	Prominent knee extension weakness
Myopathies on the spectrum of IBM		
Granulomatous myopathy [107,108]	+	+
Polymyositis with mitochondrial pathology [109]	+	+
Acquired myopathies		
AL amyloidosis [110]	+	–
Inherited myopathy with overlapping phenotype with IBM		
Myotonic dystrophy type 1 [111–113]	+	+
Myotonic dystrophy type 2 [114]	+	+/–
Dysferlinopathies [115,116]	+	+
Dystrophinopathies [117]	+	+
Filaminopathy [118]	+	+
Limb girdle muscular dystrophy D3 [119]	+	+
VCP myopathy [120]	+	+
GNE myopathy [121]	+	–
Myofibrillar myopathies [122,123]	+	+/–
Inherited myopathies with a distinct phenotype but reported rare cases overlapping with IBM		
MYH7 myopathy [124]	+	+
Pompe disease [125]	+	+
LAMA2 muscular dystrophy [126]	+	–
ACTA1 myopathy [127]	+	+

should not be used as a standalone test to diagnose IBM, a positive result helps raise suspicion for the diagnosis, especially in patients with atypical presentations or at a preclinical stage [9[•]].

LIMITED THERAPEUTIC TARGETS

Another challenge facing the treatment of IBM is that the lack of understanding of its pathogenesis and whether the disease represents an autoimmune disease, a neurodegenerative process, or potentially a combination of both [39]. Regardless of which is the cause versus the consequence, once the disease manifests clinically, the vast majority of patients display complex histopathological findings featuring inflammation, mitochondrial dysfunction, disrupted autophagy, and protein aggregation. Review of disease mechanisms is beyond the scope of this article and is nicely summarized in several articles [39–42]. Most clinical trials targeted various aspects of the inflammatory or immune response as detailed below in the treatment landscape section. However, the highly differentiated cytotoxic CD8⁺ T cells, displaying markers of senescence such as KLRG1, are thought to evade conventional immunosuppressive or immunomodulatory therapies [43,44]. Current phase 1 and phase 2/3 trials (clinical trial

NCT05721573) targeting these KLRG1 positive T cells are ongoing [45]. However, detailed knowledge of the noninflammatory pathways is lagging behind posing a major challenge to identifying therapeutic targets. Drugs with broad rather than targeted mechanisms of action have been tried as detailed below [39,41].

LIMITED DISEASE MODELS

The availability of validated disease models to understand pathogenesis and develop treatments is an important aspect in translational research. Modeling monogenic inherited diseases via gene editing is more straightforward compared to diseases such as IBM. Models for hereditary multisystem proteinopathies (MSP), mainly VCP mouse models, have been used in IBM [24,46,47]. Although also known as hereditary inclusion body myopathies, VCP and other MSP disorders are distinct entities with different clinical features and populations at risk compared to IBM. A MCK- β APP model has been reported [48]. Furthermore, cholesterol-fed rabbits and nematode *C. elegans* have also been proposed [49,50]. More recently, a xenograft animal model was developed where human muscle from IBM patients was transplanted into

Table 2. Pharmacologic clinical trials in inclusion body myositis (IBM)

First author, year	Drug	Mechanism	Primary outcome measure(s)	Study design
Witting, 2022 [64]	Botox	Neuromuscular junction blockade	Dysphagia questionnaire, time cold-water swallow test, and subjective dysphagia status	Pilot study
MacHado, 2022 [85]	Arimoclomol	Amplification of heat shock protein expression	IBMFRS change from baseline to month 20	Phase 2/3
Coudert, 2022 [80]	Testosterone + exercise	Anti-inflammatory and increases muscle mass	Blood biomarkers	Pilot study
Benveniste, 2021 [81]	Sirolimus	mTOR inhibitor	Maximal voluntary isometric knee extension strength	Phase 2b
Amato, 2021 [84]	Bimagrumab	Activin type 2 receptor-targeted monoclonal antibody	6MWT and safety	Phase 2b
Kosmidis, 2019 [76]	Canakinumab	IL-1beta-targeted monoclonal antibody	QMT	Pilot study
Mendell, 2017 [83]	Follistatin gene therapy	Increases muscle mass	6MWT	Pilot study
Schmidt, 2016 [75]	Alemtuzumab	CD52-targeted monoclonal antibody	Muscle tissue biomarkers	Pilot study
Saperstein, 2016 [74]	Natalizumab	Monoclonal antibody that targets the $\alpha 4$ chain (CD49) of the adhesion molecules $\alpha 4\beta 1$ and $\alpha 4\beta 7$ -integrin	MMT, QMT, and quality of life measures	Pilot study
Corbett, 2015 [82]	Triheptanoin	Anaplerotic therapy	6MWT, IBMFRS, and MMT	Pilot study
Kosmidis, 2013 [73]	Anakinra	Interleukin-1 receptor-targeted monoclonal antibody	MMT and grip strength	Pilot study
Sanricca, 2011 [79]	Simvastatin	Potential immunomodulatory and anti-inflammatory	IBMFRS and assessment tools proposed by International Myositis Assessment Collaborative Study group	Pilot study
Sultan, 2008 [72]	Rituximab	CD20-targeted monoclonal antibody	QMT and CK level	Pilot study
Dastmalchi, 2008 [71]	Infliximab	TNF alpha-targeted monoclonal antibody	Myositis disease activity score and MRI	Pilot study
Barohn, 2006 [77]	Etanercept	Soluble TNF alpha receptor antagonist	QMT	Pilot study
Muscle study group, 2004 [70]	Avenox	INFbeta-1a-targeted monoclonal antibody	Safety and tolerability	Pilot study
Lindberg, 2003 [128]	Methotrexate and ATG anti-T-lymphocyte globulin	Broad immunosuppression	QMT	Pilot study
Rutkove, 2002 [78]	Oxandrolone	Anti-inflammatory and potentially immunomodulatory	MVICT, MMT, and functional performance testing	Pilot study
Badrising, 2002 [69]	Methotrexate	Broad immunosuppressant	QMT	Pilot study
Dalakas, 2001 [68]	IVIG + prednisone	Immunomodulation (IVIG) and broad immunosuppression (prednisone)	QMT and MRC	Pilot study
Walter, 2000 [66]	IVIG	Immunomodulation	MMT, NSS, patient assessment, outstretched arm time, and EMG	Pilot study
Leff, 1993 [67]	Azathioprine + methotrexate	Broad immunosuppression	MMT, activities of daily living questionnaire, and serum muscle associated enzymes	Pilot study

6MWT, 6 min walk test; CK, creatine kinase; EMG, electromyography; IBMFRS, inclusion body myositis functional rating scale; MMT, manual muscle testing; MRC, medical research council; MRI, magnetic resonance imaging; MVICT, maximal voluntary isometric contraction testing; NSS, neuromuscular symptom score; QMT, quantitative muscle testing.

immunodeficient mice [51¹¹]. The xenograft recapitulated the canonical histopathological features of IBM. However, given the nature of these models, functional and behavioral evaluations cannot be performed.

Modeling the inflammatory component is also challenging. There are reported animal models for idiopathic inflammatory myopathies but not IBM. Existing models encompass infection related models of myositis [virus models such as Ross River virus (RRV) infection and Coxsackie virus B], antigen-induced, and myosin and C protein induced myositis models [52–56]. Although these models result in muscle inflammation mimicking human inflammatory myopathies, they are unlikely to recapitulate IBM features which involve CD8⁺ T-cell driven endomysial inflammation and noninflammatory findings.

LONG-TERM OUTCOMES AND SURVIVAL

IBM is associated with both increased morbidity and mortality. The median time to using a cane is about 5 years and to using a wheelchair is about 10.5 years [57]. Over time, all patients eventually require the use of a wheelchair, and nearly half of patients in a separate study were completely dependent on the wheelchair for ambulation [58]. An annual decline of 3–5% in grip strength, 3.7% in overall strength, and 6.3% in IBM functional rating scale (IBM-FRS) have been reported [58,59]. The median time to onset of dysphagia has been cited as approximately 6 years and can be seen in approximately two thirds of patients [57]. Patients with IBM are also shown to have an increased mortality [57–59]. IBM patients had a 10 year survival rate of 36% of index compared to 50% in control patients [57]. The most common cause of death in IBM arises from respiratory compromise and dysphagia (aspiration pneumonia) [60]. Furthermore, patients with IBM are more likely to have a superimposed peripheral neuropathy, Sjogren's syndrome, or T-cell large granular lymphocytic leukemia than the general population [3¹]. The slow progressive course and survival would be challenging to capture in a clinical trial.

TREATMENT LANDSCAPE

Although, there is currently no pharmacologic cure for IBM, current treatment strategies primarily revolve around implementing supportive measures to address symptoms such as dysphagia, respiratory compromise, muscle weakness, and limited mobility [24].

Dysphagia is a common symptom in IBM patients and can be debilitating [61]. Dysphagia-targeted interventions may provide temporary

relief, such as myotomy or dilation of a cricopharyngeal bar, when patients have a significant obstructive components [62,63]. Botox injections remain controversial and may pose some safety concerns [61,64]. There is anecdotal evidence for IVIG improving dysphagia in IBM [65,66]. Most importantly, regular evaluation by a speech and swallow therapist would ensure proper dietary modification to avoid aspiration.

Neuromuscular respiratory insufficiency usually occurs at advanced disease stages. Screening for and managing respiratory involvement is crucial. Patients often need referral to pulmonary specialists and/or sleep medicine physicians who can assist with initiation and management of noninvasive ventilation in the appropriate setting [24].

The biggest challenge facing treatment of IBM to date is the lack of disease-modifying therapy. Over 20 unique drug therapies or combinations have been studied in IBM as summarized in Table 2 and further detailed below.

Immunosuppressive/immunomodulatory therapies include drugs that affect broadly both the innate and adaptive immune systems such as azathioprine, methotrexate, IVIG, IVIG + prednisone, interferon beta 1a, etanercept, infliximab, anakinra, natalizumab, alemtuzumab, and canakinumab [66–77]. Drugs with pleiomorphic mechanism of action, including an anti-inflammatory effects, such as sirolimus, oxandrolone, simvastatin, and more recently testosterone in tandem with exercise training have also been tried [78–80]. Sirolimus inhibits mTOR and has pleiotropic effects on cell metabolism, autophagy, and mitochondrial function [81]. Additional investigational treatments included drugs to increase muscle mass such as follistatin gene therapy and bimagrumab, and arimocloamol addressed protein homeostasis by prolonging the activation of Heat Shock Factor-1 augmenting heat shock protein levels [82–85]. Currently, randomized controlled trials for sirolimus (clinical trial NCT04789070) and ABC008 a monoclonal antibody that selectively depletes cytotoxic T cells (clinical trial NCT05721573) are underway with highly anticipated results.

In contrast, while pharmacologic therapies have had little to no benefit in IBM, several nonpharmacologic strategies have had successes [24]. Blood flow restricted resistance training for 12 weeks in IBM patients increased muscle strength on testing indicating specific strength training exercises may be beneficial for this group of patients [86]. Other exercises programs including community exercise and home exercise programs have also increased patient exercise capacity and preserved muscle function in IBM [87,88]. Medical devices such as cyborg

hybrid assistive limb therapy and selective ankle foot orthoses have also improved ambulatory function in IBM [89,90]. An expiratory muscle strength training device to improve swallowing has also been considered [91]. Additionally, self-management training and shared medical appointments have improved social endurance and healthcare quality of life [92,93]. However, current standard-of-care guidelines in IBM are lacking.

TRIAL OUTCOME MEASURES

Six outcome measures have been used as primary and several others as secondary in IBM clinical trials [94[¶]]. The primary outcome measures included the 6-min walk distance (6MWD), IBM-FRS, quantitative muscle testing (QMT) and maximal voluntary isometric contraction testing (MVICT), manual muscle testing (MMT), and thigh muscle volume measured by MRI. Each of these measures has its own challenges, and there is no currently available outcome measure validated in IBM with content able to capture all the aspects of the disease and reflect bulbar, upper limb, and lower limb function.

For instance, the 6-min walk distance test was designed to assess exercise capacity in pulmonary diseases and may be influenced by other nonneuromuscular conditions [95]. It also has a major floor-effect and cannot be used in IBM patients who have already lost ambulation [94[¶]]. Muscle strength testing, manually or via dynamometry, lacks standardization with marked intra- and inter-rater variability. In contrast, the IBM-FRS has better content than others capturing multiple domains of disease severity [96]. This scale has been validated in IBM [97,98]. A recent study has confirmed that the intra-rater and interrater reliability for scoring using IBM-FRS is high with intraclass correlation coefficients for video ratings >0.9 [99[¶]]. However, the IBM-FRS is a clinician-administered questionnaire, not designed according to patient-reported outcome measures standards, and a relatively significant change in function is needed in order to achieve a one point change on the scale. There is a critical need to develop standardized, validated outcome measure in IBM and novel patient reported outcomes (PROs) according to FDA PRO guidelines [100]. Additionally, surrogate outcome measures may play a crucial role in monitoring progression and evaluating treatment efficacy. Quantitative muscle MRI has proven valuable in quantifying muscle loss over time, while correlating with decline in physical performance [101^{¶¶}]. However, establishing the minimal clinically important difference is yet to be determined.

From a clinical trial design perspective, a balance between cost and having a long enough trial is

needed to avoid type II errors. While the main reason for failed trials could solely be the lack of effectiveness of the investigated drug, the duration of several trials was 6 month or less which is sub-optimal in such a chronic, slowly progressive disease [66,102,103]. Furthermore, given the rarity of IBM, stratifying groups by variables of interest (sex, race, distribution of weakness, disease severity etc.) would make such trials not feasible as stratification should be accounted for during sample size calculation as it requires penalization of the p-value. Platform trials offer the advantage of sharing a placebo arm and testing several investigational medicine products simultaneously, which improves recruitment and saves costs. On the downside, any design flaw would impact several trials.

Additional limitations of clinical trials exist. Evaluation of the outcome measures used in clinical trials is often based on averaged estimates, such as mean difference and standard deviations, which may not fully capture the individual-level effect. Furthermore, the clinical trial setting is different from real life scenarios, and the placebo group's rate of decline may not align with natural history studies. Innovative designs to address these limitations have been proposed, including pragmatic trials and n-of-1 trials, both of which have their challenges not addressed in this article. The intervention in pragmatic trials is embedded in healthcare system workflow, and data are collected from electronic health records in routine clinical visits [104]. The n-of-1 clinical trial design is the closest to the concept of individualized medicine. It uses the same methodology of parallel group trials to ensure scientific rigor while generating clinically relevant treatment outcomes tailored to the patient involved [105,106].

CONCLUSION

In conclusion, inclusion body myositis (IBM) is a chronic progressive muscle disease with an unclear underlying cause. Despite its significant impact on patient morbidity and mortality, there is currently no recognized cure or disease-modifying therapy available for IBM. Clinicians, patients, and scientists face numerous challenges in the treatment of this disease including the variable clinical phenotypes at presentation and difficulties in early-stage diagnosis. A major obstacle in addressing IBM lies in the limited understanding of its pathogenesis, which in turn limits the development of targeted treatment therapies. Additionally, innovative trial outcome measures and designs are likely needed to facilitate the development of more effective treatments.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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