

# Inclusion body myositis: clinical review and current practice

## **Practice points**

- Inclusion body myositis (IBM) is the commonest acquired myopathy in patients aged over 50 years with males more frequently affected.
- Asymmetric finger flexor and knee extensor weakness are characteristic clinical features.
- Currently recognized diagnostic pathological features on muscle biopsy are highly specific in combination, but lack sensitivity.
- Immunohistochemical staining for protein aggregates using antibodies to p62, TDP-43 and LC3 shows diagnostic promise and may aid in differentiating IBM from disease mimics. Current evidence appears to favor staining for p62 as the most discriminating and reliable.
- 2011 European Neuromuscular Centre diagnostic criteria have recently been published and will potentially enable greater numbers of patients to be included in future clinical trials.
- MRI has diagnostic usefulness in IBM and potential as an outcome measure for clinical trials.
- Auto-antibodies against cytosolic 5'-nucleotidase 1A were recently described in IBM and showed good diagnostic performance.
- The pathogenesis of IBM has yet to be determined.
- There is no evidence to support the use of anti-inflammatory, immunosuppressive or immunomodulatory agents in IBM, but in rare individual cases that are atypical for the degree of inflammation, such medication could be considered.
- Supportive management is recommended by neuromuscular experts and individualized exercise programs may benefit patients.
- International efforts to address the challenges in IBM are ongoing and expanding.

Inclusion body myositis (IBM) is the commonest acquired myopathy in individuals aged over 50 years. The first description of a patient with IBM was published in 1967. Despite much research into the illness, our understanding is far from complete and IBM remains an enigmatic and often misdiagnosed condition for which there is currently no effective drug treatment. However, new pathological findings, the recent identification of muscle-specific serum auto-antibodies and the increasing use of MRI in patients with IBM are important advances that may lead to earlier diagnosis and improved understanding of the disease. The purpose of this review is to provide an update on the scientific developments in IBM with particular emphasis on current and future clinical trials.

Keywords: diagnostic criteria • IBM • inclusion body myositis • outcome measures • review trials

Inclusion body myositis (IBM) is the commonest acquired myopathy in those older than 50 years of age. Its prevalence in this age

group is estimated to be between 16.0 and 35.5 per million in Caucasian populations [1-3]. Males are affected twice as commonly

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as females and the median age at disease onset is in the seventh decade. Delay to diagnosis from symptom onset has remained unchanged over the last 25 years; 5.1 years in 1987 [4] and 4.9 years in 2011 [5]. Delay in seeking medical advice certainly contributes to this finding but additionally, there is often a considerable delay from initial presentation until diagnosis [1] and up to 86% of patients are initially misdiagnosed [2]. The most common initial misdiagnoses are motor neuron disease and polymyositis (PM).

The first description of IBM, together with a description of some of the pathological features that have become synonymous with the diagnosis, was published in 1967 [6]. The patient, a 66-year-old man, presented with progressive weakness and pronounced atrophy of the shoulder girdle and quadriceps muscles and dysphagia over a 6-year period. Muscle biopsy demonstrated an inflammatory infiltrate with tubulofilaments, membranous bodies and abnormal mitochondria visualized by electron microscopy (EM). The term IBM was coined in 1971 although ironically the case described bears little resemblance to what is recognized as IBM today [7]. IBM is classified alongside PM, dermatomyositis (DM) and immune-mediated necrotizing myopathies as an idiopathic inflammatory myopathy, but there are significant clinical differences between IBM and these other inflammatory conditions. IBM pursues a slowly progressive course, often with asymmetric weakness, early distal weakness and resistance to immunosuppressive treatment, in contrast to the other idiopathic inflammatory myopathies [5,8].

Historically, the diagnosis of IBM has been dominated by pathological findings on muscle biopsy, which reveal both inflammatory and myopathic features. The diagnostic pathological features are thought to be highly specific in combination, but clinical experience over many years and more recent studies, have shown that they lack sensitivity [9]. Using immunohistochemical techniques, a number of proteins have been reported to aggregate in IBM. Many of the proteins described are more commonly associated with neurodegenerative diseases, leading to analogies being drawn between IBM and conditions such as Alzheimer's disease (AD). Not all the histopathological observations reported have been consistently and independently reproduced [10] and it is uncertain how to incorporate the immunohistochemical data into current diagnostic criteria to achieve a meaningful diagnostic strategy for IBM [11]. However, recent evidence suggests that additional immunohistochemical staining for protein accumulation using antibodies directed toward p62, microtubule-associated protein 1A/1B-light chain 3 (LC3) and transactive DNA-binding protein-43 (TDP-43) and histochemical staining for mitochondrial changes can help discriminate IBM from other inflammatory myopathies [12,13]. Other investigations such as serum auto-antibodies and MRI may play an increasingly important future role in the early diagnosis of IBM. Recently, two independent groups identified a serum auto-antibody to cytosolic 5'-nucleotidase 1A (cN1A) in IBM that shows early promise as a diagnostic test [14,15]. MRI is increasingly used in the diagnosis of neuromuscular diseases. Although not routinely used in diagnosing IBM, imaging may have a role in monitoring disease progression and response to treatment.

Treatment for IBM has focused on immunomodulatory and immunosuppressive regimens, none of which have been shown to be efficacious in prospective [16-28] or retrospective studies [2,8,29-35]. Studies have been hampered by small patient numbers and the slowly progressive nature of the disease. However, new drugs and increasing international collaboration between IBM interest groups should translate into tangible results in the near future.

This review will focus on the scientific advances in IBM with an emphasis on past and future clinical trials.

#### **Clinical features**

# Presentation, natural history & clinical outcome measures

IBM continues to be a disabling disorder without effective treatment. It is a slowly progressive disease, characterized by the insidious onset of proximal and distal weakness, typically initially affecting the finger flexors and/or the knee extensors, often in an asymmetric manner. IBM causes significant morbidity from immobility, falls, reduced hand function, dysphagia and aspiration, with disability and impaired quality of life being common late-stage disease features [5,36-38]. However, disease progression is variable and no robust predictors of outcome have been described to date. Male gender, older age at onset and immunosuppressive treatment have been suggested as factors predictive of progression toward handicap for walking (however, these did not predict progression toward the use of a wheelchair) [5], while another study reported that older age at disease onset (but not gender or treatment) was predictive of a shorter time to requiring a walking stick [37]. Mean percentage decline in muscle strength has been reported to be 3.1-9.1% per year (measured by manual muscle testing), with considerable variability at the individual level [27,36-38].

There is limited prospective clinical trial data in IBM and defining the most appropriate outcome measures for clinical trials is a difficult task [36-38]. There are data suggesting that quantitative muscle testing (QMT) of quadriceps extensors and the IBM functional rating scale (IBMFRS) may be sensitive tools to monitor disease progression [36-37,39-40]. In an ongoing large, multicenter (estimated enrolment = 240 patients), randomized placebo-controlled trial (RCT) in IBM [41], assessment of mobility via the 6-min walk distance test (6MWT) was chosen as the primary outcome of the trial. Interestingly, a recent report suggests that the 2-min walk distance test may be a better alternative to tests of longer duration [42]. Among several other secondary and exploratory objectives, the above mentioned trial will also assess quadriceps QMT, the incidence of self-reported falls and a newly developed and still unpublished patient-reported questionnaire of physical function-the IBM Functional Assessment (sIFA) [41]. Further research is needed to determine the longitudinal relationship between changes in the different outcome measures, as well as their discriminative capacity and responsiveness.

# Investigations

# Auto-antibodies

The first auto-antibody marker for IBM has recently been described and it targets cN1A [14-15,43]. The reported difference in antigen molecular weight (43 and 44 kDA) is likely related to technical aspects of the assays. Anti-cN1A had good diagnostic performance, with sensitivities of 60–70% and specificities of 83–92% for low antibody titers, and sensitivities of 33–34% and specificities of 96–98% for high antibody titers. In combination with clinical features and other investigations, this new auto-antibody may become an important diagnostic tool in clinical practice when the test becomes commercially available. Depending on the results of future studies, consideration should be given to incorporating anti-cN1A positivity in future IBM diagnostic or classification criteria.

#### Muscle biopsy

The pathological findings on muscle biopsy from patients with IBM can be broadly described as inflammatory and myopathic (Figure 1). Pathological features considered to be synonymous with IBM are endomysial inflammation with invasion of morphologically normal fibers by inflammatory cells (partial invasion), rimmed vacuoles, amyloid deposition and 15–18 nm tubulofilaments visualized using EM. These features formed the basis of the seminal Griggs diagnostic criteria [44]. Individually they have all been documented in other myopathies; however, in combination, they are considered to be highly specific for IBM. With recognition of the characteristic clinical picture associated with IBM, recent studies have shown that the pathological features lack sensitivity and are absent in the majority of cases at presentation [9]. Other pathological features commonly observed in IBM include increased endomysial fibrosis, fiber necrosis and regeneration, mitochondrial changes, rounded fibers, neurogenic atrophy and eosinophilic inclusions. In addition to 15–18 nm tubulofilaments, ultrastructural examination of muscle tissue in IBM can show whorled membranous debris, membranous bodies containing electron dense granules, smaller intranuclear filaments (10–15 nm) and abnormal mitochondria with paracrystalline inclusions.

Immunohistochemical staining techniques have enabled the characterization of the inflammatory cell infiltrate and protein aggregates and have demonstrated a diffuse increase in expression of sarcoplasmic and sarcolemmal major histocompatibility complex class I (MHC class I) affecting the majority of fibers in IBM [12]. The inflammatory infiltrate is predominantly composed of C8+ T-cells and macrophages [45]. CD20+ B-cells are rare, but terminally differentiated CD138+ plasma cells are present in IBM in greater numbers than B cells [46]. Many of the accumulated proteins found in IBM such as ß amyloid, tau and ubiquitin are more commonly associated with neurodegenerative diseases. Their discovery led to parallels being drawn between the pathogenesis of IBM and neurodegenerative diseases, such as AD. However, the validity of some immunohistochemical findings in IBM is uncertain [10].

Immunohistochemical studies have shown that p62, TDP-43 and LC3 aggregates are frequent in muscle fibers in IBM [46-49]. Two recent quantitative studies have examined the diagnostic utility of a number of histopathological features in IBM [12,13]. The first compared immunohistochemical staining for p62, LC3 and TDP-43 in a cohort of pathologically diagnosed inflammatory myopathies [13]. To differentiate IBM and PM, staining for LC3 and TDP-43 was recommended. A subsequent retrospective cohort study investigated markers of protein aggregation, together with mitochondrial and inflammatory changes [12]. A pathological diagnostic algorithm was proposed to differentiate IBM with rimmed vacuoles from protein accumulation myopathies (sensitivity 93% and specificity 100%) and IBM without rimmed vacuoles from steroid responsive inflammatory myopathies (sensitivity 100% and specificity 73%) using immunohistochemical staining for p62, MHC class I and combined sequential cytochrome c oxidase/succinate dehydrogenase (COX/SDH) histochemical staining. In addition, the authors found the morphology and distribution of p62 aggregates was characteristic in IBM.

Mitochondrial changes are frequently observed in IBM muscle biopsies by light microscopy. These fea-



**Figure 1. Pathological features in inclusion body myositis.** Hematoxylin and eosin stained section shows variation in fiber size, increased connective tissue, an endomysial inflammatory infiltrate (white arrow) and a fiber-containing rimmed vacuoles (black arrow) (**A**). Fluorescent congophilic deposits (red) are typically observed in vacuolated fibers (white arrows) when stained with Congo red and visualized under fluorescent light (**B**). Whorled membranous debris (red arrow) and tubulofilaments (black arrow) can be seen in fibers using electron microscopy (**C**). Immunohistochemically stained tissue sections reveal endomysial CD8<sup>+</sup> T-lymphocytes invading morphologically normal fibers (partial invasion; black arrow) (**D**), increased sarcolemmal and sarcoplasmic labelling for major histocompatibility complex class I (**E**). Mitochondrial changes are frequently seen in inclusion body myositis; abnormal fibers appear blue due to the loss of brown cytochrome c oxidase staining with combined cytochrome c oxidase/succinate dehydrogenase staining (**F**). Protein aggregates commonly observed in inclusion body myositis are immunoreactive for p62 (black arrows); (**G**), transactive DNA-binding protein-43 (red and black arrows indicating intravacuolar and subsarcolemmal deposits, respectively); (**H**) and ubiquitin (black arrow) (**I**). Scale bar in (**A**) represents 100 μm in (**E**); 50 μm in (**A**), (**B**), (**F**) and (**G**); 25 μm in (**D**), (**H**) and (**I**); and 1 μm in (**C**).

tures along with MHC class I upregulation are sensitive for IBM, with their absence in a muscle biopsy making a diagnosis of IBM unlikely, but they lack specificity [9,34,50]. Despite much research into the pathology of IBM, how the pathological features relate to the pathogenesis is unknown, but as previously hypothesized [51], recent evidence suggests that some of the pathological findings may be related to disease duration [9].

# Muscle imaging

The last few years have witnessed a remarkable advance in the role of MRI in the diagnosis and management of idiopathic inflammatory myopathies and neuromuscular diseases in general [52,53]. MRI can be used to guide the muscle biopsy site, to monitor disease progression, to guide treatment decisions and to help in differential diagnosis (disease-specific patterns of muscle involvement have been described). Muscle inflammation (active muscle pathology appearing hyperintense on T2-weighted/STIR images) is less common than fatty infiltration (chronic pathology appearing hyperintense on T1-weighted images) in IBM and a suggestive pattern has been described of fatty infiltration predominantly affecting the deep finger flexors, the anterior muscles of the thighs (often with relative sparing of the rectus femoris) and all the muscles of the lower leg (particularly the medial part of the gastrocnemius) [54]. However, larger studies with disease control groups are required to confirm and/or refine this MRI pattern. In PM and DM, the pattern of muscle involvement is typically proximal, sometimes with patchy areas of muscle inflammation, and myofascial edema or a reticular subcutaneous inflammation pattern are more typical features of DM [55].

MRI is also being studied as an outcome measure for future treatment trials in IBM. Quantitative MRI techniques such as fat-fraction imaging, tissue-water relaxation time mapping, magnetization transfer imaging and diffusion imaging have shown promise as reliable and responsive techniques to monitor and quantify disease progression over time [52,53].

## **Diagnostic criteria**

Primarily due to our incomplete understanding of IBM, there is no gold-standard diagnostic test. Historically, a diagnosis of IBM rested upon the demonstration of typical pathological findings on muscle biopsy [29,44,56]. The increasing recognition of the characteristic clinical picture associated with IBM has led to the proposal of a clinically diagnosed group [11,51,57].

The first diagnostic criteria for IBM were suggested in 1987 [56]. These required the presence of tubulofilaments and rimmed vacuoles for a diagnosis of definite IBM, reflecting the belief that these pathological findings were sensitive and specific. Lotz *et al.* suggested that the essential pathological features for diagnosis were:  $\geq 1$  rimmed vacuole per low-power field;  $\geq 1$ group of atrophic fibers per low-power field; an endomysial and auto-aggressive inflammatory exudate; and EM demonstration of typical filamentous inclusions [29]. However, this proposal was based exclusively on the analysis of patients with rimmed vacuoles on muscle biopsy, so introducing a potential bias as to their significance.

The seminal Griggs criteria were published in 1995 [44]. These included clinical features recognized to be characteristic of IBM, such as finger flexion and knee extension weakness. However, a diagnosis of definite IBM could be made solely on the pathological findings: inflammation characterized by mononuclear cell invasion of non-necrotic fibers (partial invasion), rimmed vacuoles and either 15-18 nm tubulofilaments visualized using EM, or the presence of amyloid. A diagnosis of Griggs possible IBM required a combination of pathological, clinical and laboratory features. The Griggs criteria were republished with minor changes in a separate review article in 2002 [58]. The inclusion of mitochondrial changes and MHC class I upregulation was later proposed, reflecting the observed frequency of these features in IBM [59]. The first European Neuromuscular Centre (ENMC) consensus criteria for IBM were published in 1997 [60]. A significant change was the ability to make the diagnosis of IBM in the absence of rimmed vacuoles and tubulofilaments.

With increasing recognition that the pathological features lack sensitivity and are often absent in patients with the characteristic clinical picture of IBM, newer criteria [11,51], including the recent 2011 ENMC criteria (Table 1) [57], have include a category of clinically defined IBM. This enables a diagnosis of IBM to be made on clinical grounds with a supportive, but not diagnostic muscle biopsy. In a recent study, the 2011 ENMC criteria were shown to be more sensitive than the 1997 ENMC criteria and the Griggs criteria, without compromising specificity [9].

# Pathogenesis

# Inflammation

# Autoimmunity & genetic susceptibility

The association of IBM with autoimmune diseases and cases occurring in the context of retroviral infection (HIV and HTLV-1) may represent evidence for an immunopathological basis of disease [61-63]. While the disease is usually sporadic, candidate-based gene studies demonstrate the association with MHC antigens HLA-DR3, DR52 and B8 and the extended ancestral MHC haplotypes 8.1, 35.2 and 52.1 [35,64-66]. The HLA DRB1\*0301/\*0101 genotype confers the highest disease risk in IBM with an earlier age of onset and a possible influence on the rate of disease progression [64,67]. The correlation with conserved genes coding for pathways relevant to antigen presentation and autoimmune responses gives credence to a proposed dysimmune etiology, similar to PM and DM.

Rare familial cases of IBM [68–70] are distinct from the hereditary forms of inclusion body myopathy and may permit further insights from genetic studies.

# Inflammatory factors

In established disease, activated CD8+ cytotoxic T cells are selectively recruited from the circulation [71,72]. Macrophages, myeloid dendritic cells [73] and fewer numbers of plasma cells are also present in targeted muscles [46]. Some immune components are common to PM and IBM with the widespread upregulation of MHC class I antigen on muscle fibers and a restricted signature of T-cell receptor (TCR) gene expression, indicative of clonal selection and expansion within muscle [74,75]. In addition, the over expression of perforin and granzyme granules equips the T cells for direct muscle fiber injury [76] and upregulated chemokine and cytokine genes enhance the overall immune response [77]. The concept of tissue specific danger signals determining disease susceptibility is favored by the observa-

Table 1. 2011 European Neuromuscular Centre diagnos	tic criteria for inclusion l	body myositis.
Clinical and laboratory features	Classification	Histopathological features
Duration of weakness >12 months Creatine kinase ≤15× ULN Age at onset >45 years Finger flexion weakness > shoulder abduction weakness And/or Knee extension weakness ≥ hip flexor weakness	Clinicopathologically defined IBM	All of the following: Endomysial inflammatory infiltrate Rimmed vacuoles Protein accumulation <sup>†</sup> or 15–18 nm filaments
Duration of weakness >12 months Creatine kinase ≤15× ULN Age at onset >45 years Finger flexion weakness > shoulder abduction weakness <b>And</b> Knee extension weakness ≥ hip flexor weakness	Clinically defined IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Upregulation of MHC class I Rimmed vacuoles Protein accumulation <sup>†</sup> or 15–18 nm filaments
Duration of weakness >12 months Creatine kinase ≤15× ULN Age at onset >45 years Finger flexion weakness > shoulder abduction weakness <b>Or</b> Knee extension weakness ≥ hip flexor weakness	Probable IBM	One or more, but not all, of: Endomysial inflammatory infiltrate Upregulation of MHC class I Rimmed vacuoles Protein accumulation <sup>†</sup> or 15–18 nm filaments.
<sup>†</sup> Demonstration of amyloid or other protein accumulation by established met	hods (e.g., for amyloid: Congo re	d, crystal violet, thioflavin T/S, for other proteins: p62,

SMI-31, TDP-43). Current evidence favors p62 in terms of sensitivity and specificity but the literature is limited and further work is required. IBM: Inclusion body myositis; ULN: Upper limit of normal Reproduced with permission from [57]

tion that muscle fibers in IBM can behave like antigen presenting cells and actively participate in the immune response [78]. However, mature plasma cells are also transcriptionally active, arguing for a definite antigenspecific humoral component in the disease [79]. The auto-antibody to cN1A may represent a useful adjunct to diagnosis rather than denoting a pathogenic antigen target as immunoreactivity has been exclusively localized to intracellular domains [12]. Nonetheless, its recent identification does further demonstrate immune activation in IBM [80].

Overall, linked signal recognition explains the concerted action of B and T cells to antigen stimulus and possibly the target tissue [81,82]. Recognition of a tissue and site specific antigen in muscle that is implicated mechanistically in pathogenesis has yet to be proven. Undoubtedly, a disturbance in adaptive and innate immunity should be reflected in a measurable clinical response to immunomodulatory treatment which is lacking in IBM. A central role for inflammation in disease pathogenesis thus remains to be fully elucidated.

# Neurodegeneration Protein aggregation

Protein aggregation is a pathological hallmark of IBM. In excess of 70 different proteins have been described in IBM [82] with some authors referring to IBM as a promiscuous proteinopathy [83]. Whether protein aggregation in IBM is a result of abnormal synthesis, impaired degradation, or both, is uncertain. Two intracellular pathways are responsible for protein degradation - autophagy and the ubiquitin-proteasome system (UPS). Proteins are marked for destruction by ubiquitination and inhibition of the UPS leads to the accumulation of ubiquitinated proteins. Several studies have identified ubiquitin positive protein aggregates in IBM [84-86]. Two studies observed increased proteasomal subunits that colocalized with protein aggregates, but only one found proteasomal function to be impaired [87,88].

Autophagy is responsible for the degradation and recycling of cytosolic proteins and organelles. Initially autophagy was thought to be an indiscriminate process; however, there is increasing evidence that it is selective, for example, mitophagy is the selective degradation of mitochondria [89]. Impairment of autophagy in cellular models leads to the accumulation of p62 [90,91]. The polyubiquitin-binding protein p62 is one of the most common constituents of protein aggregates observed in IBM [47,49]. Other components of the autophagic pathway observed to accumulate in IBM include neighbor of BRCA1 gene 1 protein (NBR1) and LC3 autophagic effector proteins [13,92-93]. NBR1, like p62, is believed to shuttle ubiquitinated proteins for degradation [90].

Abnormalities in autophagy could explain many of the pathological features observed in IBM. Inhibition of autophagy has been shown to cause increased cell surface expression of MHC class I [94]. Impairment of autophagy would result in reduced mitochondrial turnover and consequently, the accumulation of abnormal mitochondria-harboring DNA mutations [95]. Unsurprisingly, the two protein degradation pathways interact, explaining abnormalities in both. Additionally, in IBM, studies have found an increase in proteins associated with endoplasmic reticulum (ER) stress including NF- $\kappa$ B [96.97]. Abnormal protein synthesis resulting in ER stress could, through increased NF- $\kappa$ B expression, upregulate MHC class I expression, thus explaining the diverse pathological findings observed in IBM.

Heat shock proteins (HSP) are a group of proteins increased in response to cellular stress. One of the effects of cellular stress is an alteration of cellular protein function and structure. The heat shock response (HSR) is a mammalian cytoprotective mechanism, mediated through increased expression of HSP, against acute environmental stress [98]. HSP located in cytosolic, ER and mitochondrial compartments are involved in protein folding, transport, degradation and the regulation of cell death [99]. Their differential expression is modulated by cochaperones [100]. The presence of HSP in muscle fibers in IBM is regarded as evidence of their recruitment to clear cells of misfolded and aggregated proteins by promoting repair or degradation [101]. As the efficacy of the HSR declines with age and in view of multiprotein aggregates in IBM, HSR upregulation may be a potential therapeutic strategy in IBM, as discussed below. In chronic disease, the HSR seems to be insufficient to counteract prolonged exposure to a stressful environment [102]. However, results from animal studies demonstrate the potential for timed HSP manipulation as a therapy to slow disease progression in muscular dystrophy [103].

# Myonuclear degeneration

The presence of myonuclear abnormalities was an early finding in IBM. Chou reported intranuclear tubulofilaments on EM in 1967 [6]. Abnormal myonuclei with excessively dense chromatin or an abnormal shape, were present in all six IBM cases reported by Carpenter et al. [104]. In addition, they observed intranuclear filaments, myonuclear sarcoplasmic pseudoinclusions and a degenerating myonucleus releasing filaments into the sarcoplasm. Rimmed vacuoles are often observed to lie in close apposition to myonuclei. Using immunohistochemical staining techniques, rimmed vacuoles stain for nuclear and lysosomal proteins leading to the hypothesis that they are derived from degenerating myonuclei [105-107]. However, other investigators have found that rimmed vacuoles may lack acid phosphatase and nuclear membrane markers [93,104]. Other indicators of myonuclear involvement in the pathogenesis of IBM are sarcoplasmic TDP-43 aggregates accompanied by the loss of myonuclear TDP-43 [48,108] and the

presence of ubiquitin and p62 myonuclear aggregates. TDP-43 was first identified as a major disease protein in neurodegenerative disease in 2006 [109]; pathological TDP-43 is present in frontotemporal lobar degeneration. Sarcoplasmic TDP-43 inclusions are common in IBM, reported in up to 23% of fibers [48]. The abundance of TDP-43 suggests that it may play a significant role in the pathogenesis of IBM. However, there is a marked variation in the abundance reported by different groups [47]. The exact functions of TDP-43 are uncertain and it is not known whether TDP-43 aggregates are directly pathogenic or if intracellular redistribution leads to a deleterious loss of function. There is some evidence that TDP-43 loss from the myonuclei leads to abnormalities in the morphology of nuclei and apoptosis [110]. TDP-43 aggregates have been observed in a number of other myopathies, not just in IBM [108,111-112]. This suggests that TDP-43 mislocalization may be a nonspecific cellular response to a variety of primary pathologies and not specific to IBM.

#### Mitochondrial changes

Finally, a unifying theory of pathogenesis may have to encompass the long recognized mitochondrial changes that occur with a greater frequency in IBM, in comparison to age-matched normal controls and the other inflammatory myopathies [113]. COX-deficient fibers occur in numbers significantly in excess of normal aging due to the accumulation of large-scale mitochondrial DNA (mtDNA) deletions, being present in up to 15% of fibers in 98% of biopsies from well characterized patients [114]. Ragged red fibers and ultrastructural abnormalities including mitochondrial paracrystalline inclusions also occur [115]. It has been proposed that an increased quantity of mtDNA deletions may reflect accelerated aging in IBM, or may be reflective of faulty regeneration attempts in senescent muscle [115]. As mentioned, signaling abnormalities in autophagy pathways may explain and unify the pathogenic findings in IBM [116].

# **Therapies**

# Previous trials & current therapeutic recommendations

Prospective trials have been relatively short duration studies of low power, involving small numbers of patients. Notwithstanding these limitations, they have consistently demonstrated the lack of a sustained benefit from anti-inflammatory, immunosuppressive and immunomodulatory therapies, using a range of outcome measures (Table 2). Importantly, patients recruited to these trials and previous retrospective studies have had pathologically defined IBM, most likely reflecting established disease which could be refractory to treat-

Table 2. Prospect	ive trials of immunor	modulatory therapies in inclu	ısion body m	yositis.			
Study	Study design	Treatment	Duration (months)	Mean age of treated patients (years)	No. patients enrolled/completing No. patients per treatment (Rx) vs placebo (P) group	Outcome measures Primary 1° Secondary 2°	Ref.
Soueidan and Dalakas (1993)	Open label, uncontrolled, pilot	IVIG 2 g/kg	6	53.3	4/4	1° cMRC, FDS, CK	[17]
Leff <i>et al.</i> (1993)	Open label, randomized cross- over	AZA and MTX Max. 150 mg/day and 25 mg/week PO vs iv. MTX 0.5 mg/m² twice weekly	و	54.2 <sup>†</sup>	11/8	1° MMT, ADLQ, CK	[16]
Amato <i>et al.</i> (1994)	Open-label, uncontrolled study	IVIG 2 g/kg	e	61.6	6/7	1° mMRC, AMS, FDS, CK	[18]
Barohn e <i>t al.</i> (1995)	Open label, uncontrolled pilot	Prednisolone PO Max. 100 mg OD	6–24	68.7	8/8	1° mMRC, AMS, FDS, CK, MH	[19]
Dalakas (1997)	Randomized, double-blind, placebo controlled, cross over	IVIG 2 g/kg vs dextrose in half normal saline	m	61.2	22/19 9 Rx. 10 P.	1° eMRC, MVIC by QMT, symptom and disability scores, quantitive swallowing studies	[20]
Walter <i>et al.</i> (2000)	Randomized, double-blind, placebo controlled, cross-over study	IVIG 2 g/kg vs albumin in glucose	12	59	22/20 11 Rx. 11 P.	1° mMRC 2° NSS, patients' own assessment, arm outstretched time, EMG	[21]
Muscle Study Group (2001)	Multicenter, randomized, placebo-controlled, parallel group study	β-INF1a im. I30 μg/week vs excipients without active drug	9	65.7	30/29 13 Rx. 16 P.	1° Safety and tolerability 2° mMRC, MVICT by QMT, grip strength, LBM by DEXA, ALSFRS and health survey, timed function tests <sup>§</sup>	[23]
Dalakas e <i>t al.</i> (2001)	Randomized, double blind, placebo controlled	IVIG 2 g/kg + prednisolone, max. 60 mg OD vs prednisolone + dextrose in half normal saline	m	68.2	36/36 19 Rx. 17 P.	1° MVICT by QMT, mMRC, 2° MH, patients' own assessment, ADLQ	[22]
*Mean age at diagnosis : *Controls from placebo ç *Timed function tests: pl ADLO: Activities of daily Council scale of muscle ; immunoglobulin; LBM: L isometric contraction tes Suboutaneous; SF-36; H4	specified rather than mean a groups in previous Muscle Sti acement of pegs in a Purdue living questionnaire; ALSFRS owver; CK: Cratine kinase, I eanbody mass; Max: Maxim eath status survey; BINFFa; B	ge on entry to trial. Judy Group trials, 2001 and 2004 from the board for 30 s, time to walk 15 ft., time : ALS Functional Rating Scale, AMS: Aw EXA: Dual-energy x-ray absorptiometry um dose; MH: Muscle histology – inflan ses, NOS: Not otherwise specified; NSS: -interferon-1a.	le authors' natura e to rise from a ch grage muscle scor y, EMG: Electrom nmatory paramet Neuromuscular s;	II history study (unpublish air. e; AZA: Azathioprine; <i>c/e</i> <i>rography</i> ; FDS: Functional ers on biopsy; MMT: Man ymptom score; OD: Once	ed at time of trial). /mMRC: Cumulative/expanded/ l disability score, im.: Intramuscu ual muscle testing; MTX: Metho daily; PO: Oral; QMT: Quantitat	modified British Medical Research lar, iv: Intravenous, IVIG: Intravenous trexate; MVICT: Maximum voluntary ive Muscle Strength Testing; sc.:	10

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Table 2. Prospect	ive trials of immunon	nodulatory therapies in inclu	sion body m	yositis (cont.).			
Study	Study design	Treatment	Duration (months)	Mean age of treated patients (years)	No. patients enrolled/completing No. patients per treatment (Rx) vs placebo (P) group	Outcome measures Primary 1° Secondary 2°	Ref.
Badrising e <i>t al.</i> (2002)	Randomized, double blind, placebo controlled, parallel group	MTX PO MWD: 14.6 mg vs placebo NOS	11	68	44/35 13 Rx. 22 P.	1° MVIC by QMT, MRC, 2° activity scale scores, CK, Patient self-assessment	[24]
Muscle Study Group (2004)	Multicenter, randomized, double blind, placebo controlled, pilot	β-INF1a im. 60 μg/week vs excipients without active drug	و	64.9	30/27 15 Rx. 12 P.	1° safety and tolerability 2° MVICT by QMT, MMT, LBM by DEXA, timed function tests <sup>§</sup> , ALSFRS, SF-36	[26]
Barohn e <i>t al.</i> (2006)	Open label, pilot	TNF- $\alpha$ blocker sc. 25mg twice weekly	12	66.7	9/9 9 Rx. 34 P≛	1° MVIC by QMT	[28]
Dalakas e <i>t al.</i> (2009)	Proof of principle	Alemtuzumab iv. 0.3 mg/kg/ day for 4 days	12	60	13/13	1° Disease stabilization compared to natural history measured by MVIC by QMT, mMRC, ADLQ, MH	[27]
*Mean age at diagnosis s *Controls from placebo c *Timed function tests: pl ADLQ: Activities of daily Council scale of muscle f immunoglobulin; IBM: L isometric contraction tes Subcutaneous; SF-36: He	specified rather than mean at groups in previous Muscle Stu acement of pegs in a Puckles living questionnaire; ALSFRS ower; CK: Creatine kinase; L ean body mass; Max: Maxin ting; MWD: Mean weekly dc salth status survey; βINF1a: β	ge on entry to trial. Idy Group trials, 2001 and 2004 from the board for 30 s, time to walk 15 ft., time : ALS Functional Rating Scale; AMS: Aver : ALS Functional Rating Scale; AMS: Aver DEXA: Duale-nergy x-ray absorptiometry, DEXA: Nuscle histology – inflamy um dose, MH: Muscle histology – inflamy ses: NOS: Not otherwise specified; NSS: I i-Interferon-1a.	e authors' natura to rise from a ch. rage muscle scor ; EMG : Electromy matory paramete Veuromuscular sy	I history study (unpublishe e: AZA: Azathioprine; <i>c/e, rog</i> raphy; FDS: Functional ers on biopsy; MMT: Manu ers on biopsy; MMT: Manu ymptom score; OD: Once	ed at time of trial). /mMRC: Cumulative/expanded/ disability score; im.: Intramuscu all muscle testing; MTT: Metho daily; PO: Oral; QMT: Quantitat	/modified British Medical Research ular; Iv: Intravenous; IVIG: Intravenou: otreaste, MVICT: Maximum voluntary tive Muscle Strength Testing; sc.:	0

ment. Furthermore, immunotherapies may be costly, in the case of intravenous immunoglobulin, or have potentially serious side effects in the aging population.

The finding that immunosuppressive treatments do not ameliorate the natural disease course has been reinforced by a long-term observational study of 136 patients, which showed that immunosuppressant drug therapy could have modestly exacerbated the progression of disability in IBM [5]. Antithymocyte globulin [25] and the cytotoxic drugs, mycophenylate, cyclosporin and cyclophosphamide [59] have not been assessed in large randomized controlled trials, while therapy with oxandrolone [117], simvastatin [118] and empirical treatment with agents including coenzyme Q<sub>10</sub> has not demonstrated benefit [51,57,59].

Current consensus recommendations are for supportive management and commonly no treatment will be prescribed by neuromuscular experts [11]. With insufficient data for evidence-based treatment, steroids may be used in cases of diagnostic doubt, and occasionally in younger patients with florid inflammation on biopsy. Intravenous immunoglobulin may be used in rapidly deteriorating cases or in patients with significant dysphagia. Patients with associated connective tissue disease or other autoimmune disorder are more likely to show initial response to a trial of prednisolone and an immunosuppressive drug [119].

In addition to supportive management by the multidisciplinary team, studies have evaluated safety and the effects of aerobic exercise and strength training programs in IBM patients [120–122]. It remains to be seen if exercise can produce long term disease-modifying benefits as well as enhancing the performance of activities of daily living and improving quality of life.

# **Current trials**

In the past, treatment strategies in IBM have centerd on targets informed by pathological studies, with a major focus on inflammation. There is current interest in modulating protein misfolding pathways by upregulating endogenous HSP. Arimoclomol is a molecule that co-induces the expression of HSP under stress conditions [123]. A recently completed randomized controlled safety and tolerability pilot study in 24 IBM patients (2:1 arimoclomol to placebo ratio) has shown it to be safe and has also identified a trend for slower decline in the mean IBMFRS as compared with placebo [124]. A larger study of arimoclomol administered for a longer period of time in the treatment group is being planned.

Another strategy is to focus on arresting muscle atrophy in IBM, as with the new humanized intravenous monoclonal antibody against the myostatin receptor. A recent pilot study demonstrated an increase in thigh muscle volume with improved mobility in 11 patients (compared with three placebo patients) followed up after one treatment with the monoclonal antibody BYM338 [125]. Thigh volume by MRI was employed as a primary outcome measure with a range of secondary measures of strength and functionality, including the 6MWT (clinicaltrials.gov identifier: NCT01423110). Interestingly, the pilot data indicate that potential clinical benefits may outpace the rate of functional decline in this slowly progressive disease, thus it may be possible to sufficiently ameliorate symptoms from the time of diagnosis, notwithstanding potential complications arising from long-term drug administration.

A current dose finding study to evaluate the efficacy, safety and tolerability of IV BYM338 (bimagrumab), measuring physical function, muscle strength and mobility over a time period of 1–2 years is underway in Australia, Europe, Japan and the USA (Clinical-Trials.gov Identifier: NCT01925209). Exercise trials are also in progress (ISRCTN99826269) and it is of great interest to see if these will replicate the anecdotal benefits observed in clinical practice.

# **Conclusion & future perspective**

IBM is unique among the acquired muscle disorders in which both cell-mediated inflammation and degenerative protein aggregation are likely to play synergistic roles [126]. There is no agreement as to the relative contribution of these pathways [127] and knowledge of interactions during the evolution of disease is limited to theories of cell stress [97,116]. In spite of active research, many questions remain and no effective treatment exists. The basis for selective muscle involvement is unexplained and the interplay of aging with environmental and genetic factors has not been elucidated [57,59]. However, we are now in an era of international collaboration to address these challenges.

Going forward, the new 2011 ENMC diagnostic criteria will hopefully result in greater numbers of patients being diagnosed at an earlier stage and entering into future clinical trials with an optimal chance of treatment response. Communication among experts is helping to improve and standardize natural history data collection with the aim of harmonizing and expanding patient registries [57]. This will facilitate deep phenotyping of patients on a global scale to maximize the yield of epidemiological data, increase disease awareness, identify important prognostic subgroups and assist with patient stratification in the light of emerging findings, such as the recent discovery of the autoantibody to cN1A [57]. This work will also be the vital platform for more powerful studies with greater patient numbers to permit the evaluation of MRI studies, emerging biomarkers and the proposed multicenter immunology association study [57]. It will also help to

clarify best outcome measures for trials, to determine realistic treatment responses over time and will underpin the development of standards of care and best practice guidelines that can be used in clinic and to commission healthcare for IBM patients around the world.

A new way of thinking about IBM is called for and we are now prepared to properly explore the genetic approach, using technological advances to perform massively parallel high-quality sequencing of human exomes [51]. This strategy is supported by the establishment of IBM genetic biobanks with the aim of unravelling the basis of genetic susceptibility, host factors in immunity and helping to define the earliest molecular events preceding microscopic damage and muscle weakness.

Forthcoming insights from current clinical trials are eagerly awaited on the basis of promising pilot data and parallel laboratory studies should identify new targets for treatment that will translate into real benefit for patients in the near future.

#### Disclaimer

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