



Inclusion Body Myositis: Update on Pathogenesis and Treatment

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Abstract

Inclusion body myositis is the most common acquired myopathy after the age of 50. It is characterized by progressive asymmetric weakness predominantly affecting the quadriceps and/or finger flexors. Loss of ambulation and dysphagia are major complications of the disease. Inclusion body myositis can be associated with cytosolic 5'-nucleotidase 1A antibodies. Muscle biopsy usually shows inflammatory cells surrounding and invading non-necrotic muscle fibers, rimmed vacuoles, congophilic inclusions, and protein aggregates. Disease pathogenesis remains poorly understood and consists of an interplay between inflammatory and degenerative pathways. Antigen-driven, clonally restricted, cytotoxic T cells represent a main feature of the inflammatory component, whereas abnormal protein homeostasis with protein misfolding, aggregation, and dysfunctional protein disposal is the hallmark of the degenerative component. Inclusion body myositis remains refractory to treatment. Better understanding of the disease pathogenesis led to the identification of novel therapeutic targets, addressing both the inflammatory and degenerative pathways.

Key Words Inclusion body myositis · idiopathic inflammatory myopathies · muscle homeostasis · immunotherapy neurodegenerative disorder.

Introduction

Inclusion body myositis (IBM) is the most common acquired myopathy after the age of 50, with a varying reported prevalence averaging 24.8 to 45.6/1,000,000 [1]. IBM has a distinctive clinical phenotype and histopathological findings. Despite the inflammatory infiltrate on muscle biopsy, IBM remains refractory to immunotherapy. Although IBM does not usually affect longevity, patients can be markedly disabled at advanced stages, which markedly affects their quality of life and is associated with high economic burden [2]. This resulted in a continuous strive to better understand the disease pathogenesis, and identify novel therapeutic targets.

Clinical Findings

Classically, IBM presents with progressive insidious weakness, often asymmetric, predominantly affecting the quadriceps and/or finger flexors [3] (Fig. 1). Although none of the clinical findings in isolation is specific for IBM, weakness of knee extension more than hip flexion, and finger flexion more than finger extension, strongly raise the suspicion for this disorder. Other commonly involved muscles include the biceps, triceps, anterior leg compartment, and facial and swallowing muscles with dysphagia reported in about half of the patients [4, 5]. Less commonly, IBM can present with respiratory insufficiency, camptocormia, dysphagia, or facial weakness [5–8].

Pathological Findings

The pathological features of IBM are described in Fig. 2. On muscle biopsy, IBM is characterized by the presence of an inflammatory exudate, predominantly endomysial, where the inflammatory cells surround and focally invade non-necrotic muscle fibers. Besides inflammation, IBM is characterized by the presence of vacuoles rimmed by a membranous cytoplasmic material (rimmed vacuoles), atrophic fibers, as well as congophilic inclusions that may be intra- or extravacuolar.

Invited review—theme: “Myopathies”

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Fig. 1 Clinical characteristics of inclusion body myositis. (A) Patient attempting to make a fist with both hands: asymmetric weakness of finger flexors, severe on the left. (B) Patient in a wheelchair with severe quadriceps weakness and atrophy

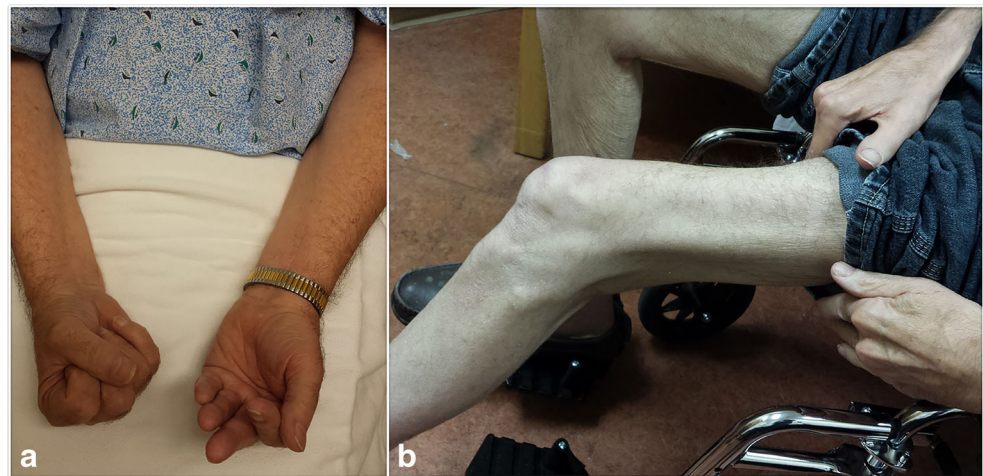
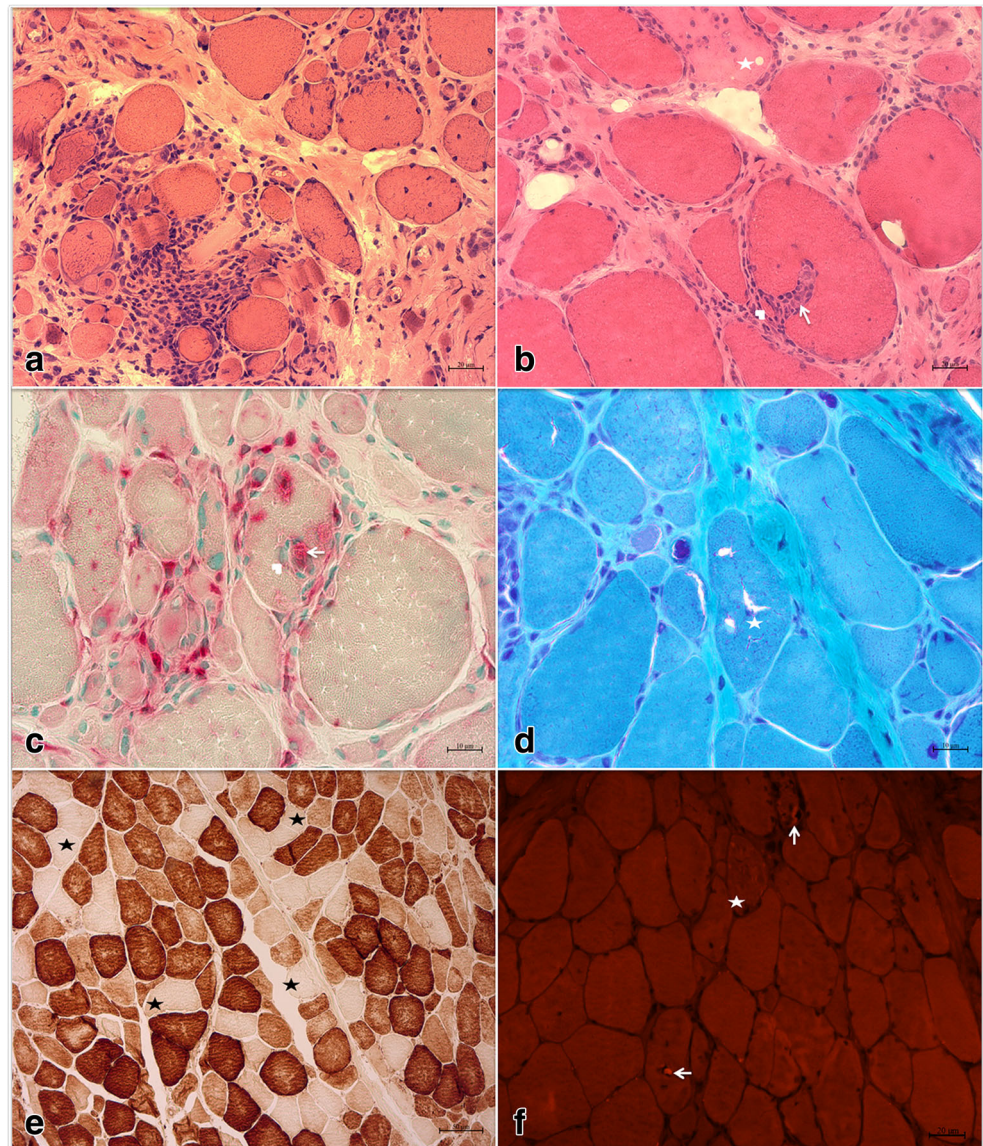


Fig. 2 Histopathological features of inclusion body myositis. (A, B) Hematoxylin & eosin stain: (A) predominantly endomysial inflammatory infiltration; (B) inflammatory cells invading a non-necrotic muscle fiber (arrow) splitting off a small portion of the fiber (arrowhead) and an adjacent necrotic fiber (star). (C) Acid phosphatase stain: mononuclear cells (likely lymphocytes) invading a non-necrotic muscle fiber (arrowhead), backed up by a macrophage (arrow) identified by its acid phosphatase reactivity, as well as myriad endomysial inflammatory cells, some of which are macrophages, surrounding and occasionally focally invading muscle fibers. (D) Trichrome stain: rimmed vacuoles (star). (E) Cytochrome c oxidase stain: multiple cytochrome c oxidase negative fibers (star) in various regions of the specimen. (F) Congo red stain viewed under rhodamine optics: 2 fibers with intravacuolar congophilic inclusions (arrowheads) and 1 fiber with extravacuolar congophilic inclusions (star)



Congophilic inclusions are more easily detected by Congo red staining viewed under rhodamine optics rather than polarized light. Mitochondrial changes, especially an increased number of cytochrome c oxidase negative fibers, are observed in the vast majority of IBM patients [9]. Therefore, the absence of cytochrome c oxidase negative fibers should raise doubts about the diagnosis of IBM. This can be helpful in muscle specimens lacking rimmed vacuoles in which differentiating IBM from other inflammatory myopathies such as dermatomyositis or polymyositis may be challenging [9, 10]. One of the potential issues with this approach is the lack of agreement on upper limit for the percentage of cytochrome c oxidase negative in normally aged muscle. Some experts, however, consider values at least exceeding 2% as the threshold for excessive cytochrome c oxidase negative fibers with aging [11]. Further studies to identify a cutoff value for the percentage of COX⁻/SDH⁺ fibers that is sensitive and specific to IBM, as compared to PM, DM, and normally aged muscles, would be extremely helpful and may facilitate future introduction of mitochondrial changes as part of clinical or research diagnostic criteria for IBM. Eosinophilic inclusions can be seen in about half of the specimens [4]. Electron microscopy can help in identifying filamentous inclusions in the proximity of vacuolated fibers and, less commonly, 10 to 14 nm intranuclear inclusions [4].

Most proposed IBM diagnostic criteria heavily relied on pathological findings. The Griggs–Barohn 1995 criteria consisted of 2 categories: definite and possible IBM, both requiring the presence of endomysial inflammation with invasion of non-necrotic muscle fibers by mononuclear cells [12]. Further evidence of vacuolated muscle fibers, and either intracellular amyloid deposits or 15 to 18 nm tubulofilaments on electron microscopy, was required for the definite IBM category. In the MRC 2010 criteria, increased MHC-I expression on the surface of intact muscle fibers was added to the pathologic features. While the criteria for definite IBM (pathologically defined IBM) remained unchanged since the Griggs–Barohn 1995 criteria, clinically defined IBM and possible IBM categories required at least 1 of the following pathological features: invasion of non-necrotic fibers by mononuclear cells, rimmed vacuoles, or increased MHC-I expression on the surface of intact muscle fibers [13]. Later on, demonstrating abnormal sarcoplasmic deposition of Tar-DNA binding protein-43 (TDP-43) or p62 via immunohistochemical staining was shown to enhance the sensitivity of a muscle biopsy for the diagnosis of IBM [14–16]. Therefore, the ENMC 2011 criteria expanded the pathological criteria to include the “presence of protein accumulation” criterion which can be fulfilled by demonstrating the presence of either intracellular amyloid deposit, or deposit of other proteins demonstrated via immunostaining with antibodies to p62, SMI-31 (phosphorylated tau marker), or TDP-43 [17].

Laboratory Testing

The variability of the clinical and histopathological findings, often resulting in delay in diagnosis, prompted the search for a serological biomarker and the identification of cytosolic 5'-nucleotidase 1A (cN-1A) antibodies [18–20]. cN-1A is a protein involved in nucleic acid metabolism. The role of cN-1A antibodies in IBM pathogenesis is unknown. Tawara et al. [21] reported that passively immunized mice with sera from cN-1A-positive IBM patients demonstrate p62-positive sarcoplasmic aggregates associated with macrophages infiltration. It is also unclear whether there is a difference in phenotype or response to immunotherapy in patients with IBM based on their cN-1A serological status [21–23]. In a small cohort of 25 patients, cN-1A seropositive patients took longer to get up and stand, whereas there was no significant difference on the 6-min walk with the seronegative group [23]. In this study, the cN-1A seropositive group was reported to have more significant bulbar involvement; however, this finding was not reproduced in a subsequent cohort [21]. A single study evaluated mortality risk based on cN-1A serological status and found a higher adjusted mortality in seropositive IBM patients [24]. Elevated cN-1A antibodies are reported to be 33 to 76% sensitive and 92 to 96% specific for IBM [19, 20]. Despite the initially claimed high specificity, cN-1A antibodies were later reported in non-IBM patients with various autoimmune disorders: Sjögren's syndrome (23–36%), systemic lupus erythematosus (14–20%), and dermatomyositis (15%) [22, 25]. Therefore, the presence of elevated cN-1A antibodies should be interpreted with caution, taking into consideration the clinical context and histopathological findings.

Creatine phosphokinase levels are very variable ranging from normal to up to 15 times upper limit of normal.

Needle electromyography usually shows increased spontaneous activity and fibrillation potentials, associated with short duration, low-amplitude, motor unit potentials often mixed with long duration, high-amplitude motor unit potentials [4]. Iterative discharges such as complex repetitive discharges and myotonic discharges could also be observed [26]. As muscle involvement can be patchy, we make sure to include needle examination of the deep finger flexors when IBM is suspected.

Diagnosis

To better define inclusion criteria for clinical trials, there have been multiple proposed diagnostic criteria over the years [12, 27, 28]. Despite the lack of effective treatment for IBM, a timely diagnosis is also important in clinical practice for patient's counseling and to avoid unnecessary immunosuppression, that maybe attempted in patients diagnosed with polymyositis. Lloyd et al. [29] evaluated the sensitivity and specificity of all the published diagnostic criteria: all the categories had very high specificity (98–100%),

whereas the sensitivity lagged behind ranging from 11 to 84%. In this study, “probable IBM” category from the ENMC 2011 criteria had the best sensitivity of 84%. The ENMC 2011 criteria consist of 3 diagnostic categories for research purposes: clinicopathologically defined IBM, clinically defined IBM, and probable IBM (Table 1) [17]. Clinically defined IBM category includes patients with weakness in the quadriceps muscles more than hip flexors, as well as in finger flexors more than shoulder abductors. In this case, patients are required to have at least 1 of the following pathological features: endomysial inflammation, rimmed vacuoles, increased MHC-I, 15 to 18 nm filaments, or accumulation of amyloid or other proteins. The sensitivity of “clinicopathologically defined IBM” was reported as 15% and clinically defined IBM as 57% [29]. Clinical guidelines for diagnosis and management of IBM are yet to be published [30].

Pathogenesis

Inflammatory Pathways

IBM is characterized by the presence of inflammatory cells surrounding and focally invading non-necrotic muscle fibers. The muscle fibers are invaded by mostly cytotoxic CD8⁺ T cells with some macrophages and surrounded by CD4⁺ T cells and macrophages, indicating a well-orchestrated immune attack [31]. Endomysial T cells display a restricted expression of T-cell receptor gene usage that persists over time [32]. When compared to peripheral blood lymphocytes,

endomysial T cells express a significantly higher degree of restriction, suggesting local antigen-driven stimulation recruiting peripheral T-cell lymphocytes to expand *in situ* [33, 34]. Furthermore, myeloid dendritic cells, serving as antigen-presenting cells, are found in abundance in IBM muscle samples in close proximity to T cells [35]. These findings indicate that the activation of T cells is an antigen-driven response. The role of the humoral response in IBM remained unexplored for a while. Recognition of antigen-directed, clonally expanded plasma cells in IBM muscles [36, 37] was followed, shortly after, by the identification of cN-1A antibodies. Furthermore, expression of MHC-I by non-necrotic muscle fibers led to the discovery of susceptibility regions in the HLA genes as will be detailed in the “Genetics” section.

The association of inclusion body myositis with viral infections such as hepatitis C virus (HCV) or HIV remains controversial. The frequency of HCV antibodies in IBM patients was reported at 28% in Japan but only 3.3% in Brazil (1 out of 30 IBM patients, but it is unclear how many patients were screened for HCV) [38, 39]. Subsequently, Tawara et al. [21] reported that only 4.5% of Japanese IBM patients with positive cN-1A antibodies had concomitant HCV antibodies, compared with 26.5% in the cN-1A seronegative IBM group ($p = 0.036$). Moreover, the increased incidence of HCV in IBM patients has not been reported yet outside of Japan. Similarly, an association between IBM and HIV infection has been suggested by reported cases of HIV patients who then developed IBM [40, 41], with muscle biopsy showing clonal expansion of viral-specific CD8⁺ cells in the endomysium [41]. However, these patients displayed the same histopathological features of IBM as in HIV-negative patients, and there was no evidence of expression of viral-specific antigens within the muscle fibers.

In 1 study of 38 patients with IBM, 58% of patients had aberrant populations of large granular lymphocytes in their blood, fulfilling criteria for T-cell large granular lymphocytic leukemia (T-LGL leukemia) [42]. T-LGL leukemia is a rare disorder with a wide spectrum of severity, ranging from benign chronic lymphocytic proliferation to malignancy, and is commonly associated with autoimmune diseases [43]. It is unclear whether the aberrant population of LGL plays a primary role in IBM pathogenesis or is just an innocent bystander resulting from chronic antigenic stimulation [44]. From a hematological perspective, the presence of a clonal expansion of large granular lymphocytes does not necessarily require treatment [45]. Therefore, there is no clear indication yet to routinely screen for T-LGL leukemia in all IBM patients. Nonetheless, a complete blood count with a peripheral blood smear could be considered first looking for cytopenia, anemia, lymphocytosis, or excess of large granular lymphocytes that may warrant further investigation via flow cytometry.

Table 1 Inclusion body myositis diagnostic criteria based on ENMC 2011

❖ Mandatory criteria:
1. Age of onset later than 45 years
2. Duration of symptoms more than 12 months
3. Serum creatine kinase level no more than 15 times upper limit of normal
❖ Clinical criteria:
1. Quadriceps more than flexors weakness
2. Finger flexors more than shoulder abductors weakness
❖ Pathological criteria:
1. Endomysial inflammatory infiltrate
2. Rimmed vacuoles
3. Protein accumulation or 15–18 nm filaments
4. Upregulation of MHC class I
❖ Classification categories:
1. <i>Clinicopathologically defined IBM</i> : mandatory criteria + at least 1 clinical criterion + pathological criteria 1, 2, and 3
2. <i>Clinically defined IBM</i> : mandatory criteria + all clinical criteria + 1 or more, but not all, pathological criteria
3. <i>Probable IBM</i> : mandatory criteria + 1 clinical criterion + 1 or more, but not all, pathological criteria

Degenerative Pathways

The pathological evidence of rimmed vacuoles with abnormal protein aggregation and deposition of congophilic inclusions within the muscle fibers, in association with mitochondrial dysfunction, supports the presence of a degenerative component. This is further substantiated by the lack of response to immunomodulatory therapy. Protein inclusions in IBM contain a wide array of proteins, mostly associated with neurodegenerative disorders such as amyloid- β peptides, ubiquitin, phosphorylated tau, TDP-43, and prion protein [14, 46–48]. Similar to Alzheimer's disease, amyloid- β peptides, including amyloid- β 42, can aggregate within the muscle fibers, with a potential cytotoxic effect suggested by the presence of A β 42 oligomers in IBM muscles [49–51]. However, amyloid- β deposit may be of nonspecific significance, and elevated amyloid- β 42 level is also found in the serum of patients with dermatomyositis [52].

Protein aggregation is the result of abnormal protein homeostasis in muscle (proteostasis) which encompasses abnormal protein production, folding, and disposal [53]. Normally, protein disposal, via the proteasomal system and autophagy, is crucial in maintaining proteostasis and avoiding protein accumulation. The 26S proteasome or ubiquitin protease system is responsible of eliminating misfolded/unfolded proteins including amyloid- β and phosphorylated tau, in part via polyubiquitination [54]. In IBM, proteasome 26S and aggregated proteins co-localize on muscle biopsy [55]. Furthermore, there is evidence of decreased 26S proteasomal activity and overexpression of amyloid- β precursor protein in IBM muscle fibers, associated with proteasomal inhibition and further protein aggregation [55].

Autophagy consists of degradation of various molecules in lysosomes. Excessive protein turnover or malfunctioning of the lysosomes can manifest with excess of endosomes, autophagic vacuoles, and autolysosomes, all of which can be commonly found in rimmed vacuoles [56]. Analysis of rimmed vacuoles content via a proteomic approach confirmed that rimmed vacuoles proteins are largely related to protein folding and autophagy [57]. The metabolic regulator mammalian target of rapamycin (mTOR) is a major autophagy mediator. By inhibiting mTOR, rapamycin induces autophagy [58]. In a valosin-containing protein (VCP) inclusion body myopathy mouse model, mTOR signaling was found to be defective, and further inhibition by rapamycin caused exacerbation of the mice muscle weakness and an increase in serum creatine kinase and the number of atrophic and vacuolated fibers [59]. Contrasting findings were reported by another group in which rapamycin-treated VCP mice had improved strength and a decreased number of atrophic and vacuolated fibers [60]. Indeed in IBM, there is evidence for both increased autophagy, as would be expected with the high protein turnover, and dysfunctional autophagy as witnessed by the diminished

lysosomal enzymatic activity, indicating lysosomal dysfunction [61–63]. p62, also known as sequestosome 1 (SQSTM1), helps in transporting polyubiquitinated proteins to both the proteasome and the lysosome [64]. Unlike in dermatomyositis and polymyositis, p62 is overexpressed in IBM [15, 65].

Another important organelle in protein folding is the endoplasmic reticulum (ER). However, ER is very sensitive to disruption of muscle homeostasis [66]. To avoid stress and the accumulation of misfolded protein, the ER heavily relies on chaperone proteins, including heat shock proteins (HSP), which are important for protein–protein interactions and maintaining conformational protein structure [67]. During stress, as a part of a cytoprotective mechanism, there is upregulation of chaperone proteins [68–70]. Furthermore, ER stress upregulates the secretion of myostatin precursor protein (MstnPP) and its metabolites [71, 72]. High levels of MstnPP can also induce ER stress, which results in aggregation of high molecular weight MstnPP cleavage products and impaired secretion of mature myostatin [73]. Myostatin, a member of the transforming growth factor β superfamily (TGF β), is an inhibitor of skeletal muscle mass development [74]. There is also evidence of mitochondrial dysfunction in IBM which is witnessed by the mitochondrial abnormalities observed on the muscle biopsy and the increased amount of mitochondrial DNA rearrangement, deletion, and depletion [75, 76].

Inflammation Versus Degeneration

It remains unclear whether the primary process is immune-mediated or degenerative in nature. There is strong evidence for the inflammatory component, as detailed above, including clonally restricted, antigen-driven, infiltrating CD8-positive T cells; the strong genetic association with HLA genes; and the association with cN-1A antibodies and other autoimmune conditions such as systemic lupus erythematosus and Sjögren's syndrome. Unlike in inclusion body myositis, these findings are not encountered in other neurodegenerative disorders. Regarding the degenerative component, there is growing evidence that inflammation can cause secondary degenerative features. In inflammatory myopathies, including IBM, inflammatory cytokines can induce the expression of the immunoproteasome (usually only expressed in hematopoietic cells) in muscle, which strongly co-localizes with fibers expressing MHC-I [77]. Overexpression of MHC-I in mice can cause severe myopathy and induce ER stress and protein unfolding [78]. In myoblast cultures, overexpression of β -amyloid precursor protein and exposure to inflammatory cytokines can both induce cytoplasmic mislocalization of TDP-43 [79]. Furthermore, pro-inflammatory mediators can upregulate the production of β -amyloid proteins and the expression of inducible nitric oxide synthase (iNOS) in skeletal muscle [80, 81]. It has also been shown that the severity of the inflammation strongly correlates with β -amyloid production and mitochondrial dysfunction [80, 82]. As mentioned above, *in vitro*

and *in vivo* passive immunization of mice with sera of patient's with cN-1A antibodies can result in p62/SQSTM1 sarcoplasmic aggregates [21]. On the other hand, overexpression of β -APP activated nuclear factor κ B in myoblast cultures [79]. Therefore, protein accumulation could theoretically trigger inflammation; however, further experimental studies in IBM patients are still needed. Nonetheless, one of the main arguments for a primarily degenerative component remains the lack of response to immunotherapy.

Genetics

Among immune- and neurodegenerative-related genes, the HLA region has the strongest association with IBM, especially HLA-DRB1 [83–85]. Furthermore, HLA-DRB1*03:01, DRB1*01:01, and DRB1*13:01 alleles can modify the phenotype and be associated with more severe muscle weakness [86]. Among neurodegenerative-related genes, there has not been any association between IBM and genes related to Alzheimer's disease, or Parkinson's disease. Three likely pathogenic or pathogenic rare missense variants in *VCP* and 4 in *SQSTM1* were found in patients with IBM [87, 88]. None of the patients had developed inclusion body myopathy with Paget's disease of bones, frontotemporal dementia, or amyotrophic lateral sclerosis, and none of the patients had family history of such disorders. All patients fulfilled clinical and pathological criteria for IBM. Although there is no clear association between apolipoprotein E and translocase of outer mitochondrial membrane 40 (TOMM40) genotypes with the risk of developing IBM, the presence of a very long polyT repeat allele in TOMM40 may delay onset of symptoms by about 5 years, especially when associated with apolipoprotein E genotype ϵ 3/ ϵ 3. [89, 90] TOMM40 encodes an outer mitochondrial membrane protein involved in the transport of peptides into the mitochondria including amyloid- β [91]. Studying the proteomics of rimmed vacuoles, rare missense variants in *FYCO1* were overrepresented in IBM patients (11.3%) compared with ALS (2.6%) patients and healthy controls (3.4%) [57]. *FYCO1* is an autophagic adaptor protein [92].

Treatment

Better understanding of the pathogenesis and further characterization of the involved degenerative pathways resulted in casting the net wide searching for a treatment addressing inflammatory and degenerative pathways (summarized in Table 2). However, there continues to be no effective treatment in inclusion body myositis.

Targeting Inflammatory Pathways

Despite the clear inflammatory component, immunosuppressive therapy (such as corticosteroids, intravenous immunoglobulin (IVIG), methotrexate, and azathioprine) offers at best a mild and transient benefit [93–98]. In an open-label uncontrolled [94] and 2 placebo-controlled studies [95, 96], IVIG treatment showed overall marginal to no improvement. Despite reported improvement in swallowing and functionally significant improvement in strength in occasional patients [95, 99], IVIG does not seem to have a sustained benefit, nor does it alter the long-term disease course [100]. Therefore, IVIG treatment is not recommended in clinical practice, although on a case-by-case basis, it can be considered in patients with marked dysphagia.

Two randomized controlled studies of β -interferon-1a at standard [101] or high dose [102] showed no improvement in muscle strength in treated patients. Similarly, clinical trials with anti-T-lymphocyte globulin treatment [103], etanercept which is a tumor necrosis factor-alpha fusion protein [104], alemtuzumab which is a humanized monoclonal antibody that causes an immediate depletion or severe reduction of peripheral blood lymphocytes [105], anakinra which is an IL1 receptor antagonist [106], and simvastatin for its pleiotropic anti-inflammatory effect [107], showed no clinically meaningful benefit in IBM.

Targeting Degenerative Pathways

Based on the multiple unsuccessful attempts to treat IBM by acting on the immune system, and regardless whether the degenerative component is primary to the pathogenesis or not, degenerative pathways have become a novel potential therapeutic target. Arimoclomol prolongs the activation of heat shock factor 1 selectively in stressed cells and, subsequently, augments HSP levels [108]. HSP inducers [109] are under investigation for various disorders such as ALS [110], sphingolipidoses [111], and inclusion body myositis [79]. There is no good animal model for IBM; however, in mutant *VCP* mice, arimoclomol ameliorated muscle strength and disease pathology [79]. A proof-of-concept safety randomized controlled trial targeting drug safety in 24 IBM patients demonstrated arimoclomol to be safe and well tolerated. Three of the efficacy secondary outcomes demonstrated trends favoring arimoclomol at 8 months. A current phase II/III trial is underway (NCT02753530).

Therapeutic effect of myostatin inhibition has also been investigated. Bimagrumab, activin receptor II (ARII) inhibitory monoclonal antibody, was studied in a pilot trial in which 10 patients were randomized to bimagrumab and 4 to placebo [112]. Thigh muscle volume evaluated by MRI was increased by 6.5% on the right and 7.6% on the left in the treated group ($p = 0.024$ and 0.009 , respectively); however, there was no

Table 2 Summary of inclusion body myositis therapeutic trials

	Targeting inflammatory pathways	Targeting degenerative pathways	Nonpharmacological therapeutic options
Treatment agent	<ul style="list-style-type: none"> • Corticosteroids • Intravenous immunoglobulins • Methotrexate • Azathioprine • β-Interferon-1a • Anti-T-lymphocyte globulin • Etanercept • Alemtuzumab • Anakinra • Simvastatin 	<ul style="list-style-type: none"> • Arimoclomol • Rapamycin • Bimagrumab* • Follistatin* • Oxandrolone* 	<ul style="list-style-type: none"> • Exercise • Cricopharyngeal myotomy • Pharyngoesophageal dilation

*Increases muscle mass

statistically significant difference in muscle function. A follow-up randomized controlled trial did not reach its primary outcomes and the results remain unpublished.

Follistatin is a myostatin antagonist [113]. In a nonrandomized open-label study, 6 IBM patients were treated with follistatin gene therapy and showed improvement in the 6-min walk test (5–153 m) [114]. However, the treated group also received high-dose prednisone and a prescribed exercise program, which was not accounted for in the matched control group [115]. Therefore, further studies are needed to determine the efficacy of follistatin gene therapy in IBM. Increasing muscle mass was also attempted via treatment with oxandrolone, an anabolic steroid, which showed only borderline benefit improving whole-body strength, with more noticeable improvement in upper extremity strength [116].

Despite the conflicting evidence regarding the effect of rapamycin on VCP mice, a recent randomized, double blind, placebo-controlled clinical trial was conducted. The study did not reach the primary outcome defined as stabilization of maximal voluntary quadriceps isometric strength assessed with a dynamometer, although in the treated group, the 6MWT deteriorated less and the forced vital capacity improved [117]. The study is yet to be published. (NCT02481453).

Nonpharmacological Therapeutic Options

There is limited data regarding the role of exercise in idiopathic inflammatory myopathies in general and IBM in particular [118]. In 3 uncontrolled trials with limited number of patients (≤ 7 patients per trial), home exercise (resistance training with or without aerobic exercise) is at least not harmful and may indeed preserve or even improve muscle strength [119–121]. In a rat model with chloroquine-induced IBM, resistance training was noted to increase muscle strength and decrease p62 levels [122].

IBM patients with dysphagia may benefit from cricopharyngeal myotomy and pharyngoesophageal dilation

which help in relaxing the upper esophageal sphincter [123]. In a retrospective study, 12 patients with IBM received botulinum toxin injection of the cricopharyngeus muscle, with subsequent improvement of their swallowing [124]. However, in a subset of patients in which dysphagia may be due to decreased hypolaryngeal excursion with normal upper esophageal sphincter relaxation, these interventions may not be helpful [125].

Future Therapeutic Options

Promising novel mechanistic approaches involve reducing endoplasmic reticulum stress, promoting autophagy, optimizing oxidative and mitochondrial dysfunction, and removal of toxic protein aggregates. There is marked patient excitement about the potential role of stem cells in IBM, but there is no current data to support the efficacy and safety of this approach.

In addition to muscle biopsies in IBM expressing large numbers of CD3⁺ cells that co-localized with Kv1.3, circulating PBMC had an increased number of Kv1.3⁺ cells in IBM as compared with healthy controls and other inflammatory myopathies [126]. Kv1.3 is frequently found on T effector memory cells, which have been implicated in T-cell-mediated autoimmune disorders, and targeting these cells in IBM may be a new promising strategy.

Prognosis

There is no clear evidence that IBM affects life expectancy. However, loss of ambulation and dysphagia remain the main source of disability. The use of a wheelchair is needed in about a third of patients 14 years from onset and nearly all patients 20 years from onset [127, 128]. During a 12-year follow-up study of 64 Dutch patients with IBM, 46 patients died during follow-up with a median age at death of 81 years [127].

Although the life expectancy was not different from an age-matched Dutch general population, death from respiratory disease, especially pneumonia, was markedly more common in the IBM group. Lastly, as mentioned above, there is preliminary evidence that patients with positive cN-1A antibodies may have mildly higher adjusted mortality risk [24].

Conclusion

IBM is an inexorably progressive muscle disorder characterized by distinctive clinical and histopathological features. Clinically, it is characterized by the predominant involvement of deep finger flexors and quadriceps muscles and, histopathologically, by the combination of inflammatory and degenerative changes. There remain many unanswered questions regarding IBM pathogenesis and, most importantly, the refractoriness to treatment. Perhaps, IBM is primarily an immune-mediated disorder, which unlike any other immune disorder, triggers downstream degenerative changes early on in the process. On the other hand, a primarily degenerative disorder with secondary inflammation is also a possibility. Regardless of the nature of the primary process, a successful treatment may necessitate addressing both the immune and degenerative components simultaneously. Alternatively, it may be that the therapeutic window of opportunity is confined, and requires intervention early on, prior to the development of the degenerative changes.

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