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REVIEW

Inclusion body myositis: therapeutic approaches

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Rohit Aggarwal
Chester V Oddis

Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Abstract: The idiopathic inflammatory myopathies are a heterogeneous group of diseases that include dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM) and other less common myopathies. These are clinically and histopathologically distinct diseases with many shared clinical features. IBM, the most commonly acquired inflammatory muscle disease occurs in individuals aged over 50 years, and is characterized by slowly progressive muscle weakness and atrophy affecting proximal and distal muscle groups, often asymmetrically. Unlike DM and PM, IBM is typically refractory to immunotherapy. Although corticosteroids have not been tested in randomized controlled trials, the general consensus is that they are not efficacious. There is some suggestion that intravenous immunoglobulin slows disease progression, but its long-term effectiveness is unclear. The evidence for other immunosuppressive therapies has been derived mainly from case reports and open studies and the results are discouraging. Only a few clinical trials have been conducted on IBM, making it difficult to provide clear recommendations for treatment. Moreover, IBM is a slowly progressive disease so assessment of treatment efficacy is problematic due to the longer-duration trials needed to determine treatment effects. Newer therapies may be promising, but further investigation to document efficacy would be expensive given the aforementioned need for longer trials. In this review, various treatments that have been employed in IBM will be discussed even though none of the interventions has sufficient evidence to support its routine use.

Keywords: inclusion body myositis, clinical features, treatment

Introduction

Inclusion body myositis (IBM) is the most common acquired muscle disease in adults aged over 50 years, with a 3:1 male preponderance and a prevalence estimated at 4 to 9/100,000[1] with an incidence rate of 0.79 per 100,000.[2] IBM is more common in Caucasians and considered to be rare among Asians and African-Americans.[3] It is a relentlessly, albeit slowly, progressive disorder that leads to markedly impaired mobility, dysphagia or even death. Most patients require an assistive mobility device within 10 years of onset.[4,5] The cause of the disease is unknown, but immunologic and degenerative features play a role in disease pathogenesis. The immunopathologic hallmarks certainly resemble those seen in polymyositis (PM), making it difficult for clinicians to distinguish IBM from PM, particularly early in the disease course. Refractoriness to treatment is usually seen in these patients.

Clinical features

Patients with IBM present with an insidious onset of slowly progressive weakness and the condition is more frequently seen in males (3:1 male to female ratio). There is a

Correspondence: Rohit Aggarwal
UPMC Arthritis and Autoimmunity Clinic, Department of Medicine, Rheumatology, University of Pittsburgh, Falk Medical Building, 3601 Fifth Avenue, Suite 2B, Pittsburgh, PA 15213, USA
Tel +1 412 648 9782
Fax +1 412 383 8864
Email aggarwalr@upmc.edu

wide range of ages at presentation from 35 years to 90 years, but most of the patients present after the age of 50 years, with a mean age of onset of around 60 years. IBM is often misdiagnosed as PM due to similar initial presentation with symmetrical proximal weakness of lower extremity with creatine kinase (CK) elevation. However, IBM has some unique clinical features that may help in distinguishing the two: often asymmetric; distal muscle involvement; and neuropathic features with early weakness and atrophy of the quadriceps, the forearm flexor muscles (ie, wrist and finger flexors), and the ankle dorsiflexors.

At least 60% of patients develop dysphagia, which can be severe as well as the presenting symptom.[6,7] The dysphagia is not necessarily due to a true pharyngeal myopathy as seen with PM or DM, and patients often complain of a "blocking sensation" with swallowing. Imaging or manometry reveals cricopharyngeal achalasia, amenable to cricopharyngeal dilatation or myotomy. CK levels are modestly elevated ($<10\times$ upper limit of normal) especially early in the course, unlike polymyositis (PM). The typical needle electromyography (EMG) finding in IBM is mixed myopathic (small short-amplitude motor unit action potential) and neuropathic (prolonged large-amplitude motor unit action potential) changes: however there are often only myopathic patterns with increased insertional activity, fibrillations, and polyphasic potentials, similar to PM. Nerve conduction studies are usually normal. Magnetic resonance imaging (MRI) is an emerging tool to help in the diagnosis of IBM and may help to differentiate it from PM. MRI abnormalities in IBM tend to be fibrofatty changes and atrophy localized to quadriceps, gastrocnemius, and anterior forearm muscle groups and show more asymmetry than in PM, although there is significant overlap in the MRI findings of the two disorders.[8]

A recent study showed that involvement of the medial compartment of the gastrocnemius, combined with relative sparing of the rectus femoris or involvement of the flexor digitorum profundus can be indicative of IBM.[8] The insidious onset and slow evolution of the disease process accounts, in part, for the misdiagnosis and delay in diagnosis, sometimes up to 6 to 8 years after the onset of symptoms.[9] Patients are often unable to date the onset of their muscle weakness, unlike those with PM or dermatomyositis (DM).

The diagnosis of IBM is often confirmed by degenerative and inflammatory features on muscle biopsy showing endomysial inflammation of nonnecrotic muscle fibers with one or more characteristic basophilic rimmed vacuoles,[10,11] but several biopsies may be necessary before the classic features are found. Eosinophilic cytoplasmic inclusions may be found adjacent to the basophilic-rimmed vacuoles on light microscopy, which are more specific for IBM but not sensitive. Within the rimmed vacuoles, amyloid deposition is evident on Congo red staining using polarized light or fluorescence techniques.[12] Electron microscopy typically demonstrates 15 nm to 21 nm cytoplasmic and intranuclear tubulofilaments within muscle fibers, which generally is considered diagnostic.[10,11] Some researchers have questioned the reliability of pathologic criteria for the diagnosis of IBM proposed by Griggs et al, since some patients with clinical features of IBM lack the canonical pathologic features (inflammatory myopathy with mononuclear cell invasion of nonnecrotic muscle fiber, vacuolated muscle fibers, and either intracellular amyloid deposits or 15–18 nm tubulofilaments by EMG[13]) of the disease even after repeated muscle biopsies.[14–16] The endomysial inflammation is characterized by the presence of T cell-mediated and MHC-I-restricted cytotoxicity; clonal expansion of autoinvasive CD8+ T cells and B cells and upregulation of cytokines, chemokines, and costimulatory molecules. The degenerative features consist of vacuolization in myofibers not invaded by T cells and intracellular deposits of amyloid and related proteins. In spite of the antigen-driven T cell response and immunopathologic features, immunotherapies have not been successful, suggesting to some authors that this argues against an autoimmune basis and points towards a more neurodegenerative pathophysiology.[17–19]

An important management consideration is how to treat patients with typical IBM features who lack the characteristic rimmed vacuoles and congophilic myofiber deposits, thus making it difficult to differentiate between PM and IBM.[14] Many such patients are treated as PM but do not meet the 2004 proposed criteria for PM,[20] although they satisfy the research criteria for possible[13] and probable IBM.[21] In a recent retrospective study of the treatment responsiveness of 16 such "PM/IBM" patients, only 29% patients had stabilization and none had sustained improvement with immunosuppressive therapy; by comparison, all 24 patients with patterns of weakness typical of PM showed improvement or stabilization with immunotherapy.[22] Similar results were reported previously.[14–16] These studies support the importance of the pattern of weakness as the distinguishing feature predicting treatment response in patients with an inflammatory myopathy. The lack of response to immunosuppressive agents in patients with an IBM pattern of weakness, but no concordant histopathologic features, suggests that these patients have IBM rather than PM. Whether these patients tend to "stabilize" with immunotherapy more than patients

with both typical pathologic and clinical features of IBM is an important question that remains to be studied.

Although inclusion body myositis is a slowly progressive disabling disease with 37% of patients requiring a wheel chair and another 38% requiring a cane after 10–15 years of diagnosis, large observational studies suggest that it is not associated with increased mortality and immunosuppressive treatments do not change the natural course of the disease.[23,24] The mean time from the first symptoms to using a walking stick and wheelchair is 11 and 16 years, respectively.[24]

Treatment

General considerations

Since all the common immunotherapeutic agents are generally ineffective, IBM has no established treatment paradigm or standard-of-care approach. Whether therapies help to slow the progression of the disease is also unclear, despite a handful of studies providing limited evidence. In fact a large observational study of 136 IBM patients showed that immunosuppressant drug therapy may modestly exacerbate the progression of disability.[23] The lack of an adequate sample size, a slow and unpredictable progression rate, the need for long (and expensive) trial durations, and the absence of validated measures of strength limit past and future IBM clinical trials. Moreover, IBM is often diagnosed years after the onset of symptoms, when muscle damage is established and advanced, thus limiting the capability of quantifying any treatment response. Therefore, the treatment approach is largely empiric, varying considerably between centers.[25] It has been estimated that in order to demonstrate a significant effect from an efficacious treatment for IBM in a placebo-controlled study, 200 subjects would need to be enrolled in a 6-month study or 100 in a year-long trial.[26] Reports in the literature have included patients lacking classic clinical features of IBM (for example very high serum CK levels), who may have been misdiagnosed based on biopsy criteria alone.[13] Only a subgroup of patients with IBM in overlap with an autoimmune disorder, occurring in about 15% of cases,[27] appeared to benefit from immunosuppressive treatment.[28,29]

Corticosteroids

Although corticosteroids are "unproven" in PM and DM, they are the first-line treatment in these idiopathic inflammatory myopathy (IIM) subsets. Conversely, patients with IBM do not consistently improve with corticosteroid treatment, and there have been no randomized or even nonrandomized studies to evaluate their efficacy in IBM. A small but very interesting and informative study by Barohn et al treated eight IBM patients with oral prednisone therapy (100 mg a day for a month, then 100 mg alternate-day for 6 months), and performed pre- and posttreatment muscle biopsies. Although the serum CK level fell and inflammation (number of nonnecrotic muscle fibers with mononuclear cell invasion) decreased in the muscle biopsy specimens, muscle strength worsened and the number of vacuolated and amyloid-positive fibers increased after prednisone. These observations support the notion that a degenerative or fibrotic process may be the primary pathogenesis[9] and the inflammatory response in IBM is secondary. A limitation of this study was its small sample size and lack of an untreated "natural history" IBM control group, which may have highlighted either a benefit or deterioration with steroids. Over a period of 2 years, Lotz et al reported that muscle strength continued to deteriorate in 25 IBM patients treated with prednisone at doses frequently effective in PM.[27] Joffe et al also noted a poor response to prednisone in patients with IBM.[30] Conversely, some reports have noted a partial response to corticosteroids or stabilization of muscle strength,[31–33] and Leff et al retrospectively reported modest clinical benefit with prednisone in 10 of 25 patients with IBM (40%).[33] Serum CK levels may fall and even normalize after corticosteroids, but this biochemical response did not predict clinical benefit.[33] The authors optimistically reported that stabilization of an otherwise deteriorating course may be an attainable goal using immunosuppressive agents in some patients with IBM, however this view is not shared by many myositis experts. There is one exception to the usually limited response to corticosteroids. Patients with IBM coexistent with other connective tissue diseases (Sjögren's syndrome, systemic lupus erythematosus, and DM rash) may benefit from steroid therapy, but it remains uncertain whether IBM features improve.[28,34,35]

Oral immunosuppressive agents

Methotrexate and azathioprine

In a randomized double-blind placebo-controlled 48-week study, Badrising et al investigated the efficacy of oral methotrexate (MTX, mean 14 mg/week) to mitigate disease progression in 44 patients with IBM (42 definite IBM, 2 probable).[36] Despite significant decreases in CK levels in the MTX group, the primary outcome of quantitative muscle strength testing by myometry was not significantly different and, in fact, declined in both the treatment groups (–0.2% for methotrexate and –3.4% for placebo). There were also no differences in manual muscle testing scores, activity scale scores and patient-reported outcomes. Post hoc analysis

showed that the study was underpowered (23%) to show any differences, due to lower than expected decline in muscle strength in the placebo group (3.4% instead of 5%), a greater than anticipated variability in muscle testing and a greater than expected dropout rate from MTX side effects (8/21). Joffe et al showed a similar poor response rate to both MTX and azathioprine.[30]

An open-label, randomized crossover trial of combination oral azathioprine (AZA) and methotrexate (AZA + MTX) and biweekly intravenous (IV) methotrexate with leucovorin rescue (IV-MTX-L) was conducted on 11 biopsy-proven IBM patients.[33] All patients were refractory to previous therapy (prednisone with AZA and/or MTX in most patients) with active inflammatory muscle disease. Each patient received one regimen and then crossed over to the other regimen for the same length of time and prednisone was tapered after 1 month using a standard regimen. Nineteen of the 22 6-month regimens were completed (9/11 AZA/MTX, 10/11 IV-MTX-L). Two patients in the AZA/MTX arm improved and four stabilized, while one improved and seven stabilized in the IV-MTX-L arm. No improvements were major and no complete clinical responses with normalization of muscle strength were noted. More than half the patients had a complete laboratory (CK) response, but CK normalization again did not predict clinical response. All three patients with clinical improvement had CK levels $>$ 1000 at baseline and greater inflammation on muscle biopsy. The limitations of this study include no untreated or placebo group, an inability to measure changes in distal muscle weakness, a short observation period of 1 year, and a carry-over effect of any crossover trial design.

A retrospective study of 25 IBM biopsy-proven patients by the same group showed similar results with 40%, 20%, and 25% of patients reporting benefits with prednisone, azathioprine, and methotrexate respectively, but none achieved complete remission.[33] Laboratory responses were more impressive with most patients normalizing or improving their muscle enzymes. The main criticism of this study was improvement solely defined by physician judgment, which was perhaps biased by observing CK improvement. No other clinical features including medication, age, race, delay in diagnosis, antinuclear antibody levels, or extracted nuclear antigen, predicted improvement or stabilization, and the authors concluded that aggressive immunosuppression might have modest benefit (ie, stabilization of muscle weakness) in up to 50% of IBM patients.

Sayers et al reported that 15 of 32 biopsy-proven IBM patients showed improvement (n = 3) or delayed progression (n = 2) after immune suppression (5 MTX/prednisone), whereas all untreated patients clinically deteriorated.[31] In another case series, immunosuppressive treatment in 16 IBM patients failed to prevent disease progression in all but one patient with associated Sjögren's syndrome.[34]

To summarize, while clinical improvement with immunosuppressive therapy is rare, there is some evidence to suggest that methotrexate and prednisone may lead to disease stabilization and/or modest improvement in some patients.

Mycophenolate mofetil

There is a single case report in a patient with biopsy-proven IBM and 5 years of progressive weakness responding to prednisone and mycophenolate with signs of deterioration within 3 months of discontinuing therapy.[37]

T-cell mediated therapies

Autoaggressive T cells may play a role in the pathogenesis of IBM.[38] Moreover, data have shown that there is identical clonal restriction of TCR expression in muscle-infiltrating T-cell lymphocytes in IBM, and these clones persist for many years, substantiating their role in a continuous, antigen-driven inflammatory reaction.[39] Thus, agents targeting T cell activation and proliferation (calcineurin inhibitors and anti-T-cell globulins) have been studied in conjunction with corticosteroids by some investigators.

A 2007study reported three patients with "biopsy-proven" IBM who responded to cyclosporine or tacrolimus;[40] but none of the patients had finger flexor, wrist flexor, or quadriceps atrophy or weakness, thus failing to meet research criteria for even possible or probable IBM.[13,21] Three IBM patients were treated with either cyclosporin-A or tacrolimus leading to a complete or major clinical response in muscle strength after 3–6 months.[40] Steroids were tapered or stopped while the clinical response was maintained after a follow-up of 2 years suggesting that calcineurin inhibitors might be helpful in IBM patients with short duration, high-activity disease with autoimmune manifestations. These patients were not typical of IBM as all were female and they had primarily proximal weakness, limited fibrosis and atrophy with no rimmed vacuoles, and high CK levels (~4000 in 2 of 3 patients). The authors countered that these patients had early stage disease (1–3 years), higher disease activity, and associated autoimmune features (in 2 of 3 thyroiditis). Although it may be difficult to discriminate between the efficacy of either high-dose steroids or calcineurin inhibitors, or both, an increase in calcineurin inhibition without reinduction with steroids was initiated and all patients improved. Calcineurin inhibitors should be further investigated based on these

favorable preliminary results, as well as data supporting T-cell targeting in IBM.[39,41] Given that lymphocyte infiltrates in IBM muscle tissue are CD8+ T cells, targeting these cells may represent a valid approach.

An open-label randomized controlled trial in 11 IBM patients compared a suboptimal dose of oral methotrexate (MTX 7.5 mg/week) versus a combination of MTX preceded by 7 days of intravenous anti-T-lymphocyte immunoglobulin treatment (ATG-MTX group). At 12 months, the CK improved and myometry showed that patients in the ATG-MTX group (n = 6) increased their mean muscle strength by 1.4% compared with an 11.1% decline in MTX group (n = 5) ($P < 0.021$).[41] Loss of muscle strength in the MTX group was commensurate with the expected average disease progression in IBM.[42] No ATG-treated patients had serum sickness. The beneficial treatment outcome in the ATG group was mainly confined to distal muscles of upper extremities: handgrip and wrist dorsal extension. Following ATG treatment, there is a need for subsequent immunosuppressive treatment in order to prevent rapid restoration of T-cell repertoire, and for this reason MTX was used as baseline therapy.

Finally, a case report of a patient with a severe IBM complicated with interstitial pneumonia showed a positive response to an aggressive immunosuppressive regimen including corticosteroids, cyclophosphamide, and intravenous immunoglobulin (IVIG).[43]

Intravenous immunoglobulin

The effectiveness of IVIG has been evaluated in two small open series and three double-blind studies, but no clear consensus of efficacy has been established due to the short duration of the trials and the slow progression of IBM. Although improvement in muscle strength and function was noted in three of four IVIG-treated IBM patients with an effect sustained for 2–4 months,[44] these results were not replicated in subsequent, larger series. In an open-label, 3-month uncontrolled study of nine IBM patients treated with IVIG, there was no objective muscle strength or functional improvement observed although there was also no worsening of strength or disability.[45] Following these small uncontrolled studies, a placebo-controlled randomized double-blind controlled crossover study of 22 IBM steroid-refractory patients was conducted to study the efficacy and safety of IVIG.[46] Patients were randomized to monthly infusions of IVIG (2 g/kg) or placebo for 6 months each, followed by crossover to the alternative treatment. Overall there was no disease progression (ie, stabilization or improvement was recorded) in 90% of patients over 12 months, unlike that which might have been expected in untreated patients. Moreover, there was a slight overall improvement of 4.9% in muscle strength for both groups after 1 year, which contrasts with the historical decline of 1.4% per month reported for untreated IBM patients.[9,42] A mild and significant improvement (11%) in clinical symptoms was noted in the IVIG group using neuromuscular symptom scores, but only a trend toward improvement was found using a modified Medical Research Council (MRC) scale. There was no difference in response to treatment with respect to CK levels or inflammatory changes on muscle biopsy specimens, but an improvement trend with IVIG was observed in patients with baseline CK levels > 500 U/L. Further efficacy of IVIG was supported by follow-up of 10 patients on IVIG and three patients off IVIG, where a trend towards slower decline in muscle strength was observed with IVIG after a mean follow up of 15.7 months (5.6–24.3 months). Thus, IVIG may be slightly effective in IBM by preventing disease progression. However, it remains unclear as to what extent the overall improvement can be attributed to specific immunomodulatory actions of IVIG or to nonspecific effects brought about by the general care of patients including physiotherapy. Similar findings have been reported by Dalakas et al in a randomized crossover, double-blind placebo-controlled study over 6 months of 19 IBM patients each treated with 3 months of monthly IVIG and placebo.[47] In this study, six patients showed functionally important improvement (>10 MRC points) that declined when crossed over to placebo. Although dysphagia improved significantly, only small trends of improvement or stabilization were noted with IVIG, and the study failed to achieve its primary end point.

Supporting the hypothesis of IBM as an immune-mediated process is the stabilization of disease after discontinuation of IVIG treatment (through 6 months of a placebo phase).[48] T-cell mediated cytotoxity along with further invasion of nonnecrotic muscle fibers may be downregulated by IVIG, as shown by histological examination of muscles before and after treatment.[49] The possible synergistic effect of prednisone with IVIG led to another double-blind randomized controlled trial in 36 patients with biopsy-proven IBM. Patients were randomized to receive IVIG or placebo monthly for 3 months; before infusions, all patients also received high dose prednisone for 3 months. When compared to baseline, there were no significant differences in muscle strength during 4 months of observation. Follow-up biopsies in 24 random patients revealed a greater reduction in the number of necrotic myofibers and endomysial inflammation in IVIG-treated patients, but this did not translate into clinical improvement.[46]

The effectiveness of IVIG in IBM-associated dysphagia has been reported, and in one report, four patients with severe dysphagia due to upper esophageal dysfunction all recovered swallowing function after treatment with 6 to 8 monthly infusions of IVIG.[50] This observation is consistent with the efficacy of IVIG seen in life-threatening steroid-resistant esophageal involvement in PM/DM patients.[51] In patients refractory to IVIG cricopharyngeal myotomy seems to be the most beneficial interventional measure.[52–54] Other interventions including botulinum toxin injection into the upper esophageal sphincter and upper esophageal dilatation have been used with variable results.[6,52–55]

The lack of definitive improvement in muscle strength in these IVIG trials is disappointing, and the therapeutic dilemma in IBM continues. Whether only certain immunopathologic changes responsible for muscle fiber injury are amenable to IVIG therapy is unclear. Since IBM begins insidiously, and the duration of the disease in a given muscle is difficult to assess objectively, the longer the duration of the disease and the greater the degree of vacuolization or replacement of muscle fibers by fibrous tissue, the more resistant these muscles may be to immunotherapies. IVIG, by inhibiting cytokines or blocking Fc receptors on macrophages, may only affect muscle groups with intense endomysial inflammation and not muscles with progressive vacuolization and fibrosis. Future long-term studies aimed at slowing down disease progression rather than improving strength may be more realistic in such a chronic, slow, progressive disease. Contributing to this therapeutic dilemma is the prohibitive expense and occasional scarcity of this drug, along with the potential for side effects such as infusion reactions and hypercoagulability. Does the moderate global benefit noted in a few patients and the mild benefit in certain muscle groups noted in others justify the use of IVIG in this disease? The present findings do not provide an answer but suggest that a large controlled study may be warranted.

Biological agents

Biologic agents targeting presumptive immunopathological processes such as B and T cell-mediated muscle inflammation and/or damage have been studied in IBM patients with variable results.

Interferon therapy

β-Interferon (β-IFN), an immunomodulatory cytokine, is known to counteract the immune-stimulatory effects of alpha-interferon (IFNα), such as the activation of cytotoxic T lymphocytes, secretion of lymphokines, and upregulation of HLA on many cell surfaces. Moreover, β-IFN inhibits lymphocyte migration across endothelial cell surfaces by decreasing T-cell production of matrix metalloproteinase-9 and other chemotactic chemokines that may play a role in the pathogenesis of IBM. Given that the inflammatory infiltrates in IBM include cytotoxic T cells and macrophages, β-IFN was studied as a candidate therapeutic agent for IBM. A 6-month multicenter, randomized, placebo-controlled pilot trial of interferon-beta-1a (30 μg intramuscularly [IM]/week) in a group of 30 patients with IBM demonstrated no improvement in muscle strength or mass.[56] A subsequent similarly designed trial using a higher dose (60 μg IM injection/week) in 30 subjects was also ineffective even though both trials met the primary outcome of safety and tolerability of β-IFN in IBM.[57] A case report noted IBM developing after IFNγ treatment for hepatitis C followed by relapse of IBM after reinitiation of IFNγ.[58] A second case report of a Japanese IBM patient who was a carrier of hepatitis C, showed significant clinical improvement in muscle weakness with β-IFN treatment.[59]

Alemtuzumab (CAMPATH)

Alemtuzumab (Campath, Campath-1H, or MabCAMPATH), approved for the treatment of T cell leukemia, is a humanized T-cell-depleting monoclonal antibody against CD52 that causes profound T cell depletion in the periphery and lymphoid tissues.[60] Based on its efficacy in multiple sclerosis,[61] Dalakas et al studied CAMPATH in IBM and demonstrated a long-lasting drop in peripheral T cells resulting in a reduction of endomysial T cells.[62] Thirteen patients were treated with alemtuzumab (0.3 mg/kg/day for 4 days) and primary end-points were disease stabilization or increased strength 6 months after treatment as compared to natural history data 12 months prior to therapy. Alemtuzumab significantly slowed disease progression during the 6 months treatment phase (11.4% improvement in manual muscle testing [MMT] over 6 months versus 13.8% worsening in the 12 month pretreatment phase), improving the strength of some patients, and reducing the inflammation and degeneration-associated molecules. The lack of blinding and placebo control makes accurate assessment difficult. Larger, blinded placebo-controlled trials with multiple infusions to assess the long-term efficacy and safety (especially important given safety concerns in recent MS trials) are warranted.[61]

Antitumor necrosis factor agents

The production of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), is increased in muscle tissue from patients with IBM as compared to normal

controls, indicating a potential role of TNF in the genesis of IBM.[63,64] Etanercept, a TNF receptor fusion protein that binds and inactivates TNF, has proven safety and effectiveness in autoimmune diseases, particularly rheumatoid arthritis. A pilot trial of nine IBM patients treated with etanercept (25 mg SQ twice weekly) noted no improvement in composite muscle strength scores at 6 months, although there was a slight improvement in grip strength after 12 months of treatment, as compared to natural history control data.[65] Similar results with infliximab (another anti-TNF agent) were seen when refractory myositis patients, including four with IBM, were treated in a 4-month, open-label uncontrolled trial.[66] One of four IBM patients had a composite clinical response, three remained unchanged, and none worsened after four infliximab infusions over 14 weeks. No significant improvement was observed in muscle tissue, muscle strength by MMT or muscle enzyme levels. Interestingly, some authors have also reported IBM after anti-TNF agents.[66–69]

Rituximab

Although B-cell-mediated inflammation was suggested to contribute to the pathogenesis of IBM,[70] the reports of B-cell depletion therapy with rituximab in IBM are limited to a few case reports without favorable outcome.[71] In a case report of IBM and rheumatoid arthritis (RA), treated with rituximab for active arthritis, no amelioration of muscle weakness was noted.[69] Given some encouraging results on rituximab efficacy for refractory PM and DM, more studies may be pursued.

Other treatment considerations

Anabolic steroids

Testosterone increases muscle bulk and strength when combined with exercise in normal males,[72] and has shown modest effects in improving strength in boys with Duchenne muscular dystrophy.[73,74] Oxandrolone (a synthetic androgen) showed a trend towards improvement in whole-body strength and a significant effect in improving upper-extremity strength in an 8-month double-blind, crossover trial of 19 IBM patients. The authors concluded that given some favorable results further study of this drug in combination with an immunomodulatory agent is warranted.[75]

Empiric therapies

Despite the lack of controlled clinical trials, clenbuterol (a β_2 agonist), coenzyme Q10 (ubiquinone), carnitine, and antioxidants have been recommended by some experts.[76]

Exercise therapy

Randomized, controlled studies of exercise training in active PM and DM have demonstrated a beneficial response and the absence of adverse effects on the disease process.[76–79] Studies in IBM also showed no worsening of muscle function, histopathology and inflammation and muscle enzyme levels after an exercise program.[80] Furthermore, aerobic and strength training in IBM patients was safe and can lead to dynamic strength improvements, and (possibly) prevent continued loss of muscle strength.[81] A more recent well-designed unblinded, uncontrolled study has shown that a closely monitored, 16-week, home-based program of strength and flexibility training can lead to significant gains in muscle strength and function in patients with IBM.[82] The protocol was well tolerated by all the patients and did not cause adverse muscle symptoms or elevation of serum CK levels. The authors further demonstrated that the addition of an aerobic exercise program was well tolerated in IBM patients and improved aerobic capacity and muscle strength when combined with resistance training.[82]

Conclusion

IBM is a complex, disabling disease, which is notoriously resistant to therapies. It is often suspected, retrospectively, when patients diagnosed with PM have failed treatment with standard immunosuppressive medications. Understanding the interplay between inflammation and degeneration and elucidating the mechanisms that drive muscle degeneration on a cellular basis is a crucial step in identifying potential therapeutic targets. Moreover, identification of susceptibility genes will be important to unravel its pathogenesis, and to provide clues to the development of targeted therapies. Due to the significant delay in diagnosis of IBM, striated muscle has undergone considerable damage and has already been replaced by fat or fibrosis by the time the condition is diagnosed. Therapies directed solely at decreasing inflammation cannot be expected to reverse weakness from atrophy and fibrosis.

Unfortunately, no comparative patient cohorts have the requisite follow-up to determine the long-term outcome after introduction of immunosuppressive agents. Thus, the more practical and achievable goal for the treatment of IBM with immunosuppressive agents is slowing the progression of muscle fiber destruction. There is an urgent need for IBM trials of adequate duration, sufficient power and the inclusion of patients with early disease. Currently, the balance of evidence suggests that immunosuppressive drugs including corticosteroids are ineffective in IBM, although

long-term randomized controlled trials are lacking. IVIG is a reasonable consideration in IBM with some suggestion of slowing the progression of the disease, but its long-term effectiveness remains unknown. Whether the modest gains noted in some IBM patients justify the high cost of IVIG remains unclear. Biological therapies, especially alemtuzumab, show some promise, but confirmation is necessary before these drugs are accepted for use in IBM. Moreover, drugs like follistatin that inhibit myostatin, a member of the transforming growth factor-β family of secreted growth factors and a potent suppressor of muscle growth that is being tested in muscle dystrophy, need to be studied as potential therapeutic targets in IBM. Other novel therapies like stem cell transplantation and autophagy pathways need to be explored in IBM due to the lack of efficacy of immunosuppressive therapies.[83]

Disclosure

The authors report no conflicts of interest related to this manuscript.

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