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Update on Treatment of Inclusion Body Myositis

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Abstract Degenerative mechanisms such as protein accumulation and vacuolar transformation in the skeletal muscle distinguish inclusion body myositis (IBM) from other inflammatory myopathies. IBM is particularly common in patients over the age of 50 years and inevitably leads to progressive muscle weakness and atrophy. Conventional immunotherapies, albeit effective in other forms of myositis, seem to have only a transient or no beneficial effect on disease progression of IBM. So far, no established evidence-based treatment exists and therapy recommendations are based on expert opinion. Recent clinical trials using monoclonal antibodies such as alemtuzumab or etanercept have failed to demonstrate efficacy. Different treatment studies with drugs that aim at degenerative disease mechanisms are planned or ongoing. This review aims to provide an overview of the current treatment options for IBM.

Keywords Inclusion body myositis · IBM · Inflammatory myopathy · Myositis · Treatment · Glucocorticosteroids · Immunosuppressants · Intravenous immunoglobulin · Alemtuzumab · Oxandrolone · Physical training · Dysphagia

Introduction

Inclusion body myositis (IBM) is characterized by progressive asymmetric weakness and atrophy of proximal and distal muscles, which slowly but progressively leads to disability. It is the most common form of inflammatory myopathy, particularly in patients over the age of 50 years [1]. Histopathology demonstrates considerable $CD8^+$ T cell-mediated endomysial inflammation as well as degenerative mechanisms including vacuolization and intrafiber deposition of protein aggregation such as β-amyloid [2]. The degenerative features in histopathology clearly distinguish IBM from other inflammatory muscle diseases. The pathogenesis of IBM remains unclear and still raises many questions [3]. Despite the fact that it is still under debate whether degeneration is consequence or cause of inflammation or an independent process itself, investigations for possible treatment options have focused on anti-inflammatory, immunosuppressant, or immunomodulatory agents. Their effects, however, are only small, of limited duration, or completely lacking. So far, no established treatment for IBM exists.

This article will summarize the therapeutic options that have been studied in IBM and aims to provide treatment advice for this disease.

Pharmacological Treatment

Glucocorticosteroids

In contrast to dermatomyositis and polymyositis, corticosteroids seem to have no beneficial effect on the disease progression in IBM. Few case reports describe temporary improvement or stabilization of strength [4–6]. One small prospective study with eight patients receiving oral prednisone for up to 12 months could not prove any benefit regarding muscle strength even though creatine kinase (CK) level and the number of necrotic muscle fibers in biopsy decreased [7]. By contrast, the amount of vacuoles and amyloid-positive fibers increased after prednisone treatment, which could indicate a possible detrimental effect of glucocorticosteroids. So far, no placebo-controlled study for

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prednisone treatment alone in IBM exists. Prednisone in combination with other immunosuppressants resulted in lower serum CK-levels, but did not yield a benefit regarding muscle strength [4].

Immunosuppressants

The effect of immunosuppressive treatment with oral methotrexate (MTX) was evaluated in a randomized double-blind placebo-controlled study with 44 patients over 48 weeks. No deceleration of disease progression with change of quantitative muscle strength defined as the primary study outcome measure could be observed [8]. Similar to patients receiving prednisone treatment, CK-levels decreased significantly, which underscores that serum creatine kinase level is not a useful marker to monitor the disease activity. A few case reports describe some clinical stabilization or improvement, but it is difficult to discriminate between treatment effects and natural fluctuations of the disease course [4, 9]. A lack of effect of MTX was observed in an open randomized trial that compared MTX alone with combination with anti-T-lymphocyte globulin (ATG) (see below for details) [10].

Mycophenolate mofetil (MMF) treatment has been reported to result in an increase in muscle strength in one patient with IBM [11], while most patients do not respond to this treatment [12]. A beneficial effect of cyclosporine A and tacrolimus has been described in a small case series [13]. The results, however, as for azathioprine, have low validity due to the small number of patients treated with those substances. No placebo-controlled trials for MMF, cyclosporine A, tacrolimus, or azathioprine have so far been carried out. Total body irradiation and repeated plasmapheresis were not effective in IBM and have not been investigated further [14, 15].

Immunomodulatory Drugs

A first randomized placebo-controlled trial of β-interferon-1a (βINF1a) in 30 patients with IBM showed that the treatment was well tolerated, but no significant differences concerning changes in muscle strength or muscle mass could be found between the βINF1a group and the placebo group [16]. A subsequent study of similar design with a higher dose of βIFN1a revealed equally disappointing results [17].

A small pilot trial, in which nine patients with IBM received 25 mg etanercept, a tumor necrosis factor (TNF) -α inhibitor, twice a week for over 12 months, did not show a significant benefit of the treatment [18]. The Washington University School of Medicine is currently conducting a double-blind randomized placebo-controlled trial with this drug (www.clinicaltrials.gov).

Intravenous Immunoglobulin (IVIG)

Most treatment trials for IBM have focused on intravenous immunoglobulin. After a first open trial yielded encouraging results with an increase in muscle strength after 2 monthly infusions of IVIG [19], placebo-controlled trials followed. However, the promising results obtained in the open pilot trial could not be reproduced. Even though the first placebo-controlled study in 19 patients with IBM revealed some increase in strength, the results did not reach statistical significance [20]. Interestingly, however, swallowing function improved significantly upon treatment with IVIG. Similar observations have been reported in small case series, which has led to the discussion of possible regional effects of IVIG on muscle function [21]. In another study, 22 patients with IBM were treated with high-dose IVIG of 2 g/kg bodyweight over a period of 6 months [22]. Of the patients, 90 % did not display a relevant disease progression and even a mild increase in strength was noted. Yet, only the neuromuscular symptom score was significantly improved and the overall effects of IVIG remained mild, if present at all. A third placebo-controlled trial of IVIG combined with high-dose prednisone for 3 months included 36 patients with the diagnosis of definite IBM [23]. Primary outcome measures were quantitative muscle strength testing and modified Medical Research Council scores. In addition, repeated open muscle biopsies were performed. No statistically significant difference between the treatment group receiving IVIG and the placebo group could be found, even though the number of necrotic muscle fibers decreased in the IVIG-group.

Many patients reported a subjective improvement regarding daily activity under the treatment with IVIG. However, since most patients could have correctly identified the treatment versus placebo periods, patients' statements have to be interpreted with care.

The treatment periods in all studies are fairly short in relation to the slow disease progression of IBM, which makes it difficult to reliably interpret the results. Trials of longer duration and larger patient number should be conducted to evaluate the efficacy of IVIG in IBM. The findings of a long-term follow-up of 16 patients treated with a mean of 10 IVIG infusions and follow-up for about 23 months suggest that there might be a short-term benefit of treatment regarding muscle strength, which does not persist very long [24•]. Since improvement has been reported repeatedly for individual patients, the authors suggest that treatment with IVIG should be tried at least for 6 months.

Alemtuzumab and Anti-Lymphocyte Immunoglobulin

Lindberg and colleagues compared IBM patients who took oral MTX for a period of 12 months with patients who

received oral MTX plus intravenous ATG for the same time period. While the ATG group showed an increase in muscle strength by 1.4 %, patients in the MTX group deteriorated by 11.1 % [10]. A randomized placebo-controlled trial would be needed to confirm the promising results of ATG as a treatment option in IBM.

In another pilot trial, 13 patients with IBM were observed regarding their natural disease course for 12 months. Subsequently, they received a 4-day treatment with 0.3 mg/kg body weight alemtuzumab, a monoclonal anti-CD52 antibody [25]. The primary endpoint was defined as disease stabilization compared to the time representing natural history when patients did not receive any treatment. Patients' total body strength during the 12-month observation period without treatment had declined by a mean of 14.9 % while 6 months after treatment with alemtuzumab, the overall decline was only 1.9 %. Four patients even showed an increase in strength by a mean of 10 % and six patients reported amelioration in daily activities. On the one hand, these data are somewhat promising and suggest that substantial immunosuppression could be effective in IBM. On the other hand, this study needs to be interpreted with caution because it was open label and the yearly disease progression was much higher than in other recent studies [26••, 27••]. These promising results are some of the first in the treatment of IBM. In view of potential side effects, a larger placebo-controlled trial should be awaited before patients are treated with this drug.

Oxandrolone

A randomized placebo controlled trial with oxandrolone, an anabolic steroid, in 19 patients with inclusion body myositis yielded promising results with an increase in whole-body strength and significant improvement of upper-extremity strength [28]. In a cross-over trial design, patients received either 20 mg oxandrolone daily or placebo for a 12-week period and were then switched to the alternate treatment after a short washout period. A larger trial would be needed to establish efficacy of oxandrolone in IBM.

Treatment with Other Drugs

Other treatment trials included simvastatin in view of its immune-modulating effects. In an open pilot trial, 14 patients received 40 mg of simvastatin over a period of 12 months [29•]. Of the 10 patients that completed the trial, none showed a significant clinical improvement. A Japanese study group suggests a large placebo-controlled trial of high-dose Vitamin C; they had observed an increase in muscle strength upon treatment with 40 mg/kg Vitamin C five times weekly for 4 weeks in three of five patients [30].

Supportive Therapy and Non-Medical Treatment

Physical Training

Strength training and physical exercise have been recommended in patients with IBM based on scientific evidence [31••]. Results of open studies have established its safety and demonstrated that no significant increase in serum CK-levels or degree of inflammation and degeneration of muscle in repeated biopsies could be seen [32, 33]. The first study reported an increase in muscle function in the least affected muscle groups after a 12-week program of progressive resistance strength training [32]. A home exercise program performed five times a week did not significantly improve strength in patients; however, no deterioration in muscle strength could be noted either [33]. An open study with seven IBM patients investigated the effects of a 12-week exercise program on aerobic capacity, muscle strength, and functional capacity [34]. The program comprised resistance exercise and aerobic stationary cycling three times a week. Aerobic capacity improved by 37 % and muscle strength increased significantly in some muscle groups tested. Other non-medical treatment options such as vascular occlusion training combined with moderate-intensity resistance training have been introduced with reports of significant effects in individual patients [35]. Larger studies are needed to confirm those promising results.

Treatment of Dysphagia

Dysphagia is a frequent symptom in IBM that deserves special attention due to its potential danger of aspiration and subsequent pneumonia. It may even have a significant impact on mortality in IBM patients. In addition, the consequences of dysphagia such as weight loss and tube feeding as the last resort severely reduce the quality of life of IBM patients.

Non-medical and non-invasive treatment options for IBM-associated dysphagia include swallowing rehabilitation by learning compensatory techniques, the Mendelson maneuver, modification of food consistency, or enteral nutrition by placing a percutaneous endoscopic gastrostomy [36•]. In addition, logopedic training with isometric lingual strengthening has been proposed as a swallowing treatment option [37].

IVIG seem to have a beneficial effect on dysphagia in patients with IBM [20, 21]. The duration of dry and wet swallows significantly improved upon treatment with IVIG [20]. In two patients, balloon catheter dilation at the upper esophageal sphincter was performed after intravenous application of IVIG 3 months earlier [38]. After treatment, subjective complaints of dysphagia disappeared and patients were able to eat solid meals again. Videofluoroscopy showed an increase in barium paste passing through the upper

esophageal sphincter. The effect, however, weakened over time. In another retrospective review only two of six patients reported beneficial effects after pharyngoesophageal dilation [36•]. Other invasive procedures include cricopharyngeal myotomy, which has been proposed as a beneficial treatment in several case reports [39–42]. A review of 24 patients with inclusion body myositis-associated dysphagia reported that 69 % of the 10 patients that underwent cricopharyngeal myotomy noted a beneficial effect [36•]. Botulinum toxin A injections into the upper esophageal sphincter has been reported to be effective in 2 patients [43], while 2 patients in another IBM-patient group did not show a benefit [36•]. Larger studies are needed to investigate the efficacy of botulinum toxin A injections into the upper esophageal sphincter in patients with IBM-associated dysphagia.

Supportive Care

Since IBM slowly leads to progressive muscle weakness and disability, most patients require care and medical support during the course of the disease. Orthoses such as ankle-foot orthoses to alleviate peroneus paresis can be of benefit to prevent frequent falls. In addition, patients should be provided with aids such as wheelchairs, crutches or canes, and adjustment of conditions at home such as elevated toilet seats or lifters, as well as home care if necessary. Psychological and emotional support should be offered to individual patients to help cope with disease burden.

Current Trials and Future Targets

An observational pilot study is investigating the use of lithium as a treatment option. The study has been completed, but results have not yet been published (www.clinicaltrials.gov). Lithium is believed to target the degenerative mechanisms: Animal experiments could show that lithium inhibits the glycogen synthase kinase-3β and thereby reduced the levels of phosphorylated tau [44]. Arimoclomol, a drug that has been investigated as a possible treatment in patients with amyotrophic lateral sclerosis (ALS), is currently administered to IBM patients in a pilot trial that was started in 2008 in the hope of a beneficial effect (www.clinicaltrials.gov). It is believed to activate chaperons and thereby reduce protein aggregation in the muscle. Another trial, which is currently enrolling patients, is aiming to investigate the effects of direct intramuscular injection of the follistatin gene in an adenoviral construct (www.clinicaltrials.gov) in order to increase the muscle mass and—potentially—strength. A clinical double-blind, placebo-controlled phase 2 trial with BYM338 has recently been completed (www.clinicaltrials.gov). As mentioned above, the Washington University School of Medicine is currently conducting a placebo-controlled double-blind trial with etanercept (www.clinicaltrials.gov).

Conclusions

The majority of patients do not seem to benefit from treatment with prednisone or IVIG. Although several case-reports and our own experience suggest that there is at least a transient effect of IVIG in some patients, treatment with this drug cannot be routinely advocated. However, in the authors' opinion, a temporary treatment attempt with, e.g., three courses of 1 g/kg IVIG once every 2 months appears to be justified. If a stabilization of skeletal muscle strength or swallowing function occurs, this treatment may be continued and tapered down to the lowest possible dose. In cases of lack of efficacy, the treatment should be discontinued. It should be pointed out that not all health care systems will cover the costs for such treatment. The use of glucocorticosteroids or immunosuppressants cannot be routinely advocated. In general, efficacy of treatment should be evaluated by muscle strength per MRC-score. Serum CK-levels should not be used to define response to treatment. In addition, physiotherapy is advisable early in the course of the disease.

A better understanding of the pathogenesis of IBM is needed to help in the identification of targets for future treatment approaches. The resistance to standard immunosuppressants might suggest that inflammation does not play a key role in the pathogenesis. Recent findings suggest that, in particular, the myotoxic and cell stress mediators should be targeted by treatment efforts [45•].

Moreover, early and correct diagnosis is essential in order to begin treatment before irreversible damage occurs. Many trials were conducted in an open design and the patient number was low. The study period was very short in the majority of trials, which, with respect to the rather slowly progressing nature of the disease, limits the validity of the results. Treatment studies that report stabilization of the disease progression might just represent natural fluctuations. A long-term observational study with a cohort of 136 IBM patients even reported a decrease in strength in patients receiving immunosuppressive treatment, while patients receiving no treatment at all occasionally displayed a stable strength for some time [26].

Larger, long-term trials in a multi-center setting are therefore needed to thoroughly investigate the efficacy of promising agents. Current efforts aim at identifying the best outcome measures for such trials [46•]. There is hope that current and future clinical trials with anti-degenerative agents will be more effective.

Conflict of Interest Maren Breithaupt declares no conflict of interest.

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