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Other CTD: Inflammatory Myopathies and Sjogren's (P Basharat and JFL Albayda, Section Editors)

In Pursuit of an Effective Treatment: the Past, Present and Future of Clinical Trials in Inclusion Body Myositis

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Abstract

Purpose of review No clinical trial in sporadic inclusion body myositis (IBM) thus far has shown a clear and sustained therapeutic effect. We review previous trial methodology, explore why results have not translated into clinical practice, and suggest improvements for future IBM trials.

Recent findings Early trials primarily assessed immunosuppressive medications, with no significant clinical responses observed. Many of these studies had methodological issues, including small participant numbers, nonspecific diagnostic criteria, short treatment and/or assessment periods and insensitive outcome measures. Most recent IBM trials have instead focused on nonimmunosuppressive therapies, but there is mounting evidence supporting a primary autoimmune aetiology, including the discovery of immunosuppression-resistant clones of cytotoxic T cells and anti-CN-1A autoantibodies which could potentially be used to stratify patients into different cohorts. The latest trials

have had mixed results. For example, bimagrumab, a myostatin blocker, did not affect the 6-min timed walk distance, whereas sirolimus, a promotor of autophagy, did. Larger studies are planned to evaluate the efficacy of sirolimus and arimoclomol.
Summary Thus far, no treatment for IBM has demonstrated a definite therapeutic effect, and effective treatment options in clinical practice are lacking. Trial design and ineffective therapies are likely to have contributed to these failures. Identification of potential therapeutic targets should be followed by future studies using a stratified approach and sensitive and relevant outcome measures.

Introduction

Sporadic inclusion body myositis (IBM) is a progressive muscle disorder characterised by the presence of both inflammatory and degenerative pathological features. Typical features on muscle biopsy include CD8+ T cell inflammatory infiltrates, rimmed vacuoles, inclusion bodies and mitochondrial abnormalities [1]. Unlike other idiopathic inflammatory myopathies (IIM), patients with IBM do not improve in response to immunosuppression, with muscle weakness progressing and culminating in significant disability.

Numerous potential IBM therapies have been assessed in observational studies and clinical trials. Here, we review these studies and assess their methodology to determine why they were unsuccessful with no ensuing change in clinical practice. Using these insights and recent advances in our understanding of IBM pathology and natural history, we then shape recommendations for future clinical trials.

Clinical trials in IBM

Relevant studies were selected from the results of a MEDLINE and Pubmed search, performed using the key words "Inclusion body myositis" and "Clinical trial" or "trial". We grouped the studies by type of intervention studied (listed in Table 1).

Conventional immunosuppressive therapies

Prednisolone, azathioprine and methotrexate

Most trials in IBM have focussed on immunosuppression. An early observational study performed in 1993 assessed the probability of clinical response to immunosuppression in IIM, including IBM as classified by Whitaker [4, 28]. Oral prednisolone 0.75 mg/kg/day was administered to 14 IBM patients, with clinical response assessed by muscle strength and laboratory investigations including serum total creatine kinase (CK). After a minimum of four weeks, eight demonstrated "partial clinical response" and six had "no response". Ten patients were additionally administered at least 5 mg/week of oral methotrexate for a minimum of eight weeks, with six not responding, and four having "partial response". CK response was not specifically reported for the IBM patients. Whilst there appears to be a positive signal, the trial was unblinded, short duration, and mostly used subjective outcome measures.

Table 1. Interventions, outcome measures and results from clinical trials in inclusion body myositis

Intervention and duration	Trial setup	Outcome measures	Results	Year	Ref.
Immunosuppressive therapies					
Azathioprine and methotrexate, IV methotrexate and leucoverin rescue	Prospective, open, randomized crossover study (n = 25)	MMT, ADL questionnaire	Azathioprine and methotrexate- 2 improvements, 4 stabilisations, 3 deteriorated. Methotrexate 1 improvement 7 stabilizations, 2 deteriorated	1993	[2]
High dose IVIg	Open label study (n = 4)	MMT	Improvement or normalisation- 3	1993	[3]
Prednisolone, Azathioprine, Methotrexate	Open label study (n = 14)	Clinical impression, MMT, laboratory investigations	Prednisolone- 8 partial clinical response, 6 no response. Fitted probabilities of response calculated for Methotrexate and Azathioprine	1993	[4]
IVIg	Open label study(n = 9)	MMT, functional disability score	No improvement	1994	[5]
IVIg, placebo	Double blind, placebo-controlled crossover study (n = 19)	Expanded MRC scale, MVICT, symptom and disability scores, swallowing studies	No significant change	1997	[6]
IVIg	Open label, trial of add on therapy IBM (n = 5)	QMT, MMT, functional assessment, CK	No significant change	1998	[7]
IVIg 2 g/kg	Randomised, double blind, placebo-controlled crossover study (n = 22)	MRC sum score, NSS, arm outstretched time, electromyographic testing, subjective assessment	Significant change only in NSS in placebo to IVIg group, which occurred between 6 and 12 months of IVIg therapy	2000	[8]
IVIg and prednisolone, prednisolone and placebo	Double blind, placebo controlled study IVIg +Pred (n = 19) v Pred (n = 17)	QMT, MRC score, muscle biopsy	No significant change in QMT or MRC score. Muscle biopsy showed significant decrease in CD2+ cells in both groups	2001	[9]
β-Interferon 1a (Avonex) 30 µg/kg IM/week	Multicenter, randomized, placebo-controlled parallel group trial (n = 29)	Safety and tolerability, composite MVICT and MMT score, grip strength, DEXA, LBM, functional testing	No significant change	2001	[10]
Methotrexate	Randomized, double blind placebo-controlled study MTX (n = 21) v placebo (n = 23)	QMT and MMT sum scores, CK	No significant difference in QMT and MMT. Significant drop in CK in MTX group	2002	[11]
Methotrexate, anti-T lymphocyte globulin and methotrexate	Open, randomized pilot study ATG and MTX (n = 6), MTX (n = 5)	QMT, CK, T lymphocyte subsets and muscle biopsy	Significant difference in muscle power in ATG and MTX (+1.4% ±SD 9.8%), v MTX (– 11.1% ± 7.2%). (p = 0.021)	2003	[12•]

Table 1. (Continued)

Intervention and duration	Trial setup	Outcome measures	Results	Year	Ref.
			after 12 months of treatment of ATG and MTX v MTX.		
β-Interferon 1a (Avonex) 60 μg/kg IM/week v placebo	Randomized, placebo-controlled parallel group study Avonex (n = 15) v placebo (n = 13)	Safety and tolerability. MVICT, MMT, DEXA, functional testing, laboratory investigations	Significant change in average grip strength- treatment effect difference 1.84 kg (95% CI 0.46–3.21) p = 0.01	2004	[13]
Etanercept	Open label pilot study, compared to placebo group from previous study and natural history controls Etanercept (n = 9) v placebo (n = 29) v natural history controls (n = 5)	MVICT	No significant difference	2006	[14]
Infliximab	Open label pilot study (n = 4)	Serology, MRI pelvis, MMT, myositis functional index, subjective assessments, muscle biopsy, type I interferon activity	One improvement in clinical outcome as per IMACS definition, three unchanged.	2007	[15•]
Alemtuzumab	Open label study (n = 13)	QMT, MMT, Muscle biopsies, Immunological studies, mRNA expression of inflammatory mediators	Significant changes: QMT- -14.9% mean decrease in power from baseline in 12 months prior to assessment, –1.9% mean decrease in power from baseline 6 months after Alemtuzumab administration, –11.6% power from baseline 12 months after Alemtuzumab administration. Decrease in lymphocyte counts, significant reduction in mRNA expression of inflammatory mediators.	2009	[16]
Anakinra	Open label study (n = 4)	MRC scale, QMT grip, laboratory investigations	No improvement in muscle strength, grip force reduced by 11% (Range 1.5–34.9%)	2013	[17]
Sirolimus	Randomized, controlled, double-blind, monocentric, phase IIb	Quadriceps MVICT, other MVICT, 6MWD, pulmonary functional tests, IBMFRS, HAQ-DI, MRI	No significant difference in quadriceps or other MVICT. 6MWD median difference: + 11.37% (95% CI 0.36 to 20.86%, p = 0.009). Significant	2020	[18••]

Table 1. (Continued)

Intervention and duration	Trial setup	Outcome measures	Results	Year	Ref.
	study sirolimus (n = 22) v placebo (n = 22)	assessment of fat replacement, IBMWCI, T-cell subpopulations	increases on IBMWCI, T-cell subpopulations, HAQ-DI, forced vital capacity and thigh fat fraction on MRI imaging		
Non-immunosuppressive therapies					
Exercise-12 week program	Open label study (n=5)	3 repetition maximum, peak isometric torque values, MRI muscle size, serum CK, epinephrine and cortisol, lymphocytes, muscle biopsy	R leg press improvement 39% ± SE 12 ($p < 0.05$) L leg press improvement 42% ± 14 ($p < 0.05$) R leg curl improvement 120% ± 20 ($p < 0.05$) L leg curl improvement 106% ± 19 ($p < 0.05$) L leg extension improvement 60% ± 20 ($p < 0.05$) Otherwise no significant change	1997	[19]
Oxandrolone	Randomized, double-blind, placebo-controlled, two-period, crossover study (n = 19)	Whole body MVICT and MMT, timed get-up-and-go, 6MWD	Whole body MVICT- median increase of 15.5 kg, GEE of treatment effect 1.27 ± SE 0.68, p = 0.061. No significant difference in other measures.	2002	[20]
Aerobic exercise-12 week program	Open label study (n = 7)	Aerobic capacity (VO_2 max), functional exercise capacity, QMT, serum CK	VO_2 max improved from 1.5 l/min ± SEM 0.2 to 2.1 l/min ± 0.3; $p < 0.05$. Shoulder abduction increased by 39% ($p < 0.001$) Hip flexion increased by 35% ($p = 0.008$) Hip abduction increased by 16.6% ($p = 0.041$) Knee flexion improved by 10.5% ($p = 0.027$)	2009	[21]
Simvastatin	Open label study (n = 14)	IMACS disease activity core set, sf-36 survey, CK, MRI imaging, muscle biopsy	No significant improvement	2011	[22]
Arimoclomol	Randomized, double-blind, placebo-controlled study	Safety and tolerability, IBMFRS, MMT, right grip MVICT, DEXA, muscle HSP70 expression	No significant difference.	2016	[23••]

Table 1. (Continued)

Intervention and duration	Trial setup	Outcome measures	Results	Year	Ref.
	Arimoclomol (n = 16) v placebo (n = 8)				
Follistatin gene therapy	Open label pilot study, gene therapy (n = 6) v placebo (n = 8)	6MWT, functional tests, serum haematology and biochemistry battery, Muscle biopsy investigations	6MWT + 62.5 m in treatment group versus – 33 m in control group (p = 0.01). Significant improvement reported in markers of fibrosis.	2017	[24]
Blood-flow restricted resistance training- 12 week program	Open label randomized trial exercise (n = 11) v control (n = 11)	SF-36, 2MWT, functional assessments, IBMPFRS, IMACS core set measures, QMT.	No significant difference	2018	[25]
Aerobic exercise- 12 week program	Single blinded crossover study (n = 17)	Multiple, including VO_2 max, Workload, IBMFRS, Isometric and isokinetic torque, 10 m walk, 6MWD, SF36	"Large" effect on VO_2 max- 1.72 ± SD 0.43 on Cohen d, 1.68 ± SD 0.42 on Hedges g	2019	[26]
Bimagrumab	Randomized, double-blind, placebo-controlled Phase IIb study Bimagrumab 10 mg/kg (n = 63) v Bimagrumab 3 mg/kg (n = 63) v Bimagrumab 1 mg/kg (n = 63) v placebo (n = 62)	6MWD, QMT, Total lean body mass-DEXA, sIFA, Short Physical Performance Battery	10 mg/kg sIFA total score change, difference between bimagrumab v placebo – 5.1 points (99% CI – 11.3 to 1.1, p=0.034) Total lean body mass, difference from placebo: + 1.1% (95%CI 1.0 to 1.1; $p < 0.0001$%) 3 mg/kg total lean body mass, difference from placebo: 1.0% (1.0 to 1.1; p = 0.0001). Otherwise no significant difference.	2019	[27••]

Abbreviations used: 6MWD – 6 Meter walking distance; ADL – Activities of daily living; ATG– Anti T-lymphocyte globulin; CI – Confidence interval; CK- Creatine kinase; DEXA– Dual-energy X-ray absorptiometry; HAQ-DI – Health assessment questionnaire disability index; IBMFRS – IBM Functional rating scale; IBMWCI – IBM Weakness composite index; IVIg – Intravenous immunoglobulins; MMT - Manual muscle test; MRC- Medical Research Council; MRI – Magnetic resonance imaging; mRNA – Messenger ribonucleic acid; MTX- Methotrexate; MVICT – Maximum voluntary isometric contraction testing; QMT- Quantative muscle; QMT – Quantitative muscle testing; SE – Standard error; sIFA – Sporadic IBM physical functioning assessment; VO2 max – Maximum volume of oxygen uptake

A prospective crossover trial by Leff et al. [2] from 1993 enrolled 11 IBM patients who did not respond to prednisolone. Participants were treated with either combination of oral azathioprine (up to 0.3 mg/kg/day) and methotrexate (up to 0.3 mg/kg/week), or weekly intravenous (IV) methotrexate (up to 0.5 g/m^2) and leucovorin rescue for 6 months [2]. No significant difference was reported in the manual muscle test (MMT) or activities of daily living (ADLs) questionnaire post-treatment. All three patients with CK > 1000 exhibited some improvement in MMT and ADL scores, compared to none with CK < 1000. A pretreatment muscle biopsy demonstrating ≥ 50 mononuclear cells in at least one focus was also associated with improvement on treatment.

Leff et al. [2] combined this study with a retrospective review of 25 IBM patients, which showed a reduction of > 40% or normalisation of CK in 21 of 24 patients treated with prednisolone, six of 13 treated with azathioprine, and 9 out of 10 treated with methotrexate. The authors hypothesised that IBM with a more active inflammatory component may have some response to immunosuppression. However, no significant clinical benefit was shown, potentially as numbers were small, patients and clinicians were unblinded, and clinical outcome measures subjective. These earlier studies used nonstandardized approaches for diagnosis, e.g. using Bohan and Peter criteria [29] and presence of rimmed vacuoles on muscle biopsy to diagnose IBM. The approach reflects practice at the time, but without including criterion referring to specific IBM weakness patterns, patients with genetic vacuolar myopathies or late IBM and irreversible muscle damage may have been included.

A larger randomized placebo-controlled trial with 44 patients comparing 5–20 mg/week of methotrexate to placebo showed no significant clinical improvement in quantitative muscle testing (QMT) or MMT in the active treatment arm after 22 or 48 weeks [11]. Mean CK levels dropped significantly in the methotrexate compared to control group (676–274 for methotrexate; 725–690 for placebo; 95%CI – 732 to – 102, $p = 0.01$) 3 months after treatment initiation. The observed improvement in CK without clinical response is consistent with findings from Leff et al. [2].

In this review QMT refers to assessments with protocols using a dynamometer. One of these protocols, maximum voluntary isometric contraction testing (MVICT), is specifically used in some trials.

IV immunoglobulin and anti-T lymphocyte globulin

A double blind, placebo-controlled crossover study from 1997 using 2 g/kg of IV immunoglobulin (IVIg) for three months showed a non-significant trend towards strength increase, measured by total Medical Research Council (MRC) scale (mean change postIVIg + 4.2; range – 16 to + 39.8 versus – 2.7 postplacebo; range – 10 to + 8; $p < 0.1$) [6]. A similar finding was noted in MVICT, a form of QMT. Some assessments of swallowing speed also significantly improved. A further similar crossover study from 2000 involving 22 patients with IBM reported no disease progression in 90% of patients after 2g/kg IVIg monthly for 6 months, and no significant improvement in MRC sum score [8]. A small but significant improvement in the neuromuscular symptom score (NSS) was found after 6 months (+ 6.2 points IVIg versus + 1.2 points placebo, $p < 0.05$). When the groups crossed over, there was + 2.6 improvement after

6 months of IVIg versus − 0.6 points after placebo ($p < 0.05$). Whilst these trials had a double-blind design, a potential confounder is that 16 of 19 patients in the first crossover study correctly guessed when they received IVIg [6].

In 2001, Dalakas et al. [9] also assessed the effect of IVIg combined with prednisolone in IBM in a double-blind, placebo-controlled study of 36 patients. All patients were treated a tapering dose of prednisolone for four weeks starting at 60 mg daily. Shortly after starting prednisolone, the first of three doses of 2 g/kg of IVIg or placebo was administered over 2 days every month for 3 months. No significant differences were noted in total MRC scores or on QMT total scores between groups or at baseline. Postintervention, muscle biopsies were performed in 24 patients from both groups and compared to earlier biopsies. The number of CD2+ cells/myofiber and foci of endomysial inflammation decreased in both groups, with a further significant decrease in the IVIg group compared to placebo. The findings suggest a decrease in markers of inflammation following immunosuppression and an additive effect of IVIg, but did not translate to clinical benefit according to the trial measures. It is likely that a decrease in inflammation will not result in immediate recovery of skeletal muscle, and the short trial period would make any effect difficult to detect. Due to an absence of clear clinical efficacy, a small risk of immune reaction or thrombus, and limited availability, most clinicians do not routinely use IVIg for IBM.

Anti-T lymphocyte globulins (ATG), animal-derived antibodies against human T cells, were administered to IBM patients in addition to methotrexate, in a small, open label, randomized study in 2003, with an ATG and oral methotrexate group (n=11) compared to oral methotrexate alone (n = 5) over 12 months[12•]. Outcome measures included QMT of various muscle groups, and an open muscle biopsy immediately before and after treatment. Overall mean muscle strength increased in the ATG and methotrexate group by 1.4% (SD ± 9.8), whereas in those treated with methotrexate alone there was 11.1% decrease (SD ± 7.2, p = 0.021). No significant changes in inflammation were reported in repeat muscle biopsies. The positive result is surprising considering that mean muscle strength was greater after a year, despite one course of ATG being administered. Given the open label nature of the study, the findings could perhaps represent a placebo response, or alternatively, there may have been a therapeutic effect which would require a larger confirmatory randomized controlled trial.

Cytokines and cytokine receptor inhibitors

β-Interferon 1a

β-Interferon 1a is an anti-inflammatory cytokine used to treat multiple sclerosis, and was assessed in a randomized, double-blind, placebo-controlled trial involving 30 IBM patients in 2001 [10]. Sixteen participants were randomized to receive 30 μg of β-Interferon 1a subcutaneously and fourteen to receive placebo for 24 weeks. The primary outcome measures were safety and tolerability. Efficacy was also assessed using composite MMT and MVICT, including assessment of grip strength, two upper and three lower limb muscle groups, muscle mass estimation by dual-energy X-ray absorptiometry (DEXA), and functional tests. No significant improvement was observed in the secondary

endpoints (e.g. mean change in composite MVICT score – 0.16 kg [SD ± 0.64] for placebo versus – 0.26 kg [SD ± 0.69] for the β-Interferon 1a, $p = 0.66$).

The study was later replicated using a higher dose of 60 μg β-interferon 1a [13]. Here, mean grip MVICT significantly improved from baseline to week 24 by 0.23 kg (SD 1.66) in the β-interferon 1a group compared to a 1.45 kg (SD 1.44) decrease in the placebo group (treatment effect 1.84, 95%CI 0.46–3.21, $p = 0.01$). Otherwise, there was no significant difference in other outcome measures, including CK and functional assessments. The improvement in grip MVICT was not evident in the composite MMT and MVIC scores, possibly because these measures included strength measures of muscle groups less affected in IBM.

TNF inhibition

Etanercept, a tumour necrosis factor alpha (TNFα) receptor fusion protein, binds and inactivates TNFα thus preventing proinflammatory effects [30], and is an established treatment for a number of conditions including psoriasis and rheumatoid arthritis [31]. In an open label study, nine IBM patients were treated with etanercept and outcomes compared to 29 controls from the previous β-interferon 1a studies [10, 13], and a second group of five IBM patients who underwent MVICT as part of clinic follow-up [14]. No significant difference was noted in MVICT composite score, but a small, significant increase in grip strength was seen after 12 months of etanercept compared to natural history controls (etanercept + 0.19 kg [SD ± 1.8] versus placebo – 7.78 kg [SD ± 6.0], $p = 0.012$).

Infliximab is a chimeric monoclonal antibody which exerts an anti-inflammatory effect by neutralising TNFα, and is licenced for a number of diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. In an open label trial, infliximab was administered to 13 IIM patients (polymyositis [$n = 5$], dermatomyositis [$n = 4$], IBM [$n = 4$]) [15•]. The primary outcome measure was muscle Functional Index (FI) [32], and secondary clinical outcomes included MMT, serum biochemistry and subjective assessments. Overall, no significant improvement in FI was noted, although one IBM patient met the International Myositis Assessment and Clinical Studies (IMACS) definition of improvement [33].

Anakinra

Interleukin 1b (IL1β) is upregulated in IBM muscle fibres and promotes β-amyloid deposition in vitro [34]. Anakinra, an IL1 receptor antagonist [35], was assessed for therapeutic effects in an open label pilot study of four IBM patients treated for a mean period of 7.7 months [17]. No improvement in muscle strength, including grip, was noted after treatment.

Alemtuzumab

Alemtuzumab is a monoclonal antibody specific for CD52 found on lymphocytes, and is effective in the treatment of chronic lymphocytic leukaemia [36] and multiple sclerosis [37]. As IBM involves infiltration of cytotoxic CD52+ T cells, a prospective open label study was undertaken in 13 patients [16]. Natural history data prior to enrolment were taken from QMT assessments in the prior 12 months and 24 months for MMT. Muscle biopsy was performed at baseline

and four doses of alemtuzumab and IV methylprednisolone administered. QMT measurements declined by 14.9% in the 12-month observational period prior to treatment. Six months post-alemtuzumab administration, there was a 13% improvement in mean QMT (ANOVA F (1,12) = 16.53, $p < 0.002$). However by 12 months, QMT measurements dropped again by a mean of 11.6% from baseline ($p < 0.01$). MMT showed similar findings.

As expected, the total lymphocyte count dropped a week after alemtuzumab administration, so that at 6 months it was 30% of baseline, and 50% at 12 months. CD45RA+ CD62L– effector memory T lymphocytes were almost fully depleted after a week, but after 3 months numbers rebounded above baseline. In contrast, central memory T lymphocytes reached a nadir 3 months post-alemtuzumab but returned to baseline levels by 8 months. These findings may be significant as clones of highly differentiated killer cell lectin–like receptor G1 (KLRG1) positive cytotoxic T cells have been found in muscle from IBM patients [38]. Whilst conventional immunosuppression (e.g. prednisolone) does not affect their numbers, the transient decrease in lymphocytes induced by alemtuzumab may explain the transient improvement in symptoms. The study was not blinded or controlled, so attribution of clinical benefits to alemtuzumab treatment cannot be confirmed.

Sirolimus (rapamycin)

Sirolimus, also known as rapamycin, is a macrolide compound which promotes autophagy and inhibits lymphocyte activity by reducing sensitivity to IL-2 through inhibition of the mammalian target of rapamycin (mTOR) pathway [39]. A phase IIb randomized, double-blind placebo-controlled trial of sirolimus enrolled 44 IBM participants [18••]. There was no significant difference in quadriceps MVICT, the primary endpoint, between groups (median difference 3.78%, 95%CI – 10.61 to 17.31, $p = 0.85$), or other outcome measures including the IBM Functional Rating Scale (IBMFRS) and QMT in individual muscle groups. The percent change in 6-min walking distance (6MWD) was significantly increased in the intervention group compared to placebo (median difference 11.37%, 95%CI 0.36 to 20.86, $p = 0.009$). Other significantly improved outcome measures included Health Assessment Questionnaire Disability Index, forced vital capacity, and thigh fat fraction as assessed by quantitative magnetic resonance imaging (MRI). These mixed results provide some evidence for the efficacy of sirolimus, and a larger phase III study is planned.

Non-immunosuppressive therapies

The pathological features of IBM include endomysial inflammatory infiltrates but also rimmed vacuoles, protein accumulation, 15–18-nm filaments and cytochrome oxidase C negative fibres [40, 41]. Protein homeostasis is usually maintained by processes involving autophagy receptor and chaperone proteins such as p62 and heat shock proteins (HSP). In IBM, inflammation contributes to failure of these mechanisms leading to protein aggregation and mitochondrial dysfunction [42, 43]. Treatments that increase protein clearance, encourage muscle growth and inhibit atrophy have therefore been trialled.

Arimoclomol

Arimoclomol augments the heat shock response by prolonging activation of heat shock factor 1, the main transcription factor for HSP expression [44], and has been assessed in a combined in vitro and in vivo study [23••]. Treatment with arimoclomol significantly reduced the formation of cytoplasmic protein inclusions in cultured myocyte models of IBM and resulted in significantly greater grip strength in valosin-containing protein (VCP) mutation mice.

Arimoclomol was assessed in a double-blind, placebo-controlled phase II study of 24 patients with definite or probable sporadic IBM [23••] according to the Griggs criteria [1]. Patients were treated for 4 months and followed up for a further 8 months. Primary outcomes were safety and tolerability, and IBMFRS, MMT and MVICT also assessed as secondary outcomes. No significant difference in deterioration was observed in secondary outcome measures between groups, but there was a trend for reduced deterioration in the Arimoclomol group after 8 months (mean change in IBMFRS, – 0.68 ± SD1.58 Arimoclomol versus – 2.50 ± SD3.31 placebo, $p = 0.055$; mean change in MMT – 0.12 ± SD0.22 Arimoclomol versus – 0.26 ± SD0.27 placebo, $p = 0.147$).

Despite the positive preclinical studies, there was a trend for clinical improvement but no significant difference between intervention and placebo arms. There are several possible factors that might be involved: (a) the primary endpoint was safety, rather than efficacy; (b) whilst arimoclomol caused a reduction in inflammatory cells in the muscle biopsies, it is not a directly immunosuppressive medication. Therefore, inflammation will be ongoing in IBM patients after arimoclomol treatment, unlike in cell and mouse models where pathology is not directly caused by inflammation; (c) arimoclomol treatment lasted 4 months in the human trial, and for 10 months in the mouse trial, therefore the treatment may have been too short. A larger study is ongoing at the time of writing [45].

Bimagrumab

The RESILIENT study was a double-blind, placebo-controlled phase IIb study to assess the effects of bimagrumab [27••], a human monoclonal antibody which targets type II A and B activin receptors, and thus preventing myostatin and activin from binding and exerting a negative regulatory function on muscle [46]. This study enrolled 251 IBM participants, randomized to receive 10 mg/kg, 3 mg/kg, 1 mg/kg of bimagrumab or placebo. The antibody and placebo were administered every 4 weeks for 48 weeks. The primary outcome measure was the 6MWD, with secondary outcomes being quadriceps QMT, total lean body mass as assessed by whole body DEXA, and the sporadic IBM Physical Functioning Assessment (sIFA) [47].

There was no significant difference between the bimagrumab groups and control groups in 6MWD, with the bimagrumab 10 mg/kg group achieving a mean 10.6 m improvement from baseline (95%CI: – 12.9 to 30.2 m) and a mean difference of 17.6 m from placebo (99% CI: – 19.6 to 54.8 m; $p = 0.22$). The sIFA score was reduced by 5.1 points (99%CI – 11.3 to 1.1; $p = 0.034$) in *t*, indicating a significant patient-reported improvement. Total lean body mass also showed a significant improvement after 10-mg/kg bimagrumab, being 102.8% of baseline mass (95% CI: 101.4 to 104.2%), which is a 1.1% (95%

CI: 1.0 to 1.1%; $p = 0.001$) difference from placebo. No significant improvement was seen in QMT of right quadriceps, Short Physical Performance Battery or falls rate.

A significant change in lean muscle mass was observed, confirming biological activity of the drug, and subjectively patients noted an improvement, but this did not translate to objective improvement. Although a pilot study with 14 patients showed a significant increase in 6MWD [48] (14.6%, $p < 0.008$; analysis of covariance), the authors and others [49] have stated that 6MWD might not have been the most appropriate choice of primary endpoint, as it is heavily dependent on cardiopulmonary reserve and can be affected by conditions unrelated to IBM. Also, bimagrumab may have an effect on muscle mass but does not affect inflammation and cell stress, and therefore muscle function may remain impaired.

Oxandrolone

Oxandrolone is a synthetic androgen and an anabolic steroid which has a myotrophic effect [50]. A trial was performed on 19 IBM patients, using a double-blind, placebo-controlled crossover study [20]. Patients were given oxandrolone or placebo for 12 weeks, then a 2-month washout, and crossover to the other treatment for 12 weeks. The primary outcome measure was whole body MVICT, with secondary outcome measures being whole body MMT, physical function testing, upper/lower extremity MMT and MVICT, and serology. No significant difference was seen between the groups calculating the generalized estimating equation (GEE) for whole body MVICT or MMT, however whole body MVICT nearly reached significance (median increase 15.5 kg, GEE of treatment effect 1.27 ± SE0.68, $p = 0.061$). Upper extremity MVICT alone showed a significant mean increase of 1.45 GEE points (± standard error 0.53; $p = 0.006$). This significant result was not replicated in upper extremity MMT, with a treatment effect of 0.74 MRC points (± SE0.57; $p = 0.20$). Both lower extremity MVICT and MMT did not show significant improvement. The reason for different outcomes between the upper and lower limbs is unclear. No further trials of oxandrolone in IBM have been reported.

Exercise

The effect of exercise programs has also been assessed in IBM following historical concerns that exercise could be harmful in patients with myositis, presumably due to findings of myalgia, raised CK and focal endomysial inflammation post-exertion [51]. A small unblinded study investigated a 12 week progressive resistance training program in five IBM patients. No significant difference was observed in mean MRC score, serum total CK, circulating lymphocytes or inflammation post-exercise program. The only positive results were significant increases in peak muscle strength when assessed using variable resistance exercise machines, most marked on knee extension (right leg press 39% improvement ± SE 12, left leg press 42% improvement ± 14, $p < 0.05$ for both) [19].

A further small open study assessed a 12-week aerobic, resistance and stretching exercise programme in seven IBM patients [21]. A significant increase in peak oxygen uptake (VO_2 max) (mean 1.5 L/min ± SE 0.2 before the

programme to 2.1 L/min ± 0.3 after, $p < 0.05$) was observed, as well as mean strength on hip abduction (16.6%), shoulder abduction (39.8%), hip flexion (35.6%), and knee flexion (10.5%, all $p < 0.05$) post-exercise programme. Some findings were replicated in a prospective randomized single-blinded crossover trial [26], where 17 IBM participants undertook a 12-week aerobic exercise programme, showing a large increase in VO_2 max (1.72 on Cohen *d* analysis ± SD 0.28, and 1.68 on Hedges *g* analysis ± SD 0.42).

An unblinded randomised control trial was performed in IBM assessing a 12-week blood-flow restricted (BFR) exercise programme against a non-exercise control group [25]. BFR involves partially inflating a cuff around a limb to restrict blood flow, then performing exercise at low loads. No improvement was noted in the Short Form Health Survey physical function domain, the primary outcome measure, although a significant decrease in knee extensor strength from baseline was seen in controls (– 9.2% change, $p = 0.023$), not seen in the BFR exercise group (+ 0.9% change, $p = 0.87$). This lack of progression in the BFR exercise group may also reflect a protective effect of exercise, although the decrease in power in control does appear faster than would be expected from natural history studies [52].

These studies confirm that exercise is safe in IBM patients, with objective improvements in strength being demonstrated. No improvement in mobility has been shown. However, as exercise has many physical and psychological benefits, most clinicians would refer to a physiotherapist for an exercise programme or recommend that patients with IBM regularly take part in moderate physical activity.

Other interventions

Follistatin is a glycoprotein which binds to myostatin and prevents it from binding to activin IIB, thus preventing inhibition of myogenesis [53]. Myostatin knockout mice overexpressing full length follistatin have much greater muscle than control mice [54], thus an alternatively spliced isoform of the *FST* gene was developed for gene therapy using an adeno-associated virus 1 (AAV1) vector. The safety and efficacy of follistatin gene therapy was assessed in an unblinded trial with six IBM patients compared to natural history data from eight patients [24]. There was significant improvement in 6MWD for the treated group compared to a decrease in the untreated group (+ 62.5 m versus – 33.0 m, $p = 0.01$), and muscle biopsies pre- and post-gene therapy suggested histopathological improvement. Whilst these results appear encouraging, there were confounders; the study was not blinded, and there were additional interventions, e.g. prednisolone and an exercise regime in the treatment group, which may have improved the 6MWD. In addition, the group used an annualised 6MWD, so that if a participant dropped out early the 12-month outcome was extrapolated from the last recorded time point, potentially contributing to further error. Overall it is not possible to attribute benefits to follistatin gene therapy from this study.

In addition to lowering cholesterol, statins have other actions including inhibition of inflammatory responses. Simvastatin was assessed in IBM a pilot study [22], where the primary outcome measures were those set by IMACS [55], including MMT and also IBMFRS [56]. None of the treated patients improved or worsened according to the IMACS criteria, and there was no improvement on MRI studies or muscle biopsies.

The future of IBM clinical trials

The experience and outcome of clinical trials in IBM to date clearly indicates a pressing need for the discovery of future efficacious therapies.

Choosing the right target

The pendulum has swung between degenerative and autoimmune hypotheses with regard to the aetiopathogenesis of IBM [57]. There is mounting evidence emphasising the importance of autoimmune T cell–mediated mechanisms [58]. Clones of cytotoxic KLRG1 expressing T cells meeting criteria for T cell large granulocytic leukaemia have been demonstrated in IBM [38]. This discovery potentially explains resistance to conventional immunosuppression and raises the possibility for novel therapies targeting receptors on these cell populations [59]. The debate regarding the relative importance of degenerative processes such as protein dyshomeostasis and impaired autophagy is ongoing. It is clear that further work is required to better understand the aetiopathogenesis of IBM and facilitate discovery of targeted therapeutic interventions.

Implementing a stratified approach

Heterogeneity within IBM is increasingly being recognised and may relate to anti-CN-1A autoantibody status [60, 61]. Other predictors of disease severity and progression are likely to be identified. Recently, our group showed that the long-term trajectory of IBM varies, and patients can be stratified by rate of dynamometry-measured strength loss (see Fig. 1 [52]). Such variability in progression may affect response to treatment and reduce sensitivity to detect change. Furthermore, patients with end-stage disease, where muscle has been extensively replaced by fatty tissue, will not respond to even the most efficacious systemic treatment. This issue has been compounded in the past by the use of diagnostic criteria for IBM which necessitated the presence of end stage disease features. Patients with shorter disease duration should be targeted for trial inclusion and thus techniques for facilitating earlier diagnosis of IBM pursued.

Using sensitive and clinically relevant outcome measures

Early clinical trials in IBM assessed strength manually using outcomes such as composite MMT and MVICT scores. More recent IBM studies have used QMT, particularly of finger flexors and quadriceps, muscles particularly affected in this condition, but these measures are technically difficult to perform and can exhibit high levels of variability. The 6MWD is a commonly used outcome measure in clinical trials, but is influenced significantly by cardiorespiratory fitness and lacks relevance in IBM. Alternative measures such as the timed up and go (TUG) test may be more appropriate [62].

Functional scoring tools including the IBMFRS [56] or sIFA [47] are focussed towards deficits seen in IBM, with the former used as the primary outcome in the pending arimoclomol study [45]. However, deficiencies in these tools are apparent, particularly with regard to assessment of hand function. There have been several attempts to create optimized tools which will require additional validation [63, 64].

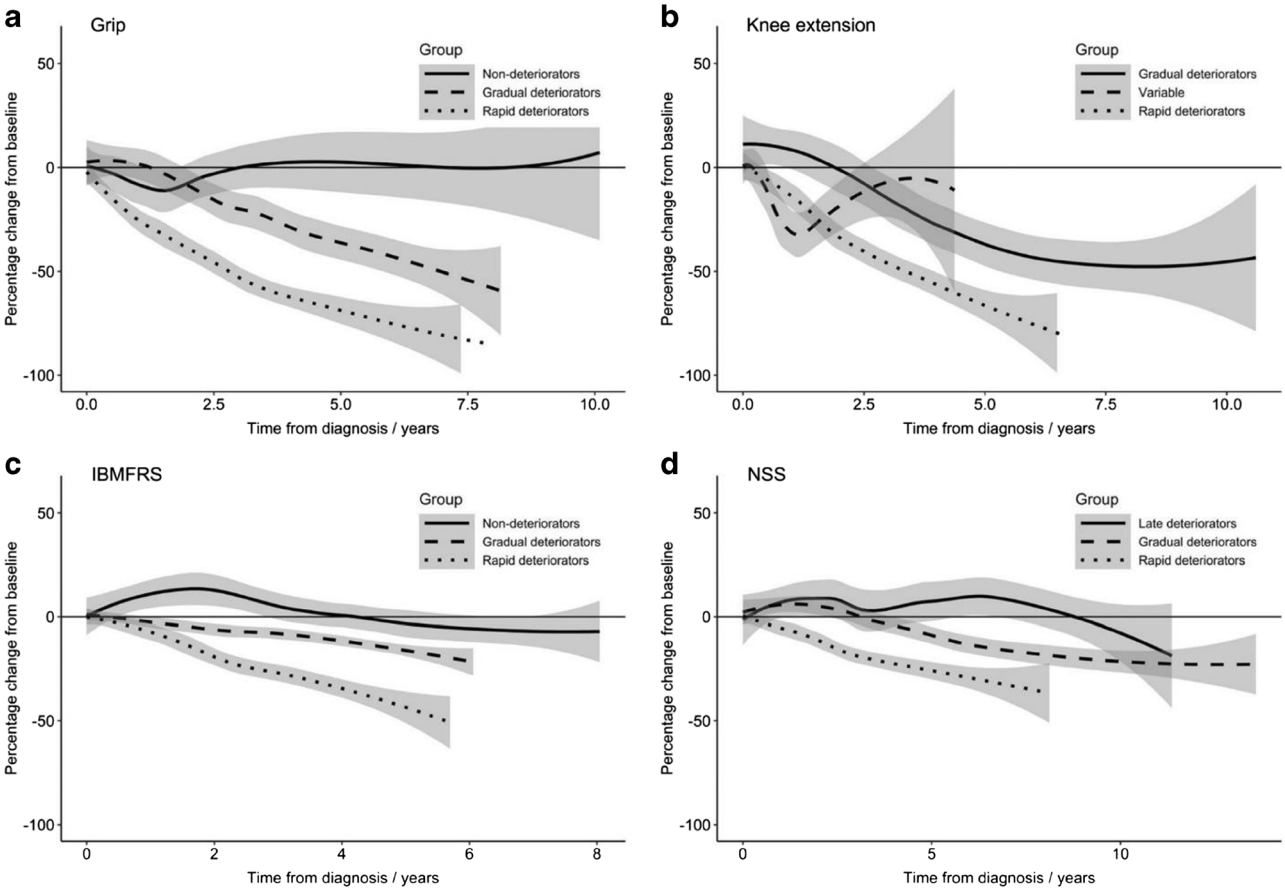

Fig. 1. Longitudinal trajectories of grip (**a**) and knee extension (**b**) strength, IBM-FRS (**c**) and NSS (**d**). Figure from Oldroyd et al. Long-term strength and functional status in inclusion body myositis and identification of trajectory subgroups. *Muscle Nerve* 62, 76–82 (2020). Reprinted under Creative Commons License 4.0

The development of objective and more sensitive radiological and blood biomarkers of IBM disease activity may be better tolerated, could identify earlier response signals, and shorten required clinical trial duration. Thigh muscle fat fraction can be determined by MRI which correlates well with the lower limb component of IBMFRS [65]. Lean body mass as determined by DEXA has also been performed [27••]. Overall, such techniques require further validation.

Conclusion

To date, clinical trials in IBM have not shown definitive benefits. Ineffective or poorly targeted treatments and issues with trial design may be contributory. Ideally, future IBM studies should be double-blind, placebo-controlled in nature, using sensitive, IBM-specific outcome measures. Trial design should also be stratified to account for disease heterogeneity. There is a risk that potentially efficacious therapies have been previously dismissed due to poor trial design. Opinion is swinging back towards considering immune-based treatments for IBM, and previous interventions may be revisited.

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Compliance with ethics guidelines

Conflict of interest
Andrew Snedden declares no conflict of interest.
James B. Lilleker has undertaken consultancy work for Roche and received speakers' bureau from Sanofi Genzyme, outside the submitted work.
Hector Chinoy has undertaken consultancy work for Orphazyme, outside the submitted work.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer
The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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- • Of importance
- •• Of major importance

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