Advances in the early diagnosis and therapy of inclusion body myositis

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Purpose of review
To describe recent advancements in diagnostic and therapeutic approaches to inclusion body myositis (IBM).

Recent findings
Our understanding of the implications of anti-cytosolic 5′-nucleotidase 1A autoantibody status in IBM and other diseases is increasing. Muscle imaging using magnetic resonance techniques and ultrasound is increasingly being performed and characteristic patterns of muscle involvement may help with diagnosis. Longitudinal imaging studies are likely to help with monitoring and as an outcome measure in clinical trials. Recent small-scale studies of Arimoclomol and Rapamycin have shown promising results and further investigation of these medications is ongoing. Exercise is likely to form an increasingly important facet of management of patients with IBM, but the optimal type of exercise programme to enrol patients in is not yet determined.

Summary
Antibody testing and muscle imaging results may improve our ability to diagnose IBM and the availability of effective disease modifying treatments targeting novel non-inflammatory pathways could soon become a reality. It remains the duty of those involved in the management of patients with IBM to facilitate involvement in clinical trials and other research studies.

Keywords
diagnostics, imaging, inclusion body myositis, serology, therapeutics

INTRODUCTION

Inclusion body myositis (IBM) is an acquired myopathy usually occurring in those aged over 50 years. IBM is conventionally grouped with the idiopathic inflammatory myopathies, but for several reasons can be seen as the 'odd one out'. Despite muscle inflammation being a prominent feature, the disease is resistant to treatment with immunosuppressive therapies, none of which lead to convincing or sustained therapeutic benefits. Recognition of this issue, the pathognomonic pattern of weakness and the characteristic histopathological features eventually allowed separation of IBM from polymyositis and other muscle disorders [1].

Disease progression in IBM is characterized by damage to selected skeletal muscles, particularly those of the volar aspect of the forearms and the anterior thigh, which are gradually replaced by fatty–fibrous tissue, leading to increasing weakness of grip and knee extension. This clinical change is mirrored by increasingly conspicuous degenerative features on muscle biopsy, including aggregation of misfolded proteins and rimmed vacuoles [2]. The exact sequence of events that eventually culminates in the severe disability seen is the subject of intense debate.

The current review will describe recent advancements in diagnostic and therapeutic approaches to IBM, focussing on publications since 2016. Detailed discussion of genetic and aetiopathological aspects of the disease are not discussed.

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KEY POINTS

- Anti-cN-1A autoantibodies may prove useful in the diagnosis and stratification of IBM.
- Muscle imaging, including MRI and ultrasound, is playing an increasingly important role in the diagnosis and monitoring of patients with IBM.
- Muscle MRI is also increasingly being used as outcome measures in clinical trials.
- Novel therapeutics targeting nonimmune disease pathways are currently being investigated in IBM.

TOOLS TO ENABLE AN EARLIER DIAGNOSIS?

Many patients with IBM continue to be initially misdiagnosed and are given treatments, including potent immunosuppressive medications, without any prospect of benefit. It is now acknowledged that early iterations of the IBM diagnostic criteria had relatively low sensitivity for those with early disease, in part because of a requirement to demonstrate the histopathological hallmarks associated with established disease which may be absent in earlier stages [3]. Although more recent diagnostic criteria have shifted towards identification of the highly specific pattern of muscle weakness seen in IBM, this potentially remains problematic in the sense that for clinical detection of such weakness, significant muscle damage must have already occurred. This may in part explain the failure to demonstrate the benefits of treatment in IBM, in which the likelihood of response is probably low if skeletal muscle tissue has already been extensively replaced by fat. Identification of a highly specific biomarker of *early* IBM is a key unmet need for patients with this condition.

Serology

Much excitement followed the description of anti-cN-1A (also referred to as NT5C1A) autoantibodies in IBM by European and American researchers [4,5]. Recent work has demonstrated a relatively poor specificity of antibody positivity for IBM, with relatively large proportions of patients with Sjögren's syndrome and systemic lupus erythematosus also seropositive, highlighting that interpretation of the result must take place in full view of the clinical context [6–8]. However, the power of anti-cN-1A autoantibody status to distinguish between polymyositis and IBM is high, potentially providing a useful tool for early confirmation of IBM, before the appearance of the pathognomonic pattern of weakness. This could help prevent patients with IBM being unnecessarily exposured to potentially harmful immunosuppressive therapies and allow earlier recruitment in to clinical trials.

The identification of anti-cN-1A autoantibodies has also offered clues regarding disease pathogenesis, potentially helping to explain the link between the inflammatory and degenerative processes evident in the disease [9]. It is noted however that anti-cN-1A autoantibody status does not appear to associate independently with a specific human leukocyte antigen genotype, in contrast to some of the established myositis-specific autoantibodies [10,11]. Taken together, anti-cN-1A autoantibodies are generally thought of as myositis-associated rather than myositis-specific autoantibodies.

Separate groups have demonstrated a more severe disease phenotype in anti-cN-1A autoantibody-positive IBM [12,13]. Stratification of the IBM population according the autoantibody status could thus prove useful in guiding patient monitoring and in understanding the response to experimental treatments. Furthermore, a recent publication has highlighted additional complexity, demonstrating the presence of anti-cN-1A autoantibodies in 27% patients with juvenile myositis, compared with 12% of healthy control children ($P = 0.002$) [14]. These autoantibody-positive patients also appeared to have a more severe phenotype exemplified by a higher proportion with pulmonary symptoms at diagnosis, more frequent hospitalizations and requirement for a greater number of medications compared with antibody negative juvenile myositis patients. These findings clearly require further explanation, but it is possible that anti-cN-1A autoantibody status is more useful as a biomarker of disease severity, rather than a diagnostic biomarker for IBM *per se*.

In attempting to understand the pathogenic relevance of anti-cN-1A autoantibodies, a recent publication described in-vitro and in-vivo passive immunization models in which p62 aggregates significantly increased in anti-cN-1A-positive IBM IgG fraction supplemented cells and mice, respectively [15▪]. However, it is possible that some other constituent within the IgG fractions used (which were derived from patients with IBM) is the truly pathogenic entity [16]. One issue of ongoing concern is the lack of standardization of antibody detection methodologies and the consequent difficulties in comparing results from different studies. The future is likely to see anti-cN-1A autoantibodies added to existing commercial myositis antibody multiplex assays.

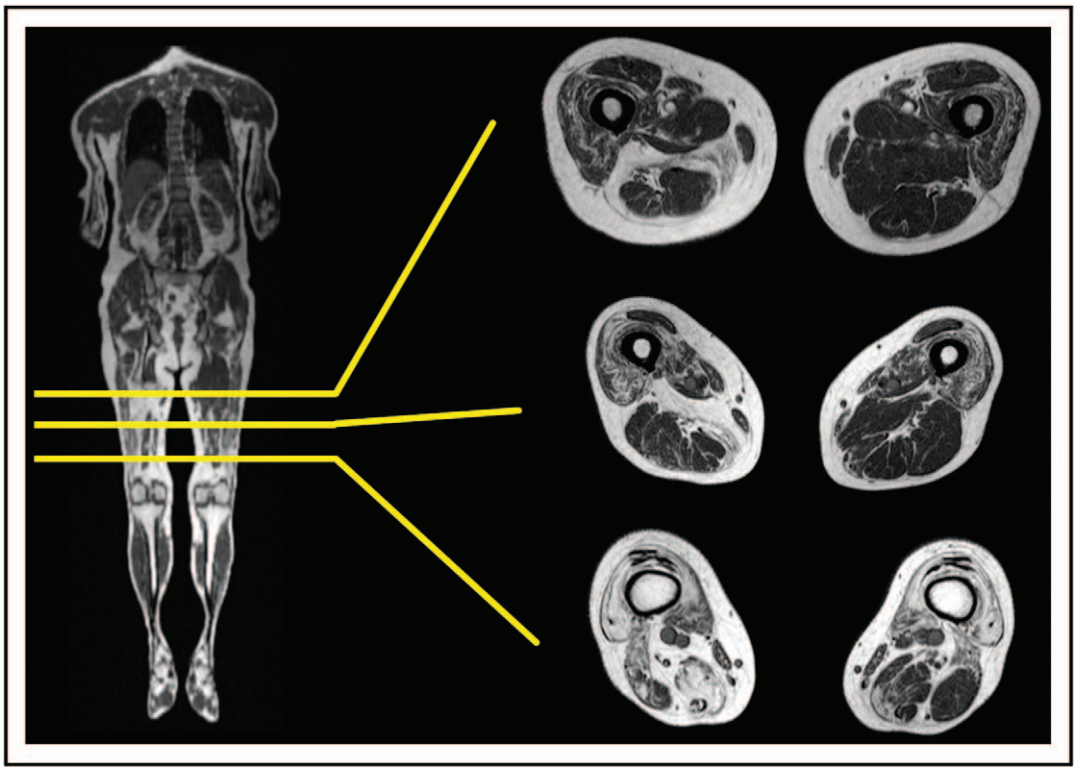

FIGURE 1. Sample images from whole body T1-weighted MRI of muscle with three axial sections through the thigh (yellow line indicates level) in a patient with inclusion body myositis. Typical fatty replacement of muscle, predominantly of the anterior thigh musculature is evident, with a gradient of increasing severity from proximal to distal musculature.

Imaging

Muscle imaging, particularly MRI and ultrasound is increasingly being performed as part of the diagnostic workup and monitoring of patients with muscle disease. Muscle MRI provides high-resolution visualization of soft tissues and can sensitively demonstrate myo-oedematous change (usually using short tau inversion recovery sequences) and fatty replacement (usually using T1-weighted sequences) (Fig. 1).

In IBM, several imaging studies have demonstrated characteristic patterns of muscle involvement, largely mirroring what is observed clinically [17]. A recent study also demonstrated some correlation between the extent of fatty infiltration and functional outcome measures [muscle strength ($r = -0.60$; $P = 0.04$) and the Modified Rankin Scale ($r = 0.48$; $P = 0.03$)] [18]. It is usually observed that fatty replacement of muscle is much more prominent in IBM than in the other inflammatory myopathies, although such changes overlap significantly, limiting usefulness as a diagnostic biomarker in clinical practice. Furthermore, conventional image analysis techniques rely on somewhat subjective, and very laborious, scoring of muscles damage using various grading systems. In future, this is likely to improve with more widespread use of quantitative magnetic resonance techniques that are amenable to automation [19].

In a recent longitudinal study, Morrow *et al.* [20▪] were able to demonstrate that intramuscular fat accumulation determined by MRI in patients with IBM was highly responsive to change and correlated with conventional functional measures, highlighting the potential usefulness as an outcome measure in clinical trials. Validation of sensitive outcome measures is a key priority in a rare disease that progresses relatively slowly. In the future, it is hoped that smaller, shorter and more efficient clinical trials could be facilitated with the use of such techniques. However, issues relating to standardization of magnetic resonance parameters between different scanner systems and complex data analysis pipelines are hurdles to overcome.

An interesting novel application of MRI was described by Olthoff *et al.* [21]. Here, a real-time MRI technique was used to assess dysphagia in patients with IBM and was compared with conventional assessment by flexible endoscopic evaluation of swallowing and videofluoroscopy. Real-time MRI was as capable at demonstrating dysphagia and the lack of radiation exposure and enhanced visualization of soft tissues were highlighted as potential

advantages. Whether these findings will be translated in to more widespread clinical use is yet to be seen, but as with other applications of MRI, issues relating to scanner availability and patient factors such as claustrophobia or implanted metal may be barriers.

Muscle ultrasound is an alternative imaging modality that has some potential advantages over MRI, particularly as it is often more easily accessible and can even be performed at the bedside during an outpatient consultation. Characteristic patterns of ultrasound abnormalities have been demonstrated in IBM, including increased echointensity in flexor digitorum profundus, gastrocnemius and rectus femoris [22]. In addition, ultrasound equipment can be used to perform shear wave elastography, giving an indication of tissue solidity. Bachasson *et al.* [23] were able to use this technique to demonstrate correlations between the muscle shear modulus and strength in patients with IBM, although the clinical value of such change is yet to be determined.

Ultrasound is prone to inter-rater reliability issues due to subjective interpretation of the images produced and technical factors related to probe positioning. Machine learning and deep learning techniques have recently been applied to ultrasound data in IBM in an attempt to overcome some of these issues. Burlina *et al.* [24▪] describe a fully automated deep convolutional neural network technique that was able to correctly distinguish IBM ($n = 19$) from polymyositis ($n = 14$) and dermatomyositis ($n = 14$) with an accuracy of 75%. It is likely that similar techniques will continue to be developed may in the future be integrated in to ultrasound equipment for use in clinical practice with minimal user intervention or training.

TREATMENT HORIZON

Pharmacological treatments

Recent times have seen a shift away from targeting immune pathways and towards targeting alternative damage-inducing mechanisms. A recently completed large phase 2b/3 multicentre study of Bimagrumab (an activin receptor inhibitor) did not meet its primary endpoint [change in 6-min walking distance (6MWD)] [25]. Arimoclomol coinduces the heat shock response by prolonging activation of heat shock factor-1 and may promote normalization of protein handling within muscle. In a recent double-blind, placebo-controlled phase 2a study of Arimoclomol, safety and promising therapeutic signals were demonstrated [26▪▪]. A larger scale phase 2/3 study has recently commenced (ClinicalTrials.gov identifier: NCT02753530). Rapamycin (sirolimus) could restore aberrant autophagic (protein degradation) pathways evident in IBM muscle by inhibiting mammalian target of rapamycin and has immunosuppressive effects mediated via inhibition of IL-2 signalling. A recent abstract described a prospective, randomized, double blind, placebo-controlled phase 2b trial conducted in France. In the study, 22 patients received oral Rapamycin and 22 received placebo over a 12-month period [27]. No difference in the primary outcome (quadriceps strength) was identified at 12 months, but significantly less fatty replacement in quadriceps and hamstrings, beneficial effects on 6MWD, the IBM weakness composite index and the forced vital capacity were observed in the actively treated arm. An open continuation of this study is ongoing to evaluate these findings further (ClinicalTrials.gov identifier: NCT02481453).

A recent study by Mendell *et al.* [28] regarding the use of Follistatin (an antagonist of myostatin) gene therapy in IBM has generated debate. This trial involved injection of the quadriceps with a Follistatin gene therapy in six patients with IBM and with outcomes compared with data obtained from a separate untreated group of eight patients from a neuromuscular clinic. The authors describe a significant improvement in annualized 6MWD and decreased fibrosis and regeneration on muscle biopsy in those receiving treatment. However, although this study potentially opens up an exciting new avenue of treatment for IBM, Greenberg [29] has highlighted several issues with the trial design, including the fact that patients (but not those in the other group) also undertook an exercise programme, the use of an unvalidated *post hoc* created outcome measure and the lack of randomization. Overall, these initial results should probably be viewed with caution and a formal randomized controlled trial would be required to investigate them further.

Of those pursuing immune treatments for IBM, Schmidt *et al.* [30,31] recently reported an additional analysis from a previous open-label study of Alemtuzumab, a mAb binding to CD52 used to treat chronic lymphocytic leukaemia, T-cell lymphoma and multiple sclerosis. The authors obtained pretreatment and posttreatment muscle biopsies and performed quantitative PCR and immunohistochemistry analysis and examined differences in markers of inflammation and degeneration. The expression levels of IL-1β and major histocompatibility complex-I correlated with positive clinical effects, but other important markers of cell stress and degeneration did not change significantly, potentially explaining the only transient effects of Alemtuzumab in the original trial. It remains to be seen whether this potential therapeutic avenue will be explored further, but it is of interest that clonal

lymphocyte expansions meeting diagnostic criteria for large granular lymphocytic leukaemia were identified in 58% (22/38) of patients screened in a recent study, potentially shedding new light on disease pathogenesis [32▪].

Other treatment modalities

Two European groups have recently described their experience in using botulinum toxin injections for the management of dysphagia in patients with IBM. Schrey *et al.* [33] performed a retrospective analysis of 12 patients with IBM that had received botulinum neurotoxin A injections to the cricopharyngeus muscle and highlighted that the rate of aspirations and aspiration pneumonia seemed to decrease after intervention. Di Pede *et al.* [34] describe their experience treating four patients with IBM receiving a multidisciplinary treatment consisting of rehabilitation combined with botulinum toxin injection to the cricopharyngeus muscle in four subjects, three of whom appeared to derive benefit. Such observational data are encouraging, although robust clinical trials will be required to confirm the optimal strategy for managing dysphagia in IBM.

The potential beneficial disease modifying effects of exercise in patients with muscle disease have long been discussed. It is now acknowledged that exertion is safe and should not be avoided in those with myositis [35]. Intriguingly, molecular studies in those without muscle disease has identified correlations between increasing levels of leisure-time physical activity and reduced C-reactive protein and IL-6 levels, potentially indicating activation of systemic anti-inflammatory pathways [36]. The effects of a seven-week resistance exercise programme on gene expression in eight patients (no controls) with polymyositis and dermatomyositis (but not IBM) has been performed to investigate molecular explanations for the effect of exercise [37]. Postintervention analysis demonstrated increased muscle strength, reduced serum muscle enzyme levels and improved disease activity scores, in addition to gene expression profiling showing reduction in proinflammatory and profibrotic gene networks compared with baseline.

However, exercise regimens come in various shapes and sizes, with little to guide the clinician as to which type of intervention might be most helpful in IBM. Blood flow restricted exercise can induce muscle hypertrophy and has previously been investigated in those with IBM [38]. Jørgensen *et al.* [39] sought to investigate this further by performing a 12-week randomized controlled trial of blood-flow restricted training versus nonexercise in a group of 22 IBM patients. Although the primary outcome measure (change in the physical function domain of the Short Form 36) was not met, between-group differences were seen in leg muscle strength favouring the intervention. Exercise is likely to increasingly become a key facet in the management of IBM and may require reorganization of clinics to ensure the regular engagement of the relevant physical therapists.

CONCLUSION

Recent years have seen expansion in the availability of diagnostic tools that may assist clinicians in the workup of patients with muscle disease. Anti-cN-1A autoantibody testing and muscle imaging could be particularly useful in the diagnosis of IBM and may become integrated in to diagnostic and/or classification criteria in the future. Once diagnosis is established, the availability of effective disease modifying treatment strategies may soon become a reality. It remains the duty of those involved in the management of patients with IBM to offer involvement in clinical trials and other research studies. Through such means, it is hoped that an effective treatment for IBM can soon be found.

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Conflicts of interest

J.B.L. is an NIHR Academic Clinical Lecturer. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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