Workshop report

188th ENMC International Workshop: Inclusion Body Myositis, 2–4 December 2011, Naarden, The Netherlands

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1. Introduction

The 188th ENMC workshop titled “Inclusion Body Myositis” was held in Naarden, The Netherlands, 2–4 December 2011. The workshop received supplementary funding from the Myositis Support Group UK. This workshop aimed to build on the work of two previous IBM workshops held in the MRC Centre London 2008 and Paris 2009 [1,2]. Its aims were to (1) review the diagnostic criteria for IBM, (2) foster future collaborative working in immunological and genetic IBM research, (3) review natural history studies and clinical trial protocols, (4) review the current status of clinical trials outcome measures and map the processes required to improve these, (5) establish the requirements for a global IBM registry, and (6) to scope the work required for the establishment of standards of care for IBM.

The workshop was attended by 24 representatives from UK, France, Germany, Belgium, Netherlands, Sweden, Denmark, Australia and USA. Participants included neurologists, rheumatologists, physiotherapists, industry representatives and patient representatives.

2. Diagnostic criteria

David Hilton-Jones led review and discussion of the diagnostic criteria for IBM. As we do not know the cause or primary pathogenic mechanisms of IBM there is no “gold standard” for diagnosis. The original IBM diagnostic criteria proposed by Griggs et al. [3] were primarily a pathological definition. Indeed in the Griggs’ criteria “definite IBM” was defined on histological features with no reference to the clinical features. When all of the major pathological features (partial invasion, vacuoles, amyloid deposition and tubulofilaments) are present, the diagnosis of IBM is secure, but extensive clinical experience since 1995 indicates that often in cases in which long-term review supports the diagnosis of IBM one or more of these pathological features may be absent from the first and even subsequent biopsies [4]. It is possible that some of the pathological features may only appear later in the course of the disease, and that adherence to them will exclude patients earlier in the course of the disease, when they may be more likely to respond to therapeutic intervention. Earlier ENMC diagnostic criteria addressed some of these issues, with respect to both clinical and pathological features [5].

Moreover, since 1995 there have been further pathological developments, notably (a) new methods for the identification of abnormal protein aggregates, and (b) the use of MHC I up-regulation as a surrogate marker of inflammation. Thus, even the purely pathological criteria for the diagnosis of IBM require revision. Furthermore, although the Griggs’ criteria did allow clinical features to make a diagnosis of “possible IBM”, this required weakness affecting both proximal and distal upper limb. In reality, as proximal upper limb weakness is a very late feature, this made a clinical diagnosis in the early stages of IBM problematic.

As well as making practical diagnosis of early IBM difficult, the existing criteria were liable to disallow the recruitment of early cases of IBM into clinical trials potentially meaning that such trials might miss an optimal therapeutic window that might only exist in the early stages of IBM. Since the publication of the Griggs criteria we have acquired a very extensive clinical experience of the presentation and evolution of IBM that can now permit a switch to a new set of diagnostic criteria emphasising clinical phenotype rather than pathology.
Clinical experience has shown that there is a highly characteristic pattern of weakness in IBM, with selective involvement of long finger flexors and quadriceps, and that this may occur in the absence of the original, "essential", Griggs pathological criteria. The absence of certain pathological findings might be due to biopsy sampling error or because some of the pathological changes appear only late in the disease if at all. The latter certainly seems the case as demonstrated by the natural history studies (see below).

We therefore discussed revision of the IBM diagnostic criteria and the following changes were highlighted.

For “Clinico-pathologically defined IBM” it was agreed that, unlike the original Griggs criteria, there should be the additional stipulation of an acceptable clinical picture.

The age at onset was increased to 45. All agreed that presentation could occur before that age, but was extremely rare and that raising the age would help to exclude wrong diagnoses without significantly limiting the number of patients eligible for clinical trials.

With respect to the original proposal that knee extensors should be weaker than hip flexors, it was noted that not infrequently there was roughly equal weakness of both. It was felt that this pattern of weakness was still highly suggestive of IBM as in most other myopathies, including polymyositis, hip flexion was always weaker than knee extension.

All agreed that EMG was not useful in confirming or excluding the diagnosis of IBM and it was therefore omitted from the diagnostic criteria.

There was debate about the significance, or otherwise, of the serum CK activity. The issues discussed included the following:

- A CK >15 times the upper limit of normal (ULN) is rare in IBM and should prompt a search for an additional cause or an alternative diagnosis to IBM.

- While genuine cases of IBM with CK >15 times ULN may represent outliers that would confound a clinical trial equally it is possible that such patients have more aggressive disease that might be more sensitive to therapeutic intervention, and should not be excluded from trials.

We therefore agreed that for the purposes of these research criteria to use a criterion of “no higher than 15 times the upper limit of normal” which would include the vast majority of patients with IBM and thus not limit numbers for entry into a clinical trial.

The revised ENMC IBM diagnostic criteria proposed by this workshop are hereby presented and should be referred to as the “ENMC IBM Research Diagnostic Criteria 2011” (Table 1) (See addendum).

3. Immunological studies

Olivier Benveniste reviewed the evidence of amyloid and phosphorylated tau deposits in certain muscle fibres of IBM patients and the arguments for protein degradation dysfunctions (at both, proteasome and autophagy levels). From different experiments in mouse models, it appears that the forced over-expression of different kind of proteins, not only amyloids (APP42, gelsolin) but also

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The ENMC IBM research diagnostic criteria 2011.</th>
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<tbody>
<tr>
<td><strong>Clinical and laboratory features</strong></td>
<td><strong>Classification</strong></td>
</tr>
<tr>
<td>Duration &gt;12 months</td>
<td>Clinico-pathologically defined IBM</td>
</tr>
<tr>
<td>Age at onset &gt;45 years</td>
<td>All of the following:</td>
</tr>
<tr>
<td>Knee extension weakness ≥ hip flexion weakness</td>
<td>- Endomysial inflammatory infiltrate</td>
</tr>
<tr>
<td>and/or</td>
<td>- Rimmed vacuoles</td>
</tr>
<tr>
<td>Finger flexion weakness &gt; shoulder abduction weakness</td>
<td>- Protein accumulation or 15–18 nm filaments</td>
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<tr>
<td>sCK no greater than 15×ULN</td>
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<tr>
<td>Duration &gt;12 months</td>
<td>Clinically defined IBM</td>
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<tr>
<td>Age at onset &gt;45 years</td>
<td>One or more, but not all, of:</td>
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<tr>
<td>Knee extension weakness ≥ hip flexion weakness</td>
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<td>sCK no greater than 15×ULN</td>
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<tr>
<td>Duration &gt;12 months</td>
<td>Probable IBM</td>
</tr>
<tr>
<td>Age at onset &gt;45 years</td>
<td>One or more, but not all, of:</td>
</tr>
<tr>
<td>Knee extension weakness ≥ hip flexion weakness</td>
<td>- Endomysial inflammatory infiltrate</td>
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* Demonstration of amyloid or other protein accumulation by established methods (e.g. for amyloid Congo red, crystal violet, thioflavin T/S, for other proteins p62, SMI-31, TDP-43). Current evidence favors p62 in terms of sensitivity and specificity but the literature is limited and further work required.
MHC class I in muscle, leads to muscle weakness, appearance of vacuoles with, in parallel, increase of proteasome and autophagy markers. Occasionally, but not usually, these amyloid deposits are accompanied by inflammatory infiltrates. It seems that, when the protein degradation systems are overloaded, amyloids appear within muscle fibres, e.g. as misfolded and/or ubiquinated protein accumulations. This situation may also exist in patients with a hereditary inclusion body myopathy due to a p97/VCP mutation, i.e. in a complex involved in the regulation of protein degradation through the proteasome and autophagy [6]. The second hallmark of IBM is the presence of inflammatory infiltrates. Evidence of immune reaction was reviewed. Effector cells can be clonally expanded and mostly consist of CD8+, CD28− T cells which can exert cytotoxic activity and are found surrounding or invading muscle fibres. The latter may present so far unknown auto-antigens to these effector cells in a MHC class I restricted manner. MHC class I overexpression at the surface of muscle fibres has become a surrogate marker of inflammation. Most of the immune abnormalities are not only observable in muscle but also in the peripheral blood. Apart from the cellular immune response, auto-antibodies are also described in IBM [7,8]. Regulation mechanisms are present in parallel, such as active regulatory T cells or activation of negative second signal pathways (e.g. the PD-1/PD-L axis). These may counteract, at least in part, the cytotoxic auto-reactivation. Crucial cytokines and chemokines were reviewed in this context, most importantly IFN-γ and IL-1β (see below).

A key question still remaining is whether the amyloid deposits are the cause or consequence of inflammation? If amyloids are a consequence of a primary immune reaction including secretion of cytokines that increased MHC class I expression to such an extent that protein degradation capabilities are overloaded, then a targeted immune intervention (such as by biotherapies) may be useful. If, however, IBM is a degenerative disease, where the accumulation of unfolded proteins causes a secondary immune reaction, an immunointervention may be of limited if any benefit.

Jens Schmidt reviewed recent evidence that supports a distinct interrelationship between inflammatory and degenerative molecules in IBM pathology. In IBM in contrast to other inflammatory myopathies, the precursor molecule of β-amyloid (APP) significantly correlates with the key inflammatory molecules IFN-γ and CXCL-9 [9]. A similar relationship, possibly mediated by the GSK-3β kinase, has been demonstrated in an animal model of the disease [10]. Apart from inflammation, an early cell stress response around αB-crystallin and nitric oxide is present in IBM muscle and may precede accumulation of β-amyloid [9,11]. The cytokines IFN-γ and IL-1β have been demonstrated to be key inducers of accumulation of β-amyloid in muscle cells. Autophagy is present in IBM and serves as a mediator between inflammation and degeneration by contributing to the processing of APP/β-amyloid and, at the same time, by presenting antigens via the MHC class 2 pathway in IBM muscle [12]. Collectively, the pathology of IBM is very complex (see Fig. 1) and improvement of future treatment efforts will only be possible by a better understanding of key mechanisms and how to target these [13].

In attempt to answer this key question, e.g. by looking for the nature of auto-antigens, the ENMC workshop...
proposed a multicentre immunology association study, and an international IBM registry to include data collection for prospective natural history studies and sample collection.

The aims of the immunology study would be to perform:

2. A MHC-I bound peptide elution from IBM muscle followed by mass spectrometry identification and functional test of T cell cytotoxicity.
3. A bank of T cell clones from IBM patients, to test cytotoxicity against:
   a. Antigen identified as targets of auto-Abs.
   b. Autologous myotubes.
   c. Amyloids.

4. Genetic studies

Merrilee Needham reviewed the genetic studies in IBM. Until recently, genetic studies in IBM have been limited to candidate gene studies due to the low incidence of IBM, (with estimates ranging from 1 per million to 14 per million) [14,15]. Using this approach, the immune features of IBM have prompted studies of the Major Histocompatibility Complex (MHC). These have discovered a susceptibility region in the 8.1 ancestral haplotype in a 172 Kb region near the HLA-DRB1*0301 (HLA-DR3) allele. This region contains 3 genes; BTNL2, HLA-DRA and HLA-DRB3 [16]. Further studies are ongoing to identify the susceptibility gene. However it is possible that epistatic interactions at this site are important in determining susceptibility, as it appears that the HLA-DR1/DR3 combination is a higher risk for developing disease than HLA-DR3 homozygotes [17].

Other candidate gene studies investigating the genes encoding some of the proteins that are deposited in IBM muscle including Amyloid Precursor Protein [18], prion protein, [19] TDP43, [20] alpha-1-antichymotrypsin [21] and apolipoprotein E [21–25] have thus far been negative. In addition, screening of other genes that cause ‘inclusion body myopathies’ including GNE, [26] VCP and the known myofibrillar genes [27] have also been negative in IBM.

Due to increasing collaboration between IBM investigators and improvements in technology, it has become possible to consider more robust genetic techniques such as whole exome/genome screening looking for other susceptibility or causative genes. Michael Hanna is currently recruiting for an exome screening project in IBM patients. This project will initially require DNA samples from around 200 individuals who are diagnosed with definite IBM. A suitable, preferably age and sex-matched control group, is also required. Any initial results of this study will need to be confirmed in a larger cohort of around 700 definite IBM patients, and gathering this number of subjects will require international collaboration. The possibility of clinicians with an interest and expertise in IBM contributing to both DNA and serum (for immunology studies) banks was discussed.

It is possible that, as in the case of other neurodegenerative disorders such as, Alzheimer’s Disease and Parkinson’s Disease, susceptibility to IBM is polygenic with multiple HLA and non-HLA genes making small individual contributions. However, there are many questions that remain unanswered. For example, are there environmental risk factors that have not yet been identified, and how might these be identified? The European Myositis Network is aiming to help answer this question (http://www.eumyonet.org/). The prevalence of IBM in different populations and ethnic groups, may provide clues to the aetiopathogenesis and the relative importance of genetic versus environmental factors. It is possible that there are some IBM cases with a monogenic cause as there are a few reports of IBM occurring within families [28–31].

Therefore additional studies looking at families with more than one affected member would also be useful.

5. Registries

Maggie Walter led a discussion on patient registries. These have been already proven to be useful tools to overcome fragmentation and to facilitate research in disease epidemiology, genotype-phenotype correlation, and natural history studies. They are also valuable for monitoring standards of care and greatly facilitate feasibility studies for clinical trials and recruitment into clinical trials. Currently there are European and global effort to set up patient registries for Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). Within the Network of Excellence TREAT-NMD, national registries for DMD and SMA collect data in a harmonized way and contribute them to a European meta-database. These databases provide a useful model for how an IBM global registry should be organised. Currently there are a number of local IBM registries but these collect differing types of data by a variety of means and are not generally available to the research community as a whole. Harmonisation of IBM registries as has been done for DMD and SMA would certainly be beneficial. In contrast to some muscle disease registries where eligibility for entry to the registry can be gene based the eligibility for IBM patients would have to be based on histopathology and specific clinical findings although in the future possible underlying genetic defects may be identified that can assist with eligibility.

The workshop agreed the need for concerted action towards setting up an international registry for IBM and participants volunteered to help set up the registry. The elements required for a global registry for IBM were discussed and a steering committee consisting of Ingrid Lundberg, Umesh Badrising, Jan de Bleecker, and James
Miller agreed to establish the requirements for a global IBM registry and work towards its implementation. We agreed upon harmonizing existing databases and decided for a web-based patient self-report system along with professional report. As a primary goal, we decided to focus the IBM registries for the tasks of trial readiness, along with natural history and epidemiology. It was felt that a future workshop dedicated solely to IBM registry planning would be the next step and discussions to set up such a workshop are on-going.

6. Natural history

Natural history studies are important in helping with clinical trials planning and the selection of the best measures of disease progression of IBM. Michael Hanna and James Miller presented data from their on-going prospective observational natural history studies in IBM. At the time of this workshop Michael Hanna’s group had enrolled 51 participants and there was one year follow up data on 21 subjects. Entry criteria included Griggs criteria or MRC 2008 criteria [2,32]. Although there have been previous studies describing the clinical features and progression of the disease most have been undertaken retrospectively or at a single time point [33–37] and only a few have prospectively followed-up the progression of the disease [38–40]. This study showed that most patients showed a typical onset but atypical presentations in this cohort included falls (25%), mild dysphagia (7%) and myalgia (7%). Mean delay to diagnosis was 4 years and almost 50% of cases were initially misdiagnosed with polymyositis, peripheral neuropathy and motor neuron disease. The latter two misdiagnoses are probably explained by seemingly neurogenic findings on electromyography (EMG) commonly found in IBM. The fact that a neuropathy can be found in over 20% of cases can also confound the diagnosis of IBM [37]. Asymmetry of symptoms was common both at onset and during progression, but the difference of strength between the two sides, as detected by MMT, was within normal range for the general population [41]. Mild dysphagia was common and was present in about half of the patients in this cohort. Sixty percent of this cohort did not show vacuolated fibres, amyloid or 15–18 nm tubulo-filaments on the muscle biopsy required to fulfill the Griggs criteria for definite or probable IBM [32,42]. However they did not differ in terms of clinical presentation and progression of disease from the group of patients with a pathologically definite diagnosis. This observation emphasises the need for revised diagnostic criteria as discussed by this workshop. This study examined retrospectively the different treatments given for IBM in this cohort and it was apparent that a wide variety of medical interventions were employed, including prednisolone and steroid sparing drugs such as azathioprine and methotrexate. Although the study was not powered to detect changes in disease progression depending on treatment, we did not observe any association between previous or current treatment and disease progression. This parallels observations in a recent large follow-up study [38]. The prevalence of autoimmune diseases in this cohort was higher compared to that in the general population, at 15.6% versus 3%, respectively [43]. Although this may have resulted from a casual association, the data could also arguably be interpreted as evidence for the role of a dysregulated immune-system in the pathogenesis of the disease [44]. This study further confirmed IBM as a disabling disease. Sixty-three per cent of patients could not ambulate independently after a median time of 7 years after symptom onset, and the majority were either using a walking stick or had used one before becoming more dependent. The mean duration of disease until using a wheelchair was 15 years, which is in keeping with previous reports [38,45]. This study found that older age at disease onset was the only factor significantly associated with starting to use a walking stick. Testing different cut-off values for age at disease onset found that subjects with onset after 55 years had the higher risk of losing their walking independence compared to those with an earlier disease onset. This confirms previous studies of IBM which have reported a shorter time to using a walking frame [46] or becoming wheelchair reliant [45] in those subjects with disease onset after 60 years. However contrary to previous studies that suggested male gender and previous treatment with steroids or immunosuppressant drugs might be associated with modestly exacerbated progression of disability [45] neither gender nor previous treatment appeared to influence prognosis in the Hanna cohort. In this study the mean yearly rate of decrease of compound MMT was 5.2%, which is intermediate between the rates of decline reported by previous studies [37–40] ranging from 3.5% to 14.9%.

James Miller presented preliminary natural history data from a cohort of 47 patients with IBM in the North-East of England. Isometric strength from 8 muscle groups was measured in 15 untreated patients using hand-held dynamometry at 6 monthly intervals over a minimum of 2 years (mean 3.5 years) and the percentage change from the initial baseline for each was calculated and averaged. The average annual percentage decline from baseline was 6% for this summed myometry in agreement with previously reported estimates. Notably there was a wide range (0–17%) and patients could be separated into slow or fast rates of progression on the basis of an arbitrary cut-off of 8%. 11 patients in the slower progression group had a mean of 3% annual progression whereas the 4 patients in the faster group deteriorated by a mean of 15% in summed myometry per year. Recognition of sub-groups of patients with distinct prognoses is crucial for the design of future clinical trials and interpretation.
of genetic studies and an important objective for natural history registries in IBM.

7. Clinical trial protocols and outcome measures

Anthony Amato, Linda Lowes, Michael Rose and Farah Seedat discussed protocols used for clinical trials in IBM and studies on the performance of outcome measures used in IBM studies. The outcome measures used in IBM were collated from the few published randomized, blinded, placebo-controlled trials in IBM [47] and from a pre workshop survey of all the participants (Table 2).

Pathology measures included muscle biopsy analysis of inflammation and attempted estimation of the levels of accumulated proteins [48,49]. These measures and various serum biochemical measures were usually relevant to the putative mechanism of the drug being tested in a proof of concept trial e.g. neopterin levels as a marker for interferon beta activity [50]. Impairment measures were related to assessment of muscle mass and strength. Muscle mass has been measured with urinary creatine excretion, CT or MRI imaging methods, or DEXA scanning. DEXA scanning which can measure lean body mass as a surrogate for muscle mass has the potential of being relatively cheap, simple to use and readily available which would be an advantage for multi-centre trials. Data kindly supplied by Rabi Tawil showed that it had good correlation with gold standard muscle mass assessment with whole body potassium counting. DEXA determination of regional limb muscle mass, eliminating some of noise from measurement of the trunk, will likely give more reliable measures of muscle mass. There is good correlation between DEXA whole body and DEXA limb values with muscle strength demonstrated for facioscapulohumeral muscular dystrophy (FSHD) and Duchenne Muscular Dystrophy (MDM) [51,52]. In normal subjects increases in lean body mass of less than 5% correlated significantly with changes in strength. For DMD slope of strength to muscle mass is very divergent from normal controls perhaps reflecting the intrinsic dysfunction of the DMD fibres compared to those of FSHD where the slope is closer to that of normal individuals. These differences suggest more mass needs to be gained in DMD than in FSHD to achieve the same gain in strength. Thus the relationships between DEXA lean body mass and muscle strength and its response to treatment would need to be established for IBM perhaps focusing on the thigh and forearm muscles. MRI scanning estimation of muscle mass has the advantage that the same scan may give useful information on the extent of inflammation and fibrosis as well as volumetric information. The workshop noted that MRI of muscle was an outcome measure for the as yet unpublished IBM trial being run by Novartis (ClinicalTrials.gov Identifier: NCT01423110). The attraction of muscle mass assessment might be in its relative ease of assessment and the fact that it might pick up first signs of treatment effect perhaps before improvement in muscle strength is seen. This might be particularly relevant for phase 2 (proof of concept) trials.

For MMT there is no consensus on which muscles were tested and the use of expanded MRC scores in an attempt to produce an ordinal scale meant that MRC scales vary between studies with some using the original 6 point scale and others using expanded scales with up to 11 points. Conversion of MRC scales to numerical values for example with a 4+ grade converted to a 4.33 and a

Table 2

<table>
<thead>
<tr>
<th>Clinical outcome measures reported in randomized, blinded, placebo-controlled clinical trials in IBM.</th>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>Dalakas et al. [67]</td>
</tr>
<tr>
<td>Walter et al. [68]</td>
</tr>
<tr>
<td>Muscle Study Group [50, 57]</td>
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<tr>
<td>Dalakas et al. [49]</td>
</tr>
<tr>
<td>Rutkove [69]</td>
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<tr>
<td>Badrising [70]</td>
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On-going or recently completed studies that are as yet unpublished

**Novartis (BYM338) trial (not published but outcomes available on clinicaltrials.gov)**

<table>
<thead>
<tr>
<th>Outcome measures utilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT, MVICT, grip strength, pinch strength, timed up and go, timed stair climb, 2 and 6 MWT, SF-36, pre- and post-treatment muscle biopsies</td>
</tr>
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</table>

**Arimoclomol trial (not published but outcomes available on clinicaltrials.gov)**

<table>
<thead>
<tr>
<th>Outcome measures utilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT, MVICT, IBMFRS, pre- and post-treatment muscle biopsies</td>
</tr>
</tbody>
</table>

MMT = manual muscle testing, MRC = Medical Research Council, QMT = quantitative muscle testing, MVICT = maximal voluntary isometric contraction testing, MWT = minute walk test, ALSFRS = amyotrophic lateral sclerosis functional rating scale, IBMFRS = inclusion body myositis functional rating scale, CK = creatine kinase.
4grade converted to a 3.67 in one study while another converts a 4+ grade to 8 and a 4− as a 6. Even with these various conversions, the numbers so obtained cannot be assumed to be an interval scale. The workshop suggested that Rasch analysis of MMT data from various trials and on-going natural history studies might allow us to rationalise the muscles tested and the MRC scale to be used. Such an approach has been utilised for MMT used in peripheral nerve disease [53].

Quantitative muscle testing (QMT) may have the advantage of producing absolute strength values. However the equipment can be expensive. Some studies assessing QMT employed hand-held dynamometry, while others used fixed maximal voluntary isometric contraction testing (MVICT). Further, some studies measured kilograms or dynes, while other looked at conversion to percentage of predicted norm and then to a Z-score (average of the standard deviation from normal of the muscle groups studied). The latter is probably most accurate as it allows the use of parametric statistics. In this regard, the Muscle Study Group collected data from 57 IBM subjects enrolled in their two Avonex trials and results suggest that the mean (SD) of the 6-month change was −0.28 (0.88) units for the composite MVICT score and −0.04 (0.19) units for the average MMT score. These values can be used to calculate sample sizes for future IBM trials. Pre-publication data was presented (some since published) that suggests that QMT of just the quadriceps muscle may be the most relevant, and perhaps only, measure required. Lowes presented data comparing MVICT with a battery of functional outcomes in 85 ambulatory subjects with IBM. This showed that marked quadriceps weakness was noted in all patients. Strength was correlated with distance walked at 2 and 6 min. Additional correlations were found with time to get up from a chair, climb stairs, and step up on curbs [54].

Olivier Benveniste presented data that patient strength correlated with the disease duration only for knee extension, which was also the only muscle function to change significantly over 9 months [55]. Hanna’s natural history data showed that there was a 27.9% fall in quadriceps power measured by QMT which was over twice that found (12.2%) by MMT assessment. These data indicate QMT quadriceps may be suitable as an outcome measure in IBM studies. It was suggested that some equipment specifically designed for quadriceps testing might increase sensitivity of this measure but the high costs, as well as the need for the evaluator to be trained, could restrict its use to a limited number of centres.

Functional rating scales and tests for IBM were discussed. As for other categories of outcome measures there is a diversity of measures that have been used in IBM and consensus as to which to use is clearly needed. Farah Seedat presented an on-going review of functional rating scales used for adult muscle disease. A total of 119 such scales have been identified with the content of 28 analysed and the performance of 19 scales assessed. Such information should provide the basis for a future impartial and informed choice of functional rating scale for IBM. The workshop discussed the IBM Functional Rating Scale (IBMFRS) which was developed as a functional rating scale by modification of the ALSFRS used in ALS clinical trials [56]. When used by the Muscle Study Group in an IBM clinical trial the IBMFRS was the most sensitive measure of change over the course of the study [57]. In the natural history study presented by Hanna there was 13.8% reduction in the IBMFRS score making it a more sensitive a measure than MMT. Assessed for quality by Farah Seedat’s assessment project the IBMFRS has published data on convergent and discriminant validity and on responsiveness but lacks quality published data on content and face validity, criterion validity, interpretability and reliability.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>sIBM weakness composite index (IWCI)</th>
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<tbody>
<tr>
<td><strong>Arms outstretched forwards</strong></td>
<td></td>
</tr>
<tr>
<td>150 s</td>
<td>15</td>
</tr>
<tr>
<td>100 s</td>
<td>10</td>
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<tr>
<td>50 s</td>
<td>5</td>
</tr>
<tr>
<td>&lt;50 s</td>
<td>0</td>
</tr>
<tr>
<td><strong>Legs held outstretched at 45 deg supine</strong></td>
<td></td>
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<tr>
<td>75 s</td>
<td>15</td>
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<tr>
<td>50 s</td>
<td>10</td>
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<td>25 s</td>
<td>5</td>
</tr>
<tr>
<td>&lt;25 s</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neck flexors, lying in bed</strong></td>
<td></td>
</tr>
<tr>
<td>Against resistance</td>
<td>10</td>
</tr>
<tr>
<td>Without resistance</td>
<td>5</td>
</tr>
<tr>
<td>Impossible</td>
<td>0</td>
</tr>
<tr>
<td><strong>From lying in bed to standing</strong></td>
<td></td>
</tr>
<tr>
<td>Without support</td>
<td>10</td>
</tr>
<tr>
<td>With support</td>
<td>5</td>
</tr>
<tr>
<td>Impossible</td>
<td>0</td>
</tr>
<tr>
<td><strong>Walk</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td>With cane(s) or walker</td>
<td>5</td>
</tr>
<tr>
<td>Impossible (wheelchair)</td>
<td>0</td>
</tr>
<tr>
<td><strong>From sitting position in a chair to standing</strong></td>
<td></td>
</tr>
<tr>
<td>Without support</td>
<td>10</td>
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<tr>
<td>With support</td>
<td>5</td>
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<tr>
<td>Impossible</td>
<td>0</td>
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<tr>
<td><strong>Force of finger flexors</strong></td>
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<tr>
<td>Normal strength (MRC: 5/5)</td>
<td>10</td>
</tr>
<tr>
<td>Slight weakness (MRC: 3 or 4)</td>
<td>5</td>
</tr>
<tr>
<td>Paralysis or severe weakness (MRC: 0, 1 or 2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Force of the quadriceps</strong></td>
<td></td>
</tr>
<tr>
<td>Normal strength (MRC: 5/5)</td>
<td>10</td>
</tr>
<tr>
<td>Slight weakness (MRC: 3 or 4)</td>
<td>5</td>
</tr>
<tr>
<td>Paralysis or severe weakness (MRC: 0, 1 or 2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Swallowing</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td>Moderate or intermittent difficulties</td>
<td>5</td>
</tr>
<tr>
<td>Severe or permanent difficulties</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>/100</td>
</tr>
</tbody>
</table>
Published data on the performance of the IBMFRS is limited to a single paper with just 30 subjects studied. This workshop however highlighted that there is more IBMFRS data available for further analysis of the IBMFRS. The workshop also suggested that a Rasch analysis of the IBMFRS data would be needed to allow for use as a primary outcome measure to get a new drug approved by drug regulatory agencies.

Olivier Benveniste and David Hilton-Jones presented the development of a composite measure for IBM severity resulting from their observational study on 136 IBM patients [58]. This IBM Weakness Composite Index (IWCI) is a 9 item scale combining evaluation of hand flexor and quadriceps strength as normal slight or severe, with the timed functional assessment of limb girdle, axial weakness, walking and swallowing (Table 3). The IWCI has a maximal score of 100 which decreases with increasing handicap for walking: for patients who did not need any walking aids, the median IWCI was 80, compared to 45, and 30 for patients who walked with aids, and those who needed a wheelchair, respectively. IWCI was negatively correlated with duration of sIBM evolution since first symptoms (correlation coefficient: \( p < 0.001 \)). IWCI has been compared to other outcomes including MMT, QMT, IBMFRS, and 6 min. walk test with a significant correlation found between IWCA and the whole strength composite QMT total score index and functional tests. IWCA and IBMFRS were also significantly correlated with most of the muscle functions tested, with a better correlation with upper limb muscle functions.

The USA Food and Drug Administration (FDA) has advocated for the use of Patient Reported Outcomes. Published IBM studies have used the SF 36 a generic quality of life measure but data is available using a muscle disease specific quality of life measure (INQoL) that could be individually analysed to test its performance with IBM [59,60].

8. Standards of care

Discussion on standards of care was led by Thomas Sejersen. The relative rarity of IBM outside of specialist muscle clinics and the variation of practice even amongst IBM experts means that care standards differ not only between individual countries but also within them. This situation weakens the call for adequate healthcare resources for those with IBM. Variations in clinical outcomes that arise from variable standards of care are also likely to compromise the valid measurement of treatment effects during clinical trial studies. Therefore having an internationally agreed best practice guideline for IBM can dramatically improve patients’ quality of life and possibly even prolong life expectancy. By producing a consensus best practice guideline agreed by doctors and patient groups across the world, it is possible to improve the care of those with IBM and make high quality care more widespread across the world. In addition an internationally agreed best practice guideline will reduce variations in diagnosis and care between different sites involved in clinical trials for IBM, thus increasing the likelihood of appropriate statistical power for the clinical trials. The workshop discussed the subject areas to which standards of care could apply.

Considering that there can be a delay in the diagnosis of IBM of up to 8 years, a best practice guideline for the diagnosis of IBM would be helpful in reducing such delay, which works to the detriment of those with IBM who often do not get access to appropriate help until a diagnosis is reached [61]. The diagnostic criteria as discussed above are primarily aimed at the selection of patients for clinical trials. There are issues that arise in the diagnosis of IBM in clinical practice that are not addressed by such research-based criteria. These include the status of the more unusual clinical presentations of IBM and the extent to which other diagnostic modalities such as muscle MRI scans can contribute to clinical diagnosis.

A Cochrane systematic review of randomised controlled trials of treatment for IBM concluded that there was insufficient evidence for the efficacy of any of the drug interventions tried for IBM [47]. The absence of definitively proven treatment means that there exists a variation in the treatment of IBM. Some clinicians, for example, feel that a trial of steroid treatment should be given in certain circumstances or that methotrexate may help. Others feel that there may be situations such as dysphagia causing nutritional impairment where treatment with expensive intravenous immunoglobulin may be helpful. A standard of care document needs to address these variations in treatments offered for IBM. In the absence of definitive treatments, the main stay of IBM care is supportive management. Health professionals looking after those with IBM would find guidelines for supportive management, such as the use of orthotics, adaptive devices and exercises, helpful. The role of the allied health professionals such as physiotherapists, occupational therapists and speech and swallowing therapists would benefit from clear guidance, especially because IBM would not be a condition that they often encounter.

There is a well-recognised methodology for the creation of best practice guidelines [62,63]. Neurological organisations and national bodies have also published their processes for agreeing guidelines of various sorts [64–66]. All these methodology guidelines stress several important key factors that will contribute to success in formulating a best clinical practice guideline and equally importantly ensuring its implementation. Key aspects include (1) the involvement of an appropriately multidisciplinary group, (2) systematic review of the evidence, and (3) linking guidelines to evidence. As the evidence base for the recommendations made in this guideline will vary it is important that the level of evidence for each recommendation is explicitly stated and that this is then linked to the grade of recommendation. As well as the clinician orientated best practice guideline document, a ‘patient friendly’ guide would also be invaluable, written in
a style that is more accessible to those without a medical background. This will empower those with IBM to ensure that they recognise and seek the best standard of care that they require. The proposed IBM best practice guideline will also be a valuable tool for lobbying at a national level to enable incorporation of these recommendations into national health systems. The best practice guideline will represent a real international consensus document including both the medical and the patient advocacy perspectives that can be used across the world as a powerful tool to recognize those centres where best is already in place and to identify gaps in care. Linked to the best practice guideline document will be suggestions for measurable outcomes that allow the monitoring of the standard of care actually delivered to those with IBM. Such measurable outcomes will be powerful information that commissioners can use to agree allocation of healthcare resources and in agreeing service level agreements for the delivery of best care to those with IBM.

This workshop therefore agreed 5 potential sections for an IBM best practice guideline, discussed the topics that might fall within each section and assigned members to working parties for each section. These are as follows:

8.1. Diagnosis

Lead – David Hilton-Jones
Participants so far – Marianne De Visser, James Miller, Merrilee Needham, Ingrid Lundberg, Jan De Bleecker, Jens Schmidt, Umesh Badrising

Potential topics anticipated to include:

- The application of the published diagnostic criteria to clinical practice.
- The need for a muscle biopsy in making the diagnosis of IBM.
- Which muscles should be used for any diagnostic biopsy.
- What muscle pathology tests should be performed.
- What might be the role of MRI scan of muscles, CK activity and neurophysiology studies in making a diagnosis and how should these be performed.
- The atypical and monosymptomatic presentations that can arise in IBM.

8.2. Neurology – drug treatment

Lead – Jens Schmidt
Participants so far – Ingrid Lundberg, Olivier Benveniste, Richard Leff, Anthony Amato, Michael Hanna

Potential topics anticipated to include:

- The application of the results of the Cochrane systematic review of IBM treatment to clinical practice.
- Role of steroids, IVIG, and other treatments that could be used despite negative results of clinical trials.
- Recommendation for the use of statins in view of its potential muscle toxicity.

8.3. Physical and practical management

Lead – Liz Dewar
Participants so far – Marianne De Visser, James Miller, Merrilee Needham, Ingrid Lundberg, Jan De Bleecker, Jens Schmidt, Umesh Badrising

Potential topics anticipated to include:

- Falls management.
- The role of orthotics.
- The role of exercise.

8.4. Respiration, nutrition, cardiac management

Lead – Umesh Badrising
Participants so far – Arno Olthoff (ENT-specialist)

Potential topics anticipated to include:

- The detection and management of dysphagia, Weight loss management.
- Perhaps liaising with the respiratory section on aspiration management.
- The relevance, or otherwise, of cardiac complication of IBM and whether, or to what extent, cardiac surveillance is required.

8.5. ‘Living with IBM’

Leads – Michael Rose and Martin Taylor (patient representative)
Participants so far – Baziel van Engelen, Martin Taylor, Tony Hindle

Potential topics anticipated to include:

- Psychosocial factors influencing QoL and how they can be modified.
- Pain and fatigue management.
- Advising on prognosis, survival, morbidity, and mortality.
- End of life issues.
The workshop emphasised that these sections and suggested topics within them were not definitive. It was also clearly stated that the aim of the project was to be inclusive and we would therefore encourage other participants to join in this enterprise. Since the workshop we are pleased to announce that AFM have agreed to fund this project. Interested parties are urged to contact Dr. Rose for further information.

9. Future projects

- Rasch analysis of IBMFRS.
- Rasch analysis of MMT data in IBM.
- Workshop on IBM registries.
- Project grant for setting Standards of Care for IBM.

10. Conclusion

The workshop set out to review and scope the work done and required for clinical trials readiness in IBM. The proposed new diagnostic criteria should enlarge the potential pool of IBM recruits and allow recruitment of cases at a stage when treatment might be more effective. There is a need for harmonisation of IBM registries as an aid to IBM recruitment as well as helping in the selection of outcome measures and identification of sub-groups of those with IBM that may more treatment responsive. It seems that phase 2 (proof of concept) trials that are usually confined to a small number of trial centres might use sensitive QMT assessment of quadriceps as an early indication of treatment effect. Larger phase 3 trials might emphasise functional rating scales or composite measures but more work is needed before any particular one could be an adopted choice.

11. List of participants

- Anthony A. Amato; Harvard Medical School, Boston, Massachusetts, USA.
- Baziel van Engelen; Nijmegen Neuromuscular Centre, The Netherlands.
- Brian Tseng; Novartis Pharmaceuticals Corporation, New Jersey, USA.
- Christina Buccirechtweg; Novartis Pharmaceuticals Corporation, New Jersey, USA.
- David Hilton Jones; John Radcliffe Hospital, Oxford, UK.
- Farah Seedat; Kings College Hospital, London, UK.
- Ingrid E. Lundberg; Karolinska University Hospital, Sweden.
- James Miller Royal Victoria Infirmary, Newcastle Upon Tyne, UK.
- Jan De Bleecker; Universitair Ziekenhuis Gent, Gent, Belgium.
- Jens Schmidt; University Medical Centre, Germany.
- John Vissing; University of Copenhagen, Denmark.
- Linda Lowes; Nationwide Children’s Hospital, Columbus, Ohio, USA.
- Liz Dewar; Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK.
- Maggie C. Walter; Friedrich-Baur-Institute, Dept. of Neurology, Ludwig-Maximilian, University of Munich, Germany.
- Marianne de Visser; Academic Medical Centre, Amsterdam, The Netherlands.
- Martin Taylor; Patient representative.
- Merrilee Needham; Neuromuscular Research Institute and Dept. of Neurology, Australia.
- Michael Hanna; Institute of Neurology and National Hospital for Neurology and Neurosurgery, UK.
- Michael Rose; Kings College Hospital, London, UK.
- Olivier Benveniste; Centre de Référence des Pathologies Neuromusculaires Paris France.
- Richard Leff; Chadds Ford, Pennsylvania, USA.
- Thomas Sejersen; Karolinska University Hospital, Sweden.
- Tony Hindle; representative Myositis Support Group UK; www.myositis.org.uk
- Umesh Badrising; Leiden University Medical Center, Leiden, The Netherlands.
- Rabi Tawil (in absentia); University of Rochester, New York, USA.

Acknowledgements

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Addendum

Since the workshop, two groups have recently, and simultaneously, reported that as many as two-thirds of patients with IBM have autoantibodies directed against cytosolic 5’-nucleotidase IA (cN-IA), whereas their prevalence in dermatomyositis, polymyositis, and other neuromuscular disorders is much less\(^2\). This may serve


as a useful diagnostic test, and early review of the current proposed diagnostic criteria (Table 1) is now required. Indeed, this emphasizes that until the cause of IBM is determined, there will need to be continuing review of diagnostic criteria as new insights develop.

References