IBM: 
*Clinical Features and Progression*

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Overview of Inclusion Body Myositis

• Clinical features
• Diagnostic tests: how can they help vs be misleading?
• Treatment trials
• Progression/Management
Clinical Features
Clinical Features of IBM

• Most common acquired myopathy > age of 50 years

• Slow progressive muscle disease
  • Atrophy and asymmetric weakness
  • Predominantly affecting finger flexors, hip flexors, and knee extensors

• Males > Females

• Autoimmune vs neurodegenerative (or both?)
Leg Weakness: Slow progressive in IBM

• Falls
• Gait difficulty
• Arising from low seated position
• Difficulty climbing stairs
• Foot drop (dorsiflexion weakness)
• Knee buckling (quadriceps)
Grip weakness in IBM

- Grip difficulty
- Opening jars
- Manipulating keys
- Writing
- Carrying objects
- Upper arm weakness over time
Swallowing difficulty in IBM

• Frequent, embarrassing and potentially dangerous
• Initially, describe a “stuck” sensation when swallowing
• Unintended weight loss
• Higher incidence of Aspiration pneumonia
• Prevalence ranging from 40-80%
Diagnostic Evaluation
Diagnostic studies: How these tests may be helpful vs misleading in IBM?

- Muscle Enzymes (Creatine Kinase)
- Nerve conduction/Needle EMG studies
- Muscle biopsy
- Antibodies
- Muscle MRI
Creatine Kinase levels

- Normal to Moderate Elevation in many
- If Normal
  - May not think of muscle diseases
- If Markedly elevated in some (>1000 U/L)
  - May think of polymyositis or a muscular dystrophy

Table 7 Retrospective studies on the natural history of sporadic IBM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Male (%)</th>
<th>Age at onset (years)</th>
<th>Age at diagnosis (years)</th>
<th>Creatine kinase level (IU/L)</th>
<th>Patients receiving immunosuppressors (%)</th>
<th>Progression despite therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringel et al., 1987</td>
<td>19</td>
<td>79</td>
<td>57.8</td>
<td>62.9</td>
<td>197</td>
<td>72.5</td>
<td>80.2</td>
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<td>Lotz et al., 1989</td>
<td>40</td>
<td>72.5</td>
<td>56.1</td>
<td>62.4</td>
<td>1145</td>
<td>97.5</td>
<td>46.4</td>
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<td>Sayers et al., 1992</td>
<td>32</td>
<td>62.5</td>
<td>58</td>
<td>61</td>
<td>279</td>
<td>97.5</td>
<td>93.75</td>
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<tr>
<td>Beyenburg et al., 1993</td>
<td>36</td>
<td>58.3</td>
<td>47</td>
<td>53.1</td>
<td>698</td>
<td>98.8</td>
<td>75</td>
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<td>Lindberg et al., 1994</td>
<td>18</td>
<td>55.5</td>
<td>60.4</td>
<td>62.7</td>
<td>444</td>
<td>73.3</td>
<td>100</td>
</tr>
<tr>
<td>Amato et al., 1996</td>
<td>15</td>
<td>86.6</td>
<td>58</td>
<td>64</td>
<td>417</td>
<td>49</td>
<td>100</td>
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<td>Peng et al., 2000</td>
<td>78</td>
<td>78.2</td>
<td>56.5</td>
<td></td>
<td>267</td>
<td>35.9</td>
<td>82.6</td>
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<tr>
<td>Felice and North, 2001</td>
<td>35</td>
<td>65.7</td>
<td>64.3</td>
<td>70</td>
<td>444</td>
<td>49</td>
<td>100</td>
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<tr>
<td>Badrising et al., 2005</td>
<td>64</td>
<td>67.2</td>
<td>57.6</td>
<td>66</td>
<td>417</td>
<td>35.9</td>
<td>82.6</td>
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<tr>
<td>Present study 2011</td>
<td>136</td>
<td>57.3</td>
<td>61</td>
<td>66</td>
<td>267</td>
<td>52.2</td>
<td>100</td>
</tr>
</tbody>
</table>
Muscle Histopathology in IBM

Karpati made most definitive description:
Neurology 1978 28(1): 8-17

Endomysial inflammation, inflammatory cells surrounding myofibers, invasion of non-necrotic muscle fibers

Variation in fiber size, angular fibers (neurogenic atrophy), fibrosis (chronicity)

Rimmed vacuoles in some fibers- commonly visible on Gomori trichrome- vacuoles contain degraded nuclei and membranous material

Tubulofilamentous inclusions on EM- within nuclei or in clumps in sarcoplasm suggestive of former nuclei devoid of nuclear membrane
No Rimmed Vacuoles, yet Clinical Features of IBM?

<table>
<thead>
<tr>
<th></th>
<th>RVs present</th>
<th>Clinical IBM</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation N (%)</td>
<td>49 (60.5%)</td>
<td>14 (17.3%)</td>
<td>18 (22.2%)</td>
</tr>
<tr>
<td>At follow up N (%)</td>
<td>ND</td>
<td>29 (36%)</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

RV: Rimmed vacuoles (Patients with histopathological diagnosis of IBM with RV)
Clinical IBM: >45 yrs, FF > shoulder abductor and KE ≥ HF weakness
Unclassified: Clinical features of IBM, but not fulfilling all criteria

Nearly 40% of patients had clinical features of IBM, yet no rimmed vacuoles
Blood Biomarker: Anti-NT5c1A Antibody Aids in Diagnosis of IBM

- **Initial reports in 2013:**
  - Sensitivity 60-70%
  - Specificity 83-92%

- **Subsequent reports:**
  - Sensitivity 33-80%
  - Specificity 92-100%

A vacuole with NT5c1a immunoreactivity (Red) lining myonuclei (blue)
Larman HB et al. Ann Neurol 2013

Larman HB et al. Ann Neurol 2013
Pluk et al. Ann Neurol 2013
**NT5C1A Antibody in IBM vs. Autoimmune diseases**

**Cytosolic 5′-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases**

THOMAS E. LLOYD, MD, PhD¹, LISA CHRISTOPHER-STINE, MD, MPH¹, IAGO PINAL-FERNANDEZ, MD, PhD², ELENI TINIAKOU, MD¹, MICHELLE PETRI, MD, MPH¹, ALAN BAER, MD¹, SONYE K. DANOFF, MD, PhD¹, KATHERINE PAK, MD³, LIVIA A. CASCIOLA-ROSEN, PhD¹, and ANDREW L. MAMMEN, MD, PhD⁴

*Arthritis Care Res (Hoboken)*, 2016 January

- Detected in 61% of 117 patients with IBM
- 5% with PM
- In Sjogrens (23%) & SLE (14%)- but no muscle weakness
- **NT5C1A Ab may be helpful in differentiating IBM from PM**
Seropositivity for NT5c1A antibody in sporadic inclusion body myositis predicts more severe motor, bulbar and respiratory involvement

N A Goyal,¹ T M Cash,¹ U Alam,¹ S Enam,¹ P Tierney,¹ N Araujo,¹ F H Mozaffar,¹ A Pestronk,²,³ T Mozaffar¹,⁴

J Neurol Neurosurg Psychiatry 2015;0:1–6. doi:10.1136/jnnp-2014-310008

• 25 sIBM patients enrolled in the study

• NT5C1A antibodies detected in 18/25 subjects (72%)

• May predict more severe phenotype
  • Greater motor deficits (assistive devices)
  • Dysphagia
  • Respiratory insufficiency
Results:

NT5c1A Ab positive IBM patients are significantly more likely to have:

- **Dysphagia**
- **Increased Motor Deficits**
- **Reduced FVCs**

Goyal et al. J Neurol Neurosurg Psychiatry 2015
Cytosolic 5′-nucleotidase 1A autoantibody profile and clinical characteristics in inclusion body myositis

European Retrospective study
N=311

NT5c1A Ab positive patients:
- Increased respiratory events
- Presence of dysphagia
- Facial weakness
- Trend towards mobility aid use
- Higher mortality risk

Median survival of 17.6 yrs (Ab positive) vs 24.2 (Ab negative) group
Muscle Imaging
Muscle Imaging (MRI)

- Easy technique to visualize affected muscles and pattern of muscle involvement
- Detect subclinical changes (prior to detectable weakness on exam)
- May help measure disease progression/activity
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox¹, Monique Reijnierse², Carla S. P. van Rijswijk², Axel R. Wintzen¹, Jan J. Verschuuren¹ and Umesh A. Badrising¹

MRI forearm:
Severe fatty infiltration of Flexor digitorum profundus (FDP)

MRI Upper thigh:
Severe fatty infiltration of Vastus lateralis, relative sparing of rectus femoris and hamstrings
Muscle Imaging MRI- in sIBM especially helpful if mild finger flexor weakness and want to confirm muscle involvement

“Increased T2 signal in medial forearm flexor compartment muscles”
Treatment?/Management in Inclusion body Myositis
Model of Pathomechanisms in IBM

Unclear if primary inflammatory myopathy or primary degenerative myopathy with secondary inflammatory response?
Therapeutic Agents Investigated without Sustained Improvement in IBM

1990s

- **Corticosteroids**
  - Barohn et al. Neurology 1995
- **Methotrexate**
  - Badrising et al. Ann Neurol 2002
- **Azathioprine**
  - Leff et al. Medicine 1993

2000s

- **IVIg**
  - Amato et al. Neurology 1994
  - Dalakas et al. Neurology 1997
  - Walter et al. J Neurol 2000
  - Cherin et al. Neurology 2002
- **Anti-T-lymphocyte globulin treatment**
  - Lindberg et al. Neurology 2003
- **Oxandrolone**
  - Rutkove et al. Neurology 2002
- **βINF1a (Avonex)**
  - MSG Neurology 2001
  - MSG Neurology 2004
- **Etanercept (TNF)**
  - Barohn et al. Neurology 2006

2010s

- **Alemtuzumab (Campath 1-H)**
  - Dalakas et al. Brain 2009
- **Simvastatin**
  - Sancricca et al. Neurol Sci 2011
- **Anakinra (IL1)**
  - Kosmodis et al. J Neurol Sci 2013
Does Treatment with Immunotherapy make sIBM worse in the long run?

Table 5 Comparison of treated and untreated patients with sporadic IBM

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Untreated (n = 65)</th>
<th>Treated (n = 71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (n = 136)</td>
<td>40 (61.5)</td>
<td>38 (53.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Age at first symptoms, years (n = 136)</td>
<td>63 (57–72)</td>
<td>60 (53–65)</td>
<td>0.02</td>
</tr>
<tr>
<td>First symptoms (n = 136)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Muscle weakness and swallowing difficulties</td>
<td>4 (6.1)</td>
<td>7 (10.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Muscle weakness only</td>
<td>59 (90.8)</td>
<td>60 (84.5)</td>
<td></td>
</tr>
<tr>
<td>Swallowing troubles only</td>
<td>2 (3.1)</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Previous diagnosis (n = 136)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>53 (81.5)</td>
<td>41 (57.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>4 (6.1)</td>
<td>19 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (12.3)</td>
<td>11 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Delay between first symptoms and sporadic IBM diagnosis, months</td>
<td>59 (33–86)</td>
<td>58 (25–98)</td>
<td>0.71</td>
</tr>
<tr>
<td>Status at the last visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since sporadic IBM diagnosis, months (n = 136)</td>
<td>18 (3–46)</td>
<td>50 (13–87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, years (n = 136)</td>
<td>73 (66–79)</td>
<td>71 (65–76)</td>
<td>0.21</td>
</tr>
<tr>
<td>Muscle weakness (n = 136)</td>
<td>65 (100)</td>
<td>71 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe proximal weakness(a) (n = 136)</td>
<td>28 (43.1)</td>
<td>36 (52.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Severe distal weakness(a) (n = 136)</td>
<td>25 (38.5)</td>
<td>28 (39.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Swallowing troubles (n = 136)</td>
<td>29 (44.6)</td>
<td>33 (46.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Creatine kinase, IU/l (n = 87)</td>
<td>367 (219–649)</td>
<td>209 (117–559)</td>
<td>0.11</td>
</tr>
<tr>
<td>Grip strength kgN (n = 76)</td>
<td>13.4 (11.0–17.2)</td>
<td>13.5 (9.0–18.0)</td>
<td>0.84</td>
</tr>
<tr>
<td>Walton (n = 113)</td>
<td>4 (3–6)</td>
<td>6 (3–6)</td>
<td>0.007</td>
</tr>
<tr>
<td>RMI (n = 88)</td>
<td>1 (9–13)</td>
<td>10 (4–11)</td>
<td>0.004</td>
</tr>
<tr>
<td>IWCI (n = 71)</td>
<td>50 (30–65)</td>
<td>40 (25–50)</td>
<td>0.04</td>
</tr>
<tr>
<td>Current handicap for walking (n = 136)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20 (30.8)</td>
<td>13 (18.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>One or two canes</td>
<td>26 (40.0)</td>
<td>26 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Wheelchair</td>
<td>19 (29.2)</td>
<td>32 (45.1)</td>
<td></td>
</tr>
</tbody>
</table>

Treated group:
Less independent mobility,
Increased use of wheelchair.
Newer Agents Trialed in IBM
Myostatin Mutations in Animals and Humans

Myostatin negatively regulates skeletal muscle growth

In 1997, Myostatin mutation in Mice and Belgian Blue Cattle found to have Increased Muscle Mass (Double-muscling)

In 2004, report of German child born extraordinarily muscular, found to have a mutation in myostatin gene Schuelke et al. NEJM 2004

Inhibition of myostatin results in hypertension of skeletal muscles
14 sIBM patients (11 active, 3 placebo):
- Increased thigh muscle volume in treated patients 8 weeks after dosing (1° outcome)
- Improved 6 minute walk distance in treated patients 16 weeks after dosing
**Bimagrumab (BYM338) Phase 2b/3 Trial**

**RESILIENT (Core) study design, objective and endpoints**

**Main inclusion criteria:**
- Aged 36–85 years
- Biopsy confirmed IBM as per modified 2010 Medical Research Council (MRC) criteria\(^1\,\,2\)
- Ambulatory

**Screening (28 days)**

**Treatment period (52 weeks of exposure):**
- Bimagrumab 10 mg/kg
- Bimagrumab 3 mg/kg
- Bimagrumab 1 mg/kg
- Placebo

**Maintenance treatment period:**
- Bimagrumab 10 mg/kg
- Bimagrumab 3 mg/kg
- Bimagrumab 1 mg/kg
- Placebo

**Post-treatment follow-up (28 days)**

**Randomization (Day 1)**

**Primary analysis (Week 52)**

**End of maintenance treatment (Week 104)**

**Post-treatment follow-up (28 days)**

**Aim:** To evaluate efficacy, safety and tolerability of bimagrumab in participants with IBM

**Study outcomes:** outcome measures at Week 52 includes the following:

- **Primary outcome:** 6MWD
- **Secondary outcomes:** physical function (sIFA), muscle strength measurements (quadriceps quantitative muscle testing [QMT]), and changes in muscle mass (LBM)

- Safety assessments included reporting of adverse events (AEs) and serious AEs
251 Patients Randomized

RESILIENT (Core) study: Results at Week 52

6MWD: No significant differences were observed between placebo and any of the 3 bimagrumab dose groups (10, 3, and 1 mg/kg) on the 6MWD (all P > 0.1).

sIQA: Treatment with bimagrumab 10 mg/kg showed significant improvement versus placebo on the sIQA total score (*P = 0.03). Proportion of responders (defined as a change in sIQA score of ≤0) increased in the bimagrumab 10 mg/kg versus placebo groups (55% vs. 30%, respectively; P = 0.01).

QMT: No significant differences in right quadriceps QMT were observed in the bimagrumab versus placebo groups (all P > 0.1).

LBM: Treatment with bimagrumab 3 and 10 mg/kg resulted in significant dose-dependent increase in LBM versus placebo (p ≤ 0.0001), confirming the biological activity of bimagrumab on the skeletal muscle mass.

Amato A.A., et al. | The 70th Annual AAN Meeting | Los Angeles, CA | April 21–April 27, 2018

Permission from Novartis, In Press, accepted Lancet Neurology 2019
Bimagrumab (BYM338) Phase 2b/3 Trial

Conclusion

- None of the outcome measures of physical function (muscle strength or 6MWD) revealed dose-dependent and clinically meaningful improvements during the study.
- Extension study was terminated due to the core study not meeting its primary endpoint (6MWD). Consequently, about one-third of the participants did not reach Week 104.
- Significant relative benefits of bimagrumab therapy as per PRO (sIFA) at Week 52 showed further increases at Week 78. This trend, however, did not hold true at Week 104.

Also being studied in: hip fracture recovery & sarcopenia
Arimoclomol in IBM

May augment Heat Shock Protein Expression

Benarroch E et al. Neurology 2011
Arimoclomol in IBM (Phase 2a Study)

Double-Blind, Placebo Controlled

2 Sites (Kansas, USA and London, UK)

2: 1 Randomization

Arimoclomol 100mg tid
N=16

Placebo
N=8

4 months treatment duration

Safe and Well tolerated

Arimoclomol in IBM (Phase 2a Study)

No statistically significant difference in secondary outcomes

However, trends in favor of arimoclomol at 8 months:

**Change in IBMFRS over time**

- Arimoclomol vs Placebo at 8 months:
  - $-0.68 \pm 1.58$ vs. $-2.50 \pm 3.31$; $p=0.055$

**Change in Grip Strength over time**

- Arimoclomol vs Placebo at 8 months:
  - $1.26 \pm 2.63$ vs. $-0.54 \pm 1.86$; $p=0.064$

**Arimoclomol in IBM: Phase 2/3 Study**

- **Double-Blind, Placebo Controlled** *(NCT0275350)*
- 12 Sites (11 in US and 1 in London)
  - N=150 Patients
- 1:1 Randomization
- **Arimoclomol 400mg tid**
- **Placebo**
- 20 month duration

**Primary outcome:**
Rate of decline in IBMFRS

**Secondary Outcomes:**
- Manual muscle testing
- Maximal voluntary isometric contraction of quadriceps
- Timed up and go
- Grip and pinch test
- 6 minute walk (2 minute distance captured)
Rapamycin

Li J et al. Cell Metabolism 2014
Sirolimus (Rapamycin) Phase 2b study in IBM

Double-blind, placebo-controlled (6/2015-4/2017),
Single site, (Paris, France)

44 patients (22 on 2mg/d rapamycin: 22 on placebo)
12 month treatment period

6 MWD

Significantly Less fatty replacement in quadriceps in the treated arm

p=0.025

Courtesy of: Benveniste (unpublished)
Prognosis/Progression
IBM Prognosis: Slow, gradual progression

Natural history: mean decline in muscle strength by manual muscle testing

3.5% +/- 1.6% decline per year

5.2% +/- 5.9% decline over 1 year

Cox et al. Brain 2011

Cortese et al. Neuromuscul Disord 2013
Life Expectancy in sIBM: Normal

Survival seems to be similar to the general population

During a 12 year follow up study:
46 of 64 patients died during follow up period
Median age at death = 81 years
In Netherlands, life expectancy 79 years

Figure 3 Kaplan-Meier curve showing a comparable survival between sIBM patients and an age- and sex-matched Dutch general population. The curve for the general Dutch population is adjusted for life expectancy for each individual sIBM patient based on the age of onset and gender.
Late Stage disease can cause very significant morbidity

Leading causes of Death:
- Respiratory (pneumonia)
- Cachexia (severe wasting with loss of weight and muscle mass)

![Table 2 Causes of death in the Dutch population in the age category 80–85 years and the sporadic IBM cohort](image)
Management: Multidisciplinary Care

• **Mobility**
  • Assistive devices (AFOs, cane, braces, walker, wheelchair)
  • Risk of falls

• **Dysphagia**
  • Diet modification
  • Dilation, cricopharyngectomy
  • Gastrostomy tube
  • Risk of aspiration pneumonia

• **Respiratory insufficiency**: Noninvasive ventilation (BiPAP)

• **Adaptive Equipment**
  • Shower chair, stair lift, safety rails, hospital bed
  • Home safety evaluations and bathroom modifications

• **Role of Exercise**: May slow progression
Take Home Points

• IBM may be diagnostically challenging

• Careful attention to clinical exam for clues to correct diagnosis

• Diagnostic process
  (in addition to muscle biopsy, helpful toots):
  • Antibodies (NT5C1A Ab)
  • Muscle imaging (Pattern of muscle involvement seen in IBM)

• Consider re-evaluation if given PM diagnosis and no improvement on immunotherapy

• Multidisciplinary team care improves quality of life
Thank you