IBM:
Clinical Features and Progression

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TMA Minneapolis
September 6, 2019

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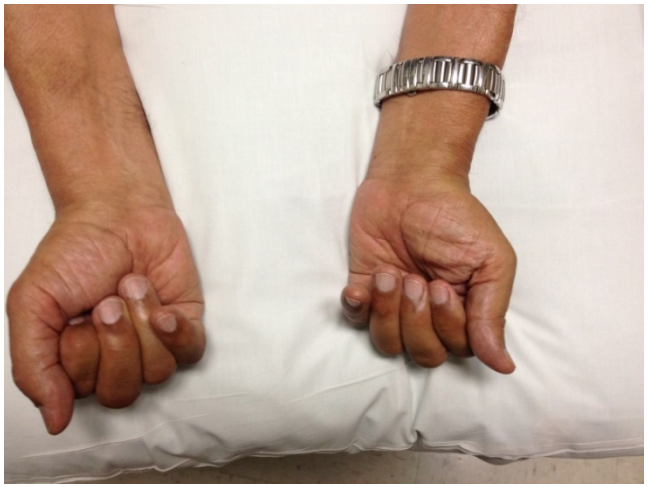
Overview of Inclusion Body Myositis

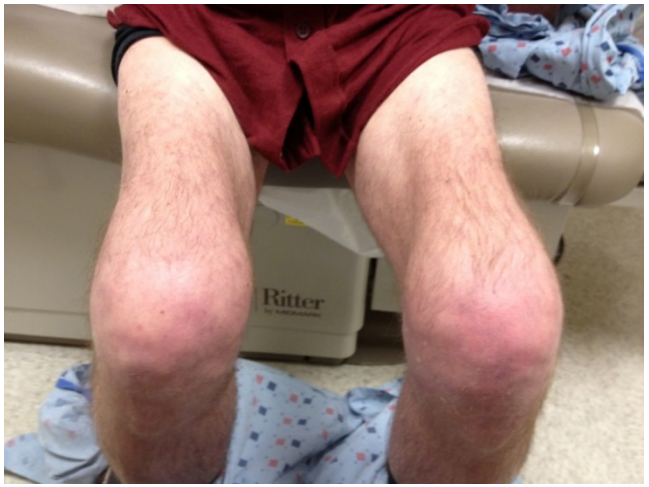
- Clinical features
- Diagnostic tests: how can they help vs be misleading?
- Treatment trials
- Progression/Management

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?)





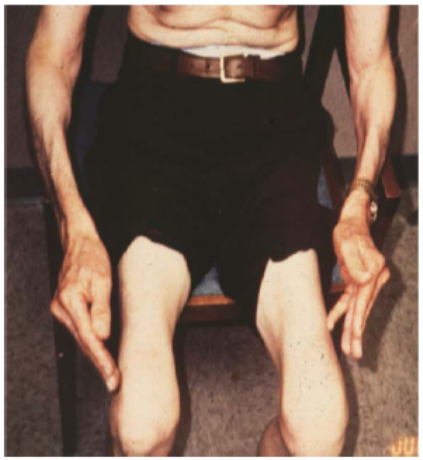


Figure 1. s-IBM patient who has typical prominent weakness and atrophy

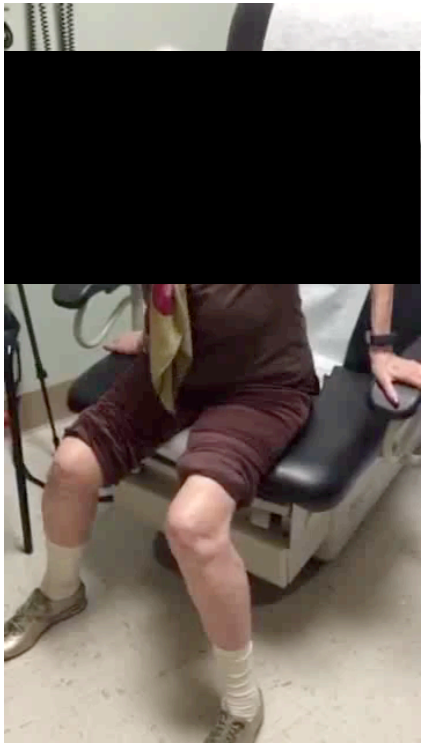
Inclusion-body myositis

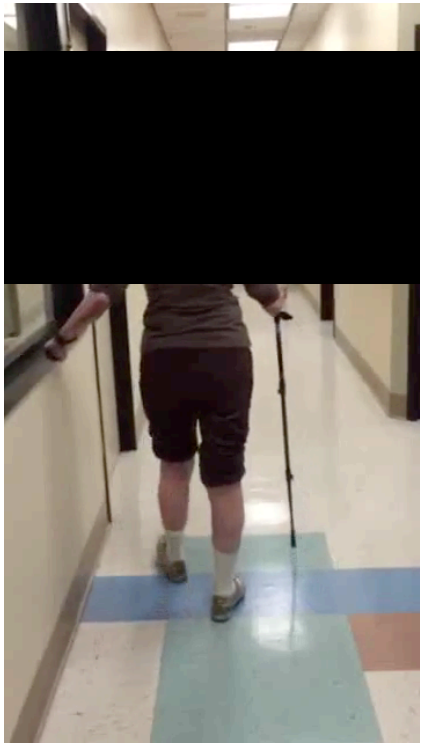
Clinical, diagnostic, and pathologic aspects

W. King Engel, MD; and Valerie Askanas, MD, PhD

Leg Weakness: Slow progressive in IBM

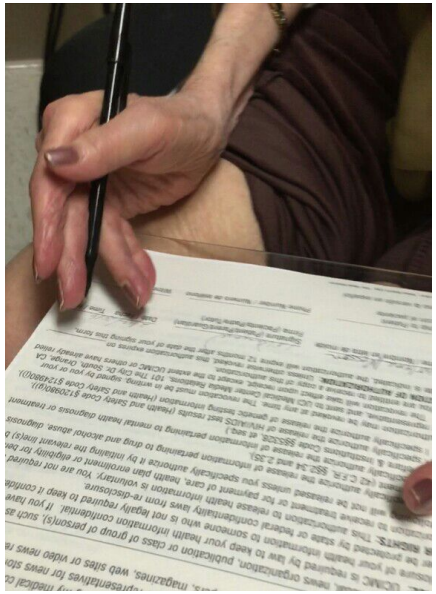
- Falls
- Gait difficulty
- Arising from low seated position
- Difficulty climbing stairs
- Foot drop (dorsiflexion weakness)
- Knee buckling (quadriceps)





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

Reference	*n*	Male (%)	Age at onset (years)	Age at diagnosis (years)	Creatine kinase level (IU/l)	Patients receiving immunosuppressors (%)	Progression despite therapy (%)
Ringel *et al.*, 1987	19	79	57.8	62.9			
Lotz *et al.*, 1989	40	72.5	56.1	62.4	197	72.5	80.2
Sayers *et al.*, 1992	32	62.5	58	61	1145	87.5	46.4
Beyenburg *et al.*, 1993	36	58.3	47	53.1	279	44.4	93.75
Lindberg *et al.*, 1994	18	55.5	60.4	62.7		88.8	75
Amato *et al.*, 1996	15	86.6	58	64	698	73.3	100
Peng *et al.*, 2000	78	78.2	56.5				
Felice and North, 2001	35	65.7	64.3	70	444	49	100
Badrising *et al.*, 2005	64	67.2	57.6		417	35.9	82.6
Present study 2011	136	57.3	61	66	267	52.2	100

Brain 2011: 134; 3176–3184

Muscle Histopathology in IBM

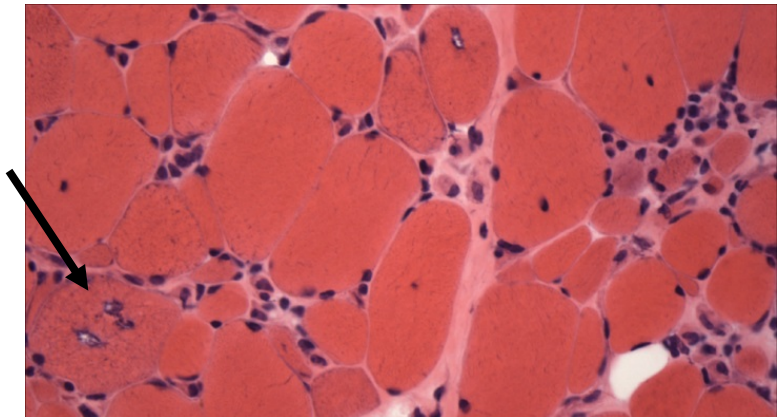
Karpati made most definitive description:
Neurology 1978 28(1): 8-17

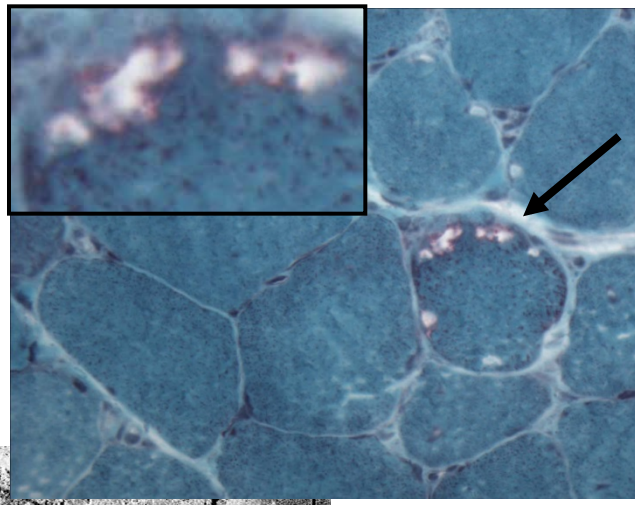
Endomysial inflammation, inflammatory cells surrounding myofibers, invasion of non-necrotic muscle fibers

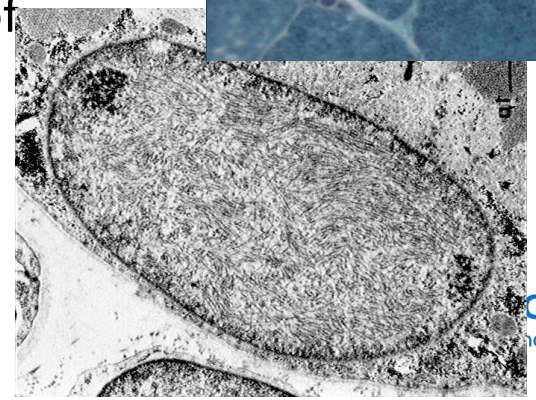
Variation in fiber size, angular fibers (neurogenic atrophy), fibrosis (chronicity)

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?

Classification at baseline and at follow up in 81 patients with endomysial mononuclear cell infiltrates with invasion of non-necrotic muscle fibers.

	RVs present	Clinical IBM	Unclassified
At presentation N (%)	49 (60.5)	14 (17.3)	18 (22.2)
At follow up N (%)	ND	29 (36)	3 (4)

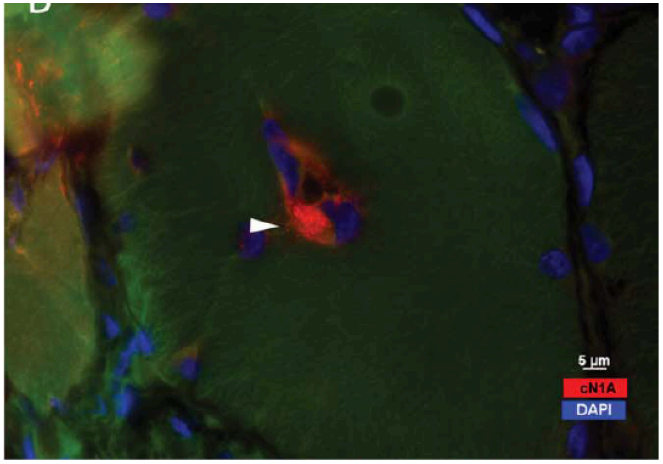
RV: Rimmed vacuoles (Patients with histopathological diagnosis of IBM with RV)
Clinical IBM: >45 yrs, FF > shoulder abductor and KE ≥ HF weakness
Unclassified: Clinical features of IBM, but not fulfilling all criteria

Nearly 40% of patients had clinical features of IBM, yet no rimmed vacuoles

van de Viekkert J et al. Neuromuscul Disorders 2015

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

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NT5C1A Antibody in IBM vs. Autoimmune diseases

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

THOMAS E. LLOYD, MD, PhD[1], LISA CHRISTOPHER-STINE, MD, MPH[1], IAGO PINAL-FERNANDEZ, MD, PhD[2], ELENI TINIAKOU, MD[1], MICHELLE PETRI, MD, MPH[1], ALAN BAER, MD[1], SONYE K. DANOFF, MD, PhD[1], KATHERINE PAK, MD[3], LIVIA A. CASCIOLA-ROSEN, PhD[1], and ANDREW L. MAMMEN, MD, PhD[4]

Arthritis Care Res (Hoboken). 2016 January

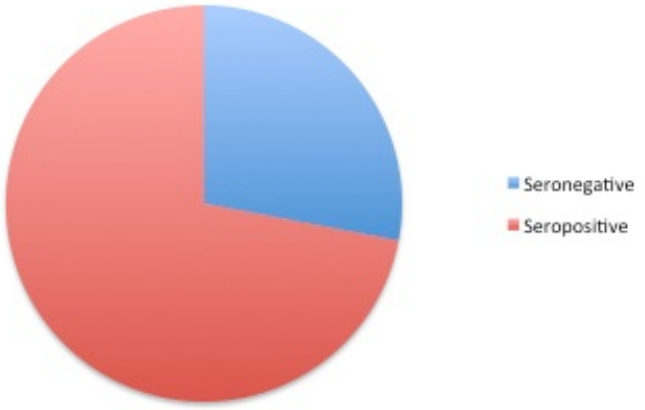
- Detected in 61% of 117 patients with IBM
- 5% with PM
- In Sjogrens (23%) & SLE (14%)- but no muscle weakness
- NT5C1A Ab may be helpful in differentiating IBM from PM

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 Mozaffar[1,4]

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



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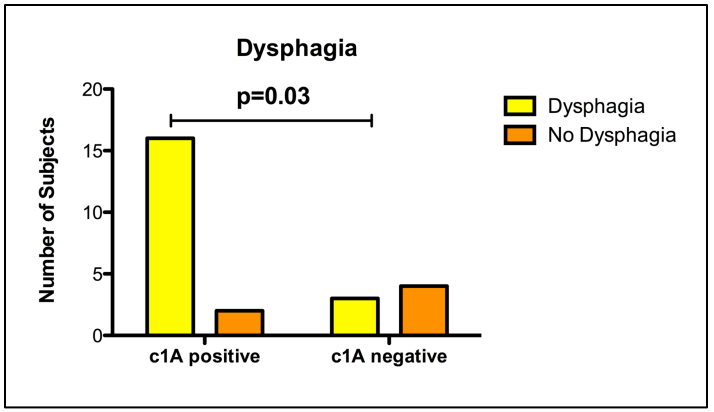
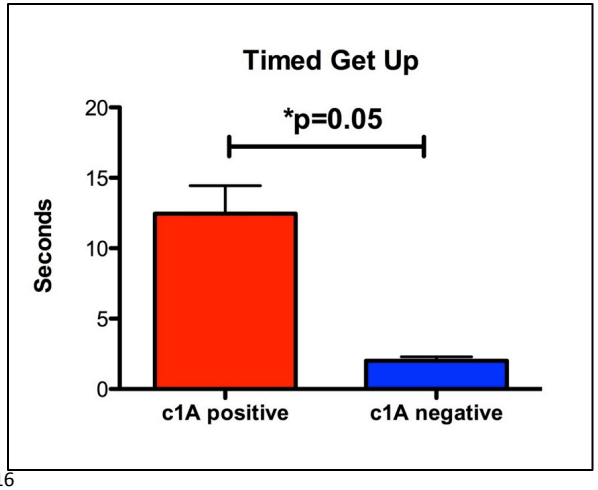
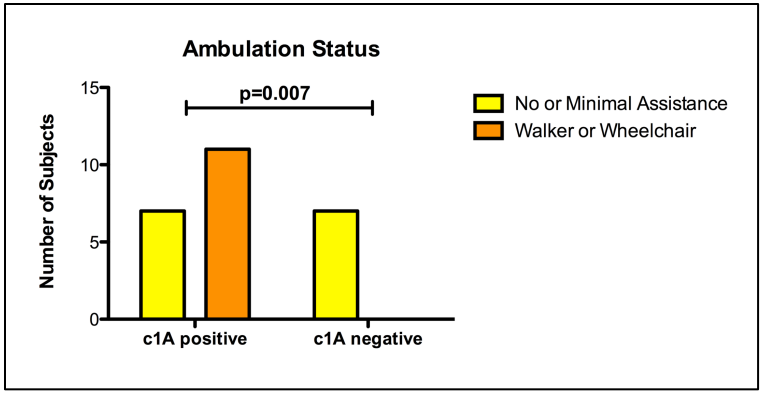
Results:

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

- Dysphagia
- Increased Motor Deficits
- Reduced FVCs







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Goyal et al. J Neurol Neurosurg Psychiatry 2015

EXTENDED REPORT

Cytosolic 5′-nucleotidase 1A autoantibody profile and clinical characteristics in inclusion body myositis

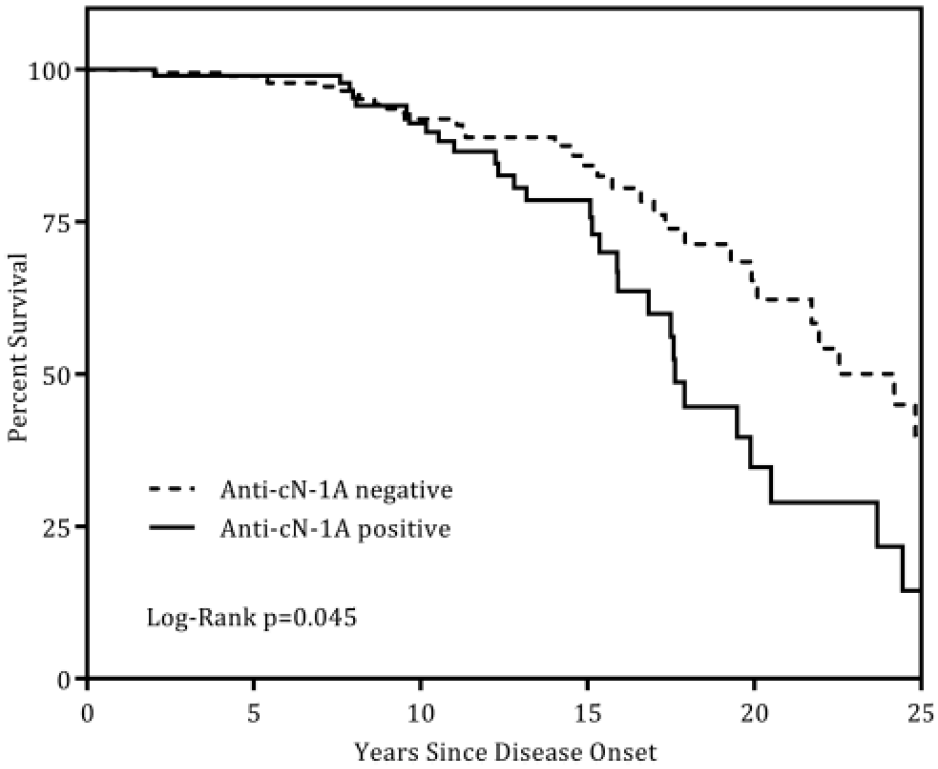

Figure 1 Kaplan-Meier survival curves stratified by anti-cN-1A antibody status. X-axis truncated at 25 years from disease onset.

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

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Lilleker JB et al. Ann Rheum Dis 2017

Muscle Imaging

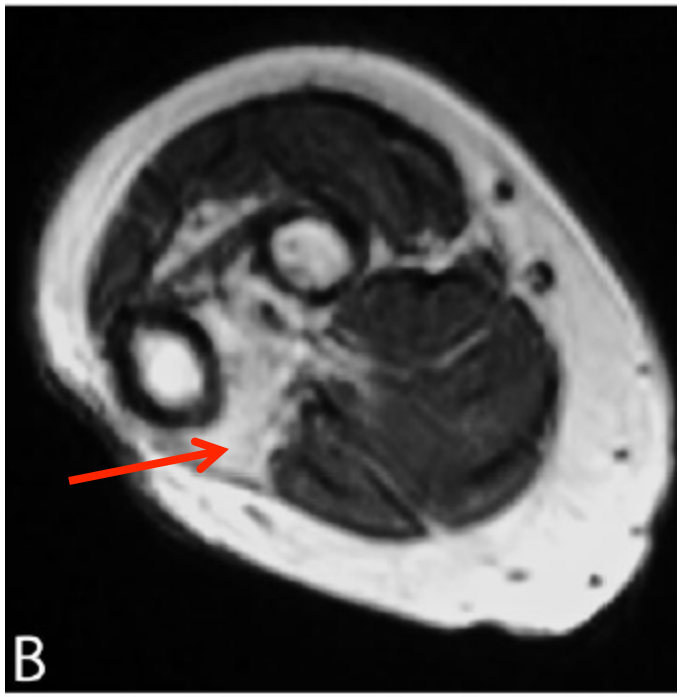
Muscle Imaging (MRI)

- 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

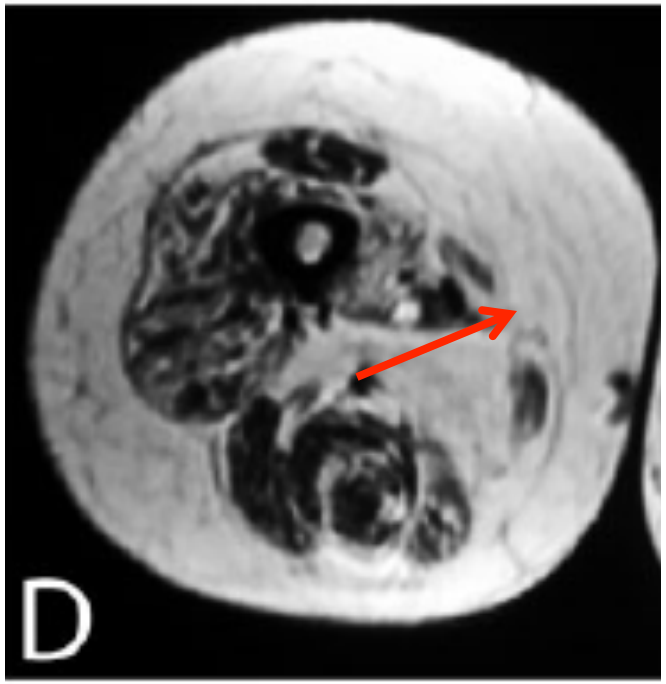
Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis

Fieke M. Cox[1], Monique Reijnierse[2], Carla S. P. van Rijswijk[2], Axel R. Wintzen[1], Jan J. Verschuuren[1] and Umesh A. Badrising[1]

Rheumatology 2011;50:1153–1161
doi:10.1093/rheumatology/ker001



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

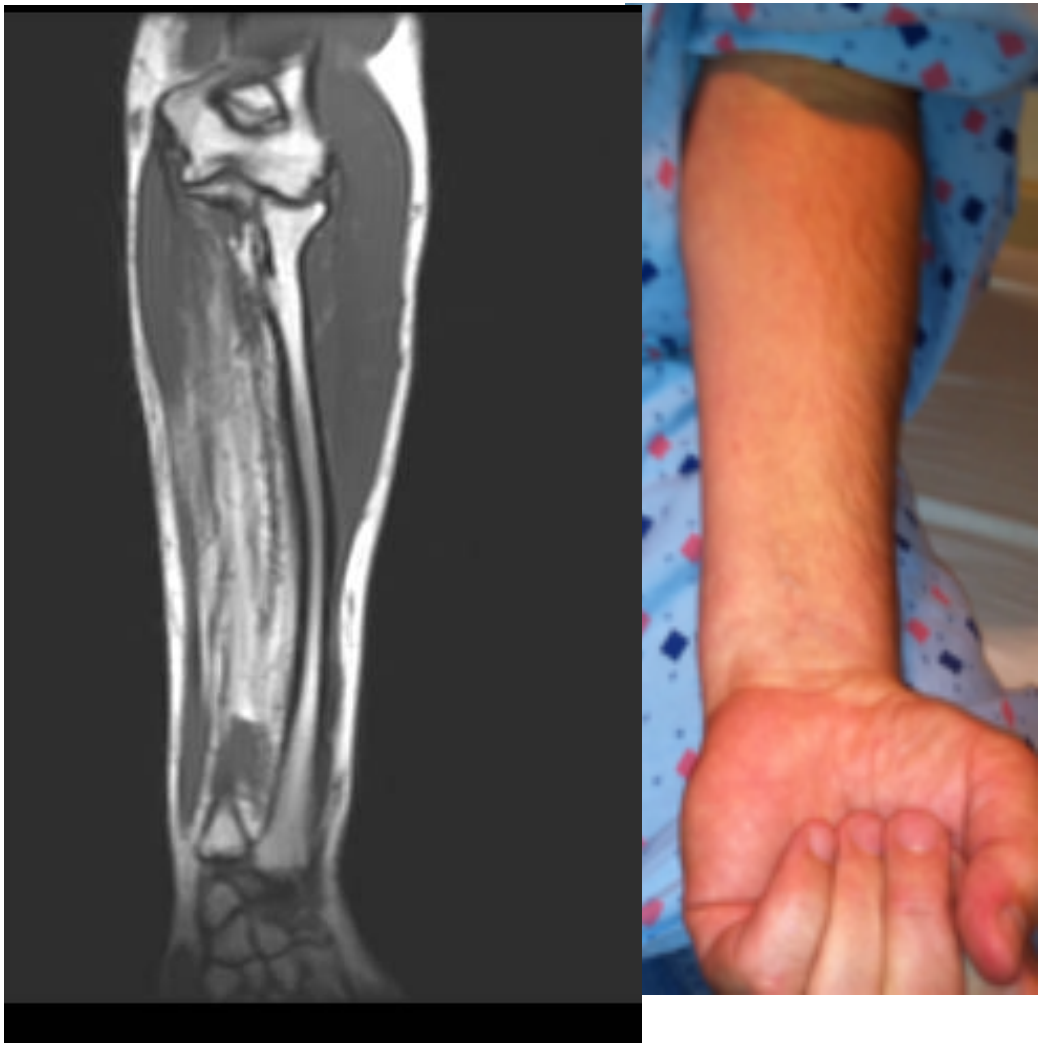


MRI Upper thigh:
Severe fatty infiltration of Vastus lateralis, relative sparing of rectus femoris and hamstrings

Muscle Imaging MRI- in sIBM

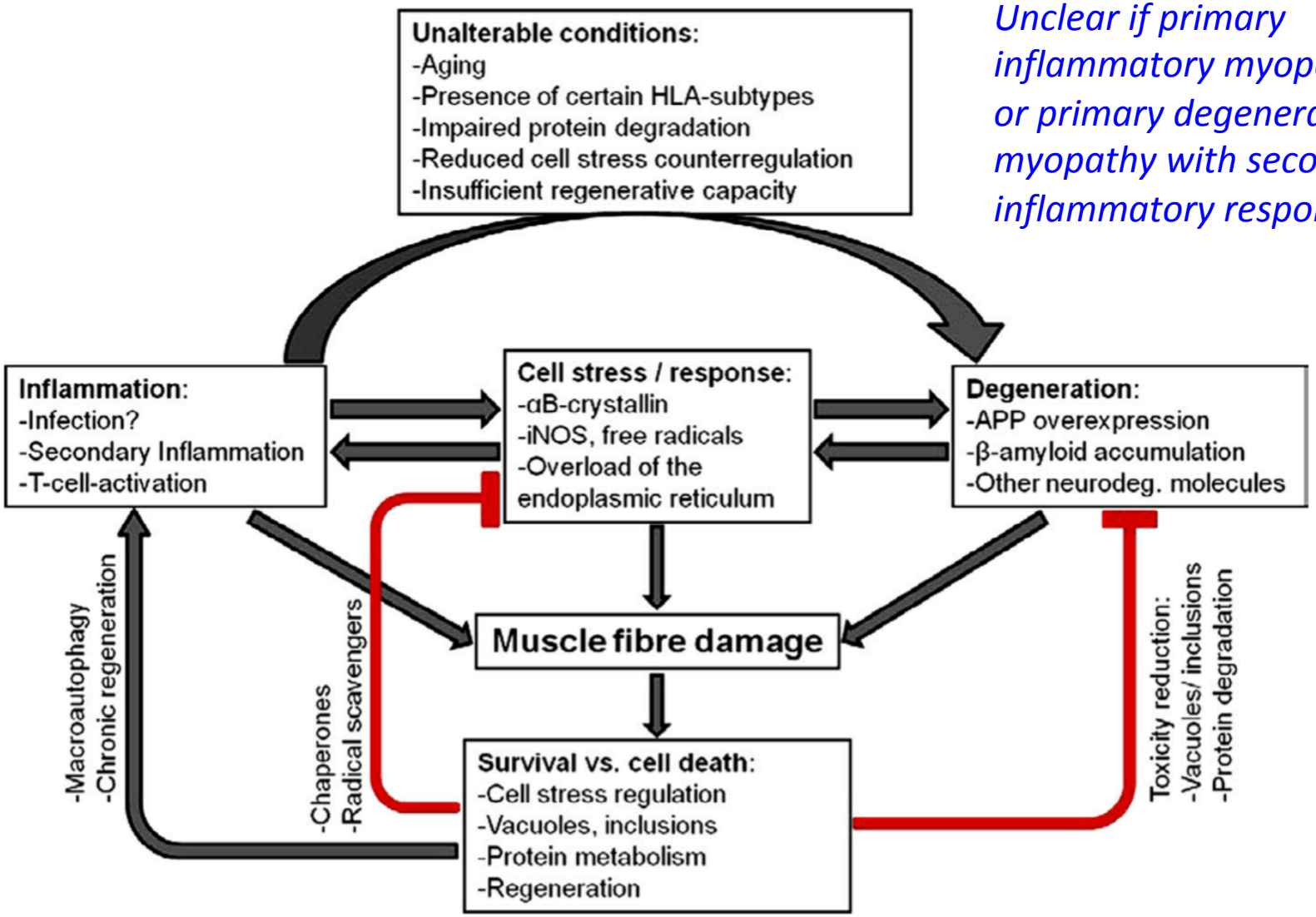
especially helpful if mild finger flexor weakness and want to confirm muscle involvement

"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

Corticosteroids
Barohn et al. Neurology 1995

Methotrexate
Joffe et al. Am J Med 1993
Badrising et al. Ann Neurol 2002

Azathioprine
Joffe et al. Am J Med 1993
Leff et al. Medicine 1993

IVIg
Amato et al. Neurology 1994
Dalakas et al. Neurology 1997
Walter et al. J Neurol 2000
Cherin et al. Neurology 2002
Dobloug et al. Clin Exp Rheum 2012

Anti-T-lymphocyte globulin treatment
Lindberg et al. Neurology 2003

Oxandrolone
Rutkove et al. Neurology 2002

βINF1a (Avonex)
MSG Neurology 2001
MSG Neurology 2004

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

Etanercept (TNF)
Barohn et al. Neurology 2006

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Does Treatment with Immunotherapy make sIBM worse in the long run?

Table 5 Comparison of treated and untreated patients with sporadic IBM

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

Treated group:
Less independent mobility,
Increased use of wheelchair

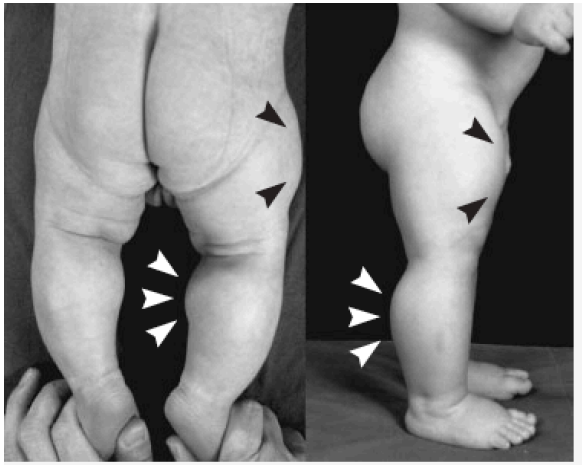
Brain 2011: 134; 3176–3184

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)

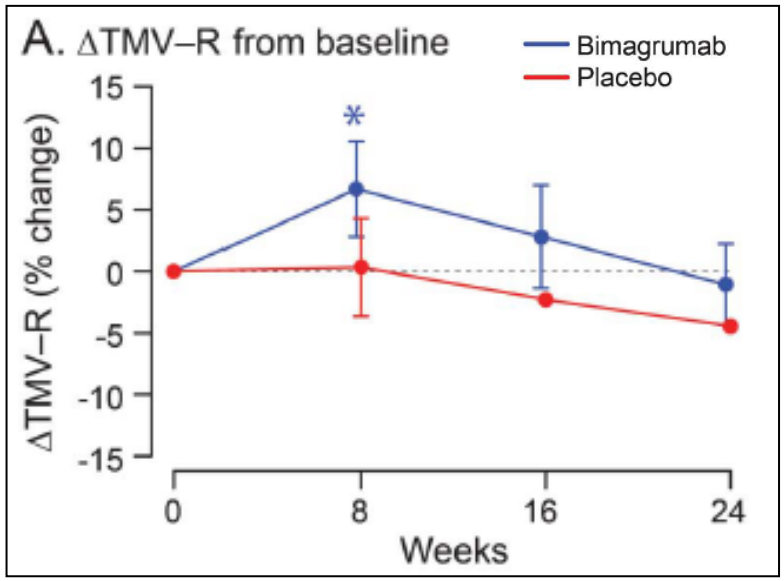


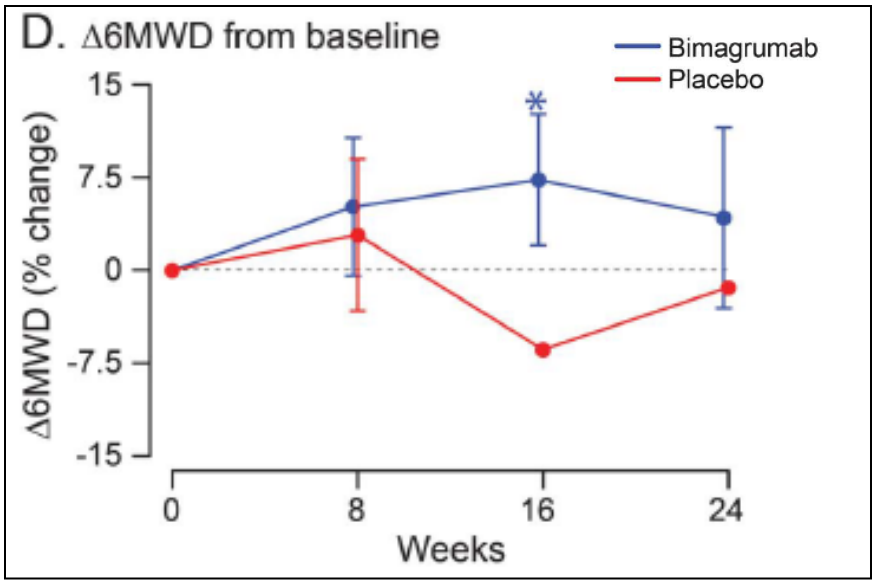
In 2004, report of German child born extraordinarily muscular, found to have a mutation in myostatin gene Schuelke et al. NEJM 2004

Inhibition of myostatin results in hypertrophy of skeletal muscles

Treatment of sporadic inclusion body myositis with bimagrumab

Effect of bimagrumab compared with placebo on primary and secondary study endpoints over 24 weeks





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

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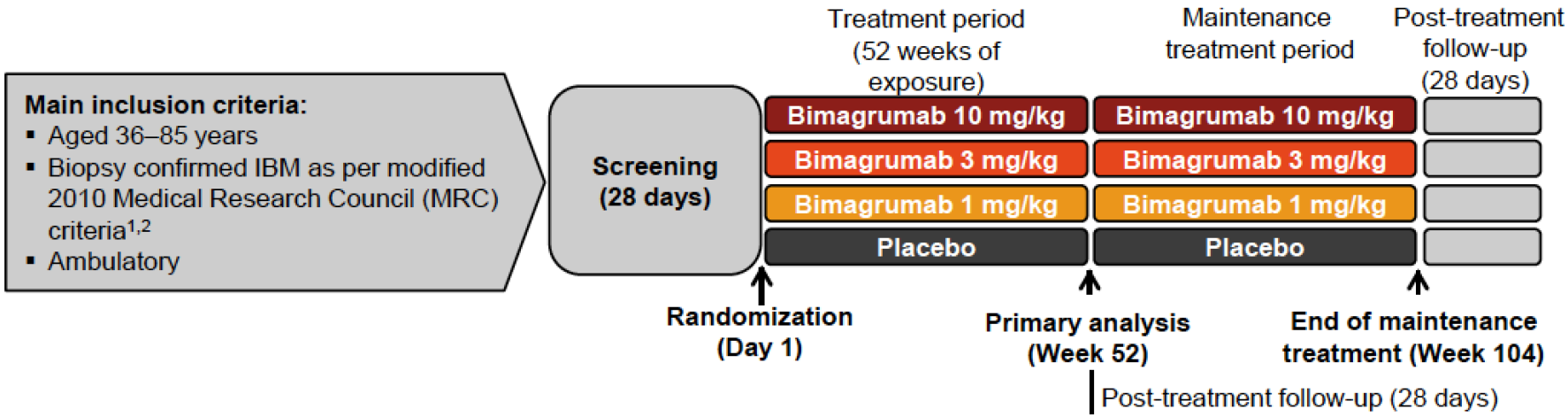
Amato A, Sivakumar K, Goyal N et al. Neurology 2014

Bimagrumab (BYM338) Phase 2b/3 Trial

RESILIENT (Core) study design, objective and endpoints



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

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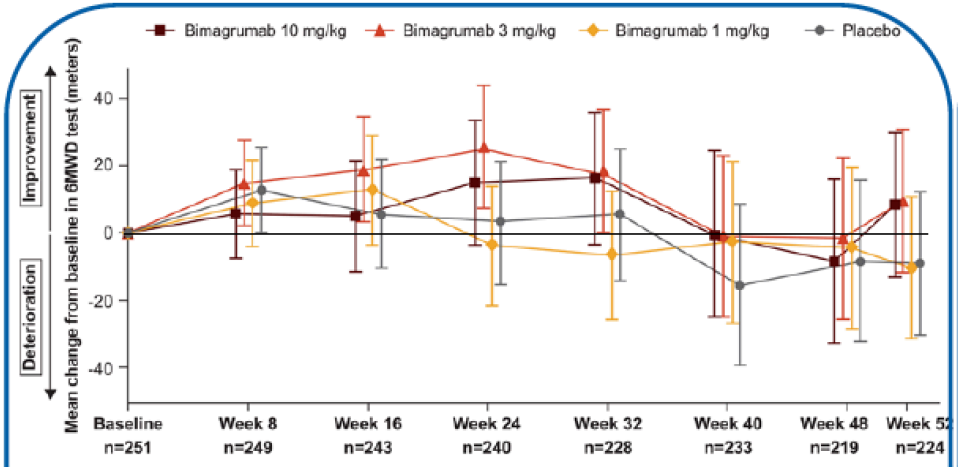
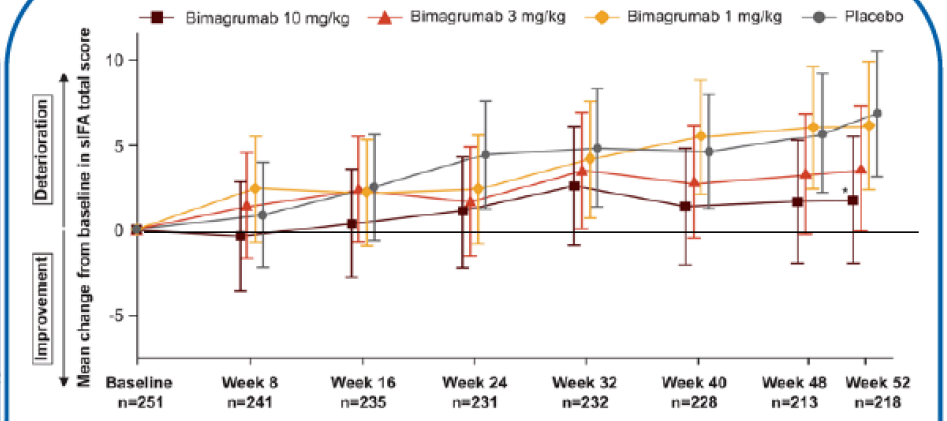
251 Patients Randomized

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)



sIFA: Treatment with bimagrumab 10 mg/kg showed significant improvement versus placebo on the sIFA total score (*P=0.03). Proportion of responders (defined as a change in sIFA 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 AA, et al. Neurology Apr 2017, 88 (16 Suppl) P1.111

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Bimagrumab (BYM338) Phase 2b/3 Trial

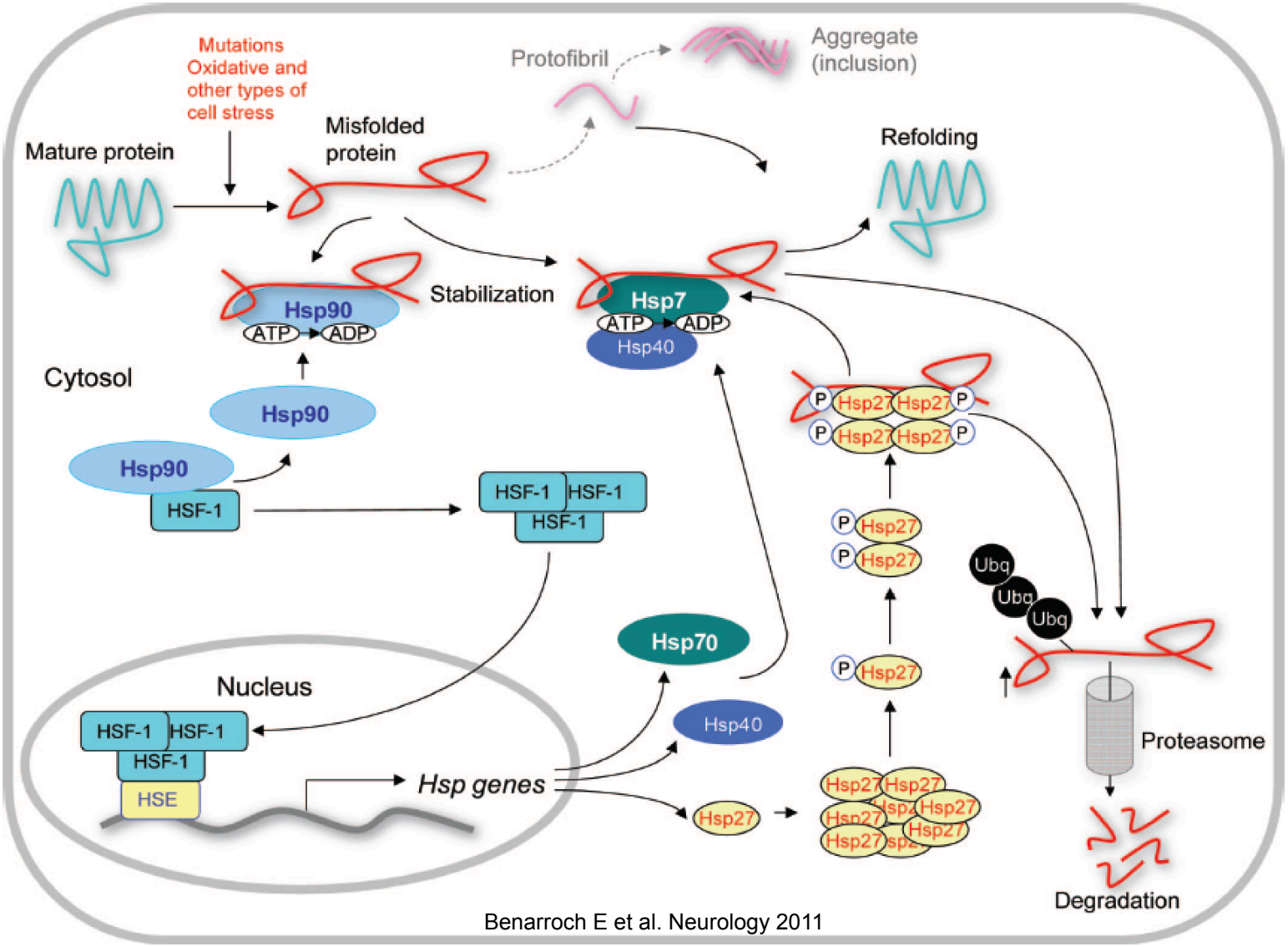
Conclusion

- 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

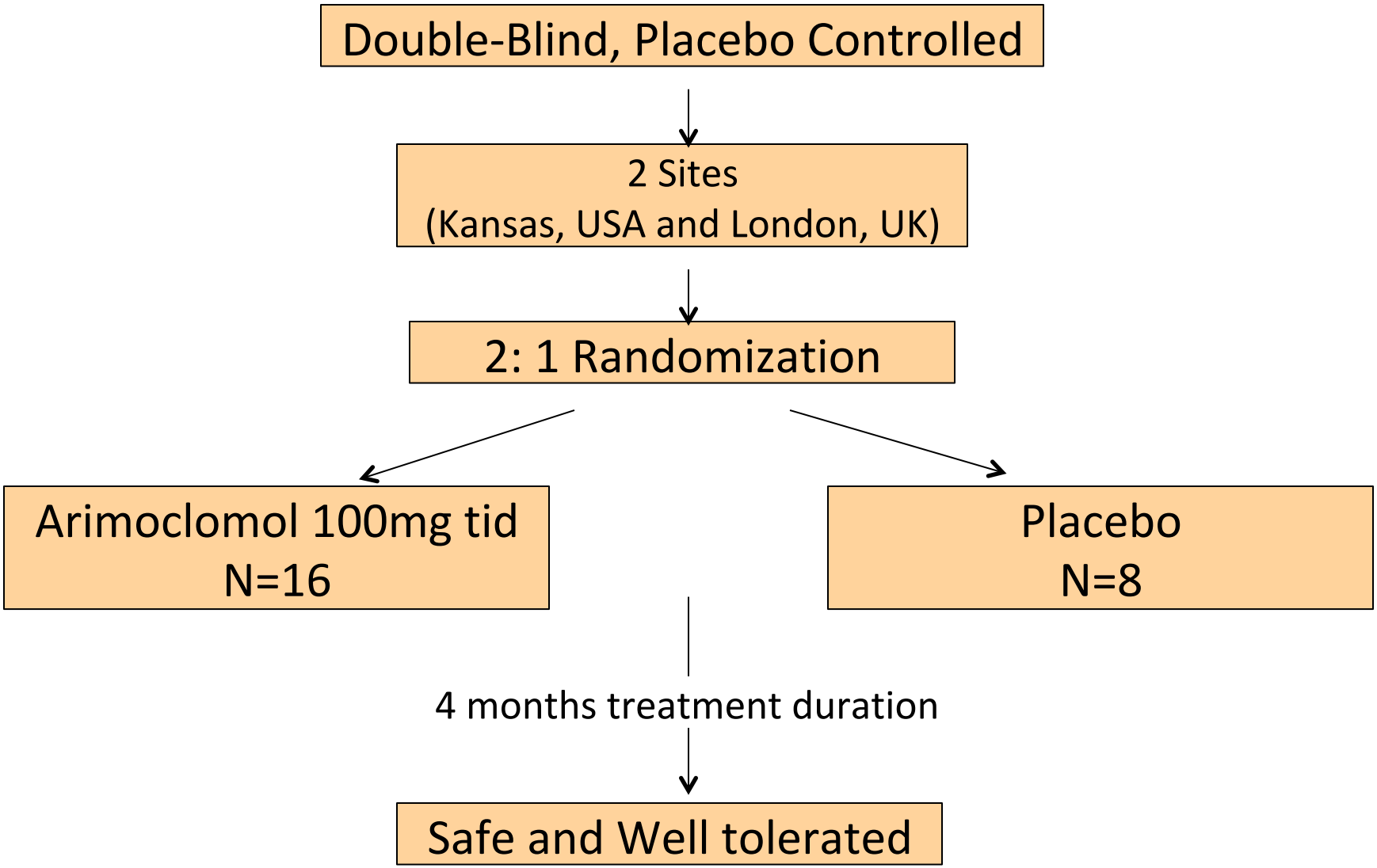
Arimoclomol in IBM

May augment Heat Shock Protein Expression



Benarroch E et al. Neurology 2011

Arimoclomol in IBM (Phase 2a Study)



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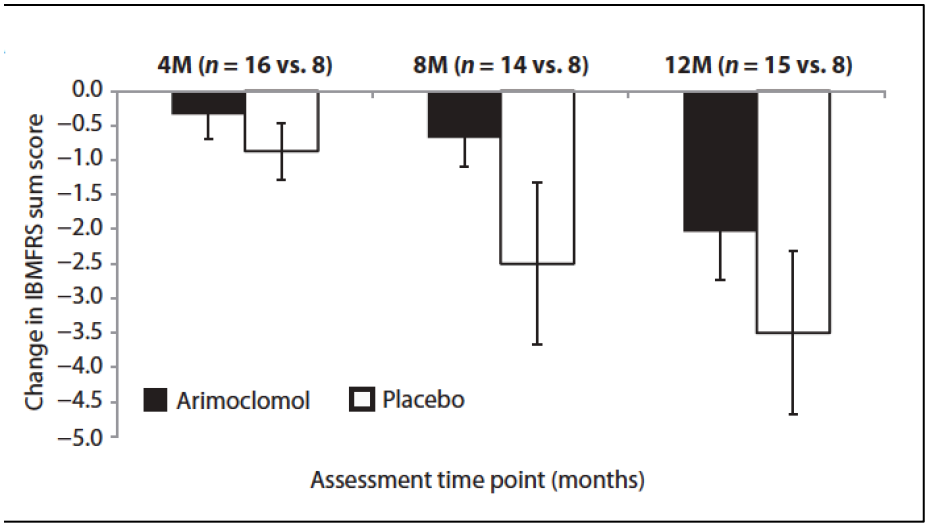
Machado P et al. Ann Rheum Dis 2013

Arimoclomol in IBM (Phase 2a Study)

No statistically significant difference in secondary outcomes

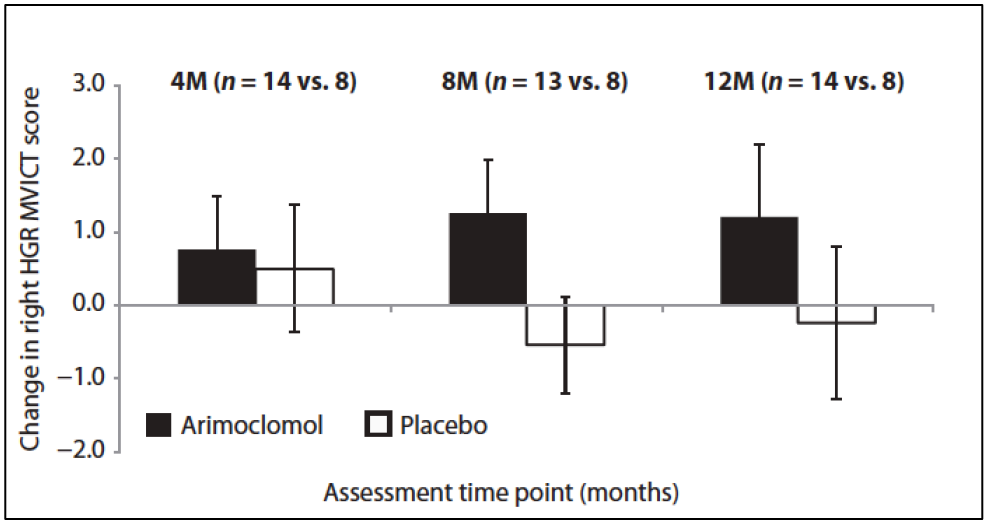
However, trends in favor of arimoclomol at 8 months:

Change in IBMFRS over time



Arimoclomol vs Placebo at 8 months
-0.68 ± 1.58 vs. -2.50 ± 3.31; p=0.055

Change in Grip Strength over time

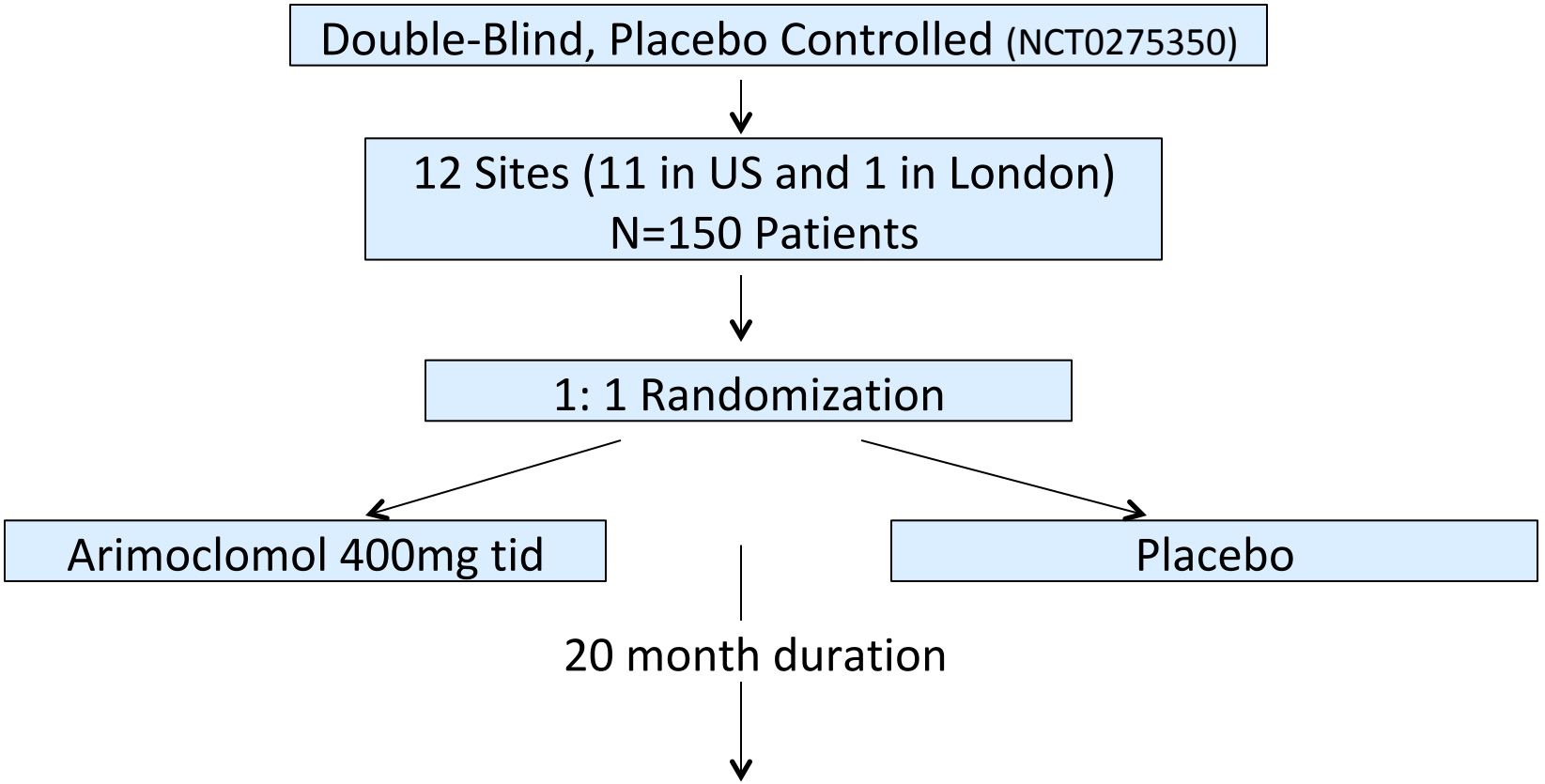


Arimoclomol vs Placebo at 8 months
1.26 ± 2.63 vs. -0.54 ± 1.86; p=0.064

UC Irvine Health
School of Medicine

Ahmed M et al. Science Translational Medicine 2016

Arimoclomol in IBM: Phase 2/3 Study

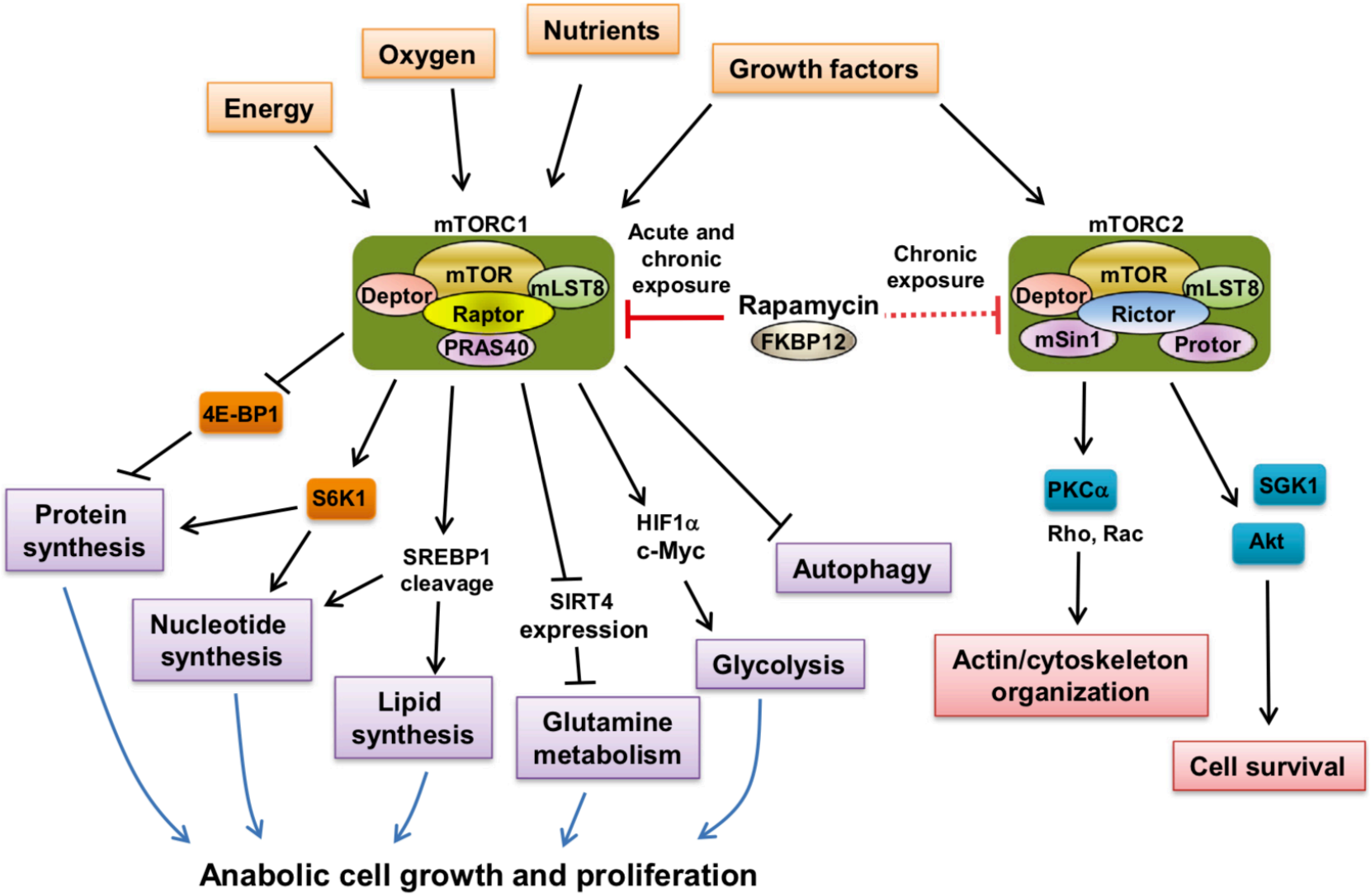


Primary outcome:
Rate of decline in IBMFRS

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



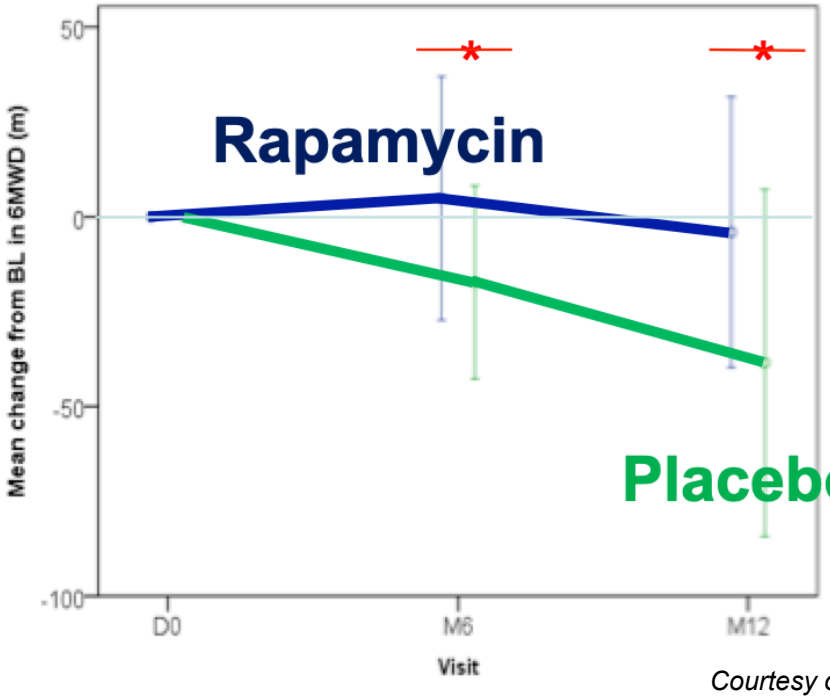
Li J et al. Cell Metabolism 2014

Sirolimus (Rapamycin) Phase 2b study in IBM

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

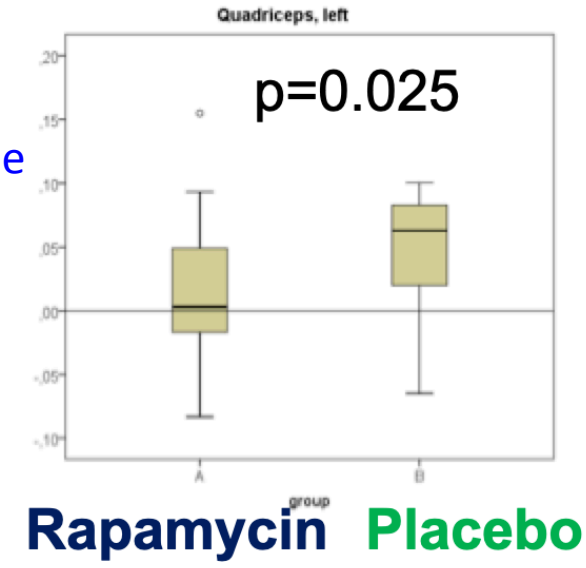
44 patients (22 on 2mg/d rapamycin: 22 on placebo)
12 month treatment period

6 MWD



Significantly Less fatty replacement in quadriceps in the treated arm

qMRI, Quadriceps, T1

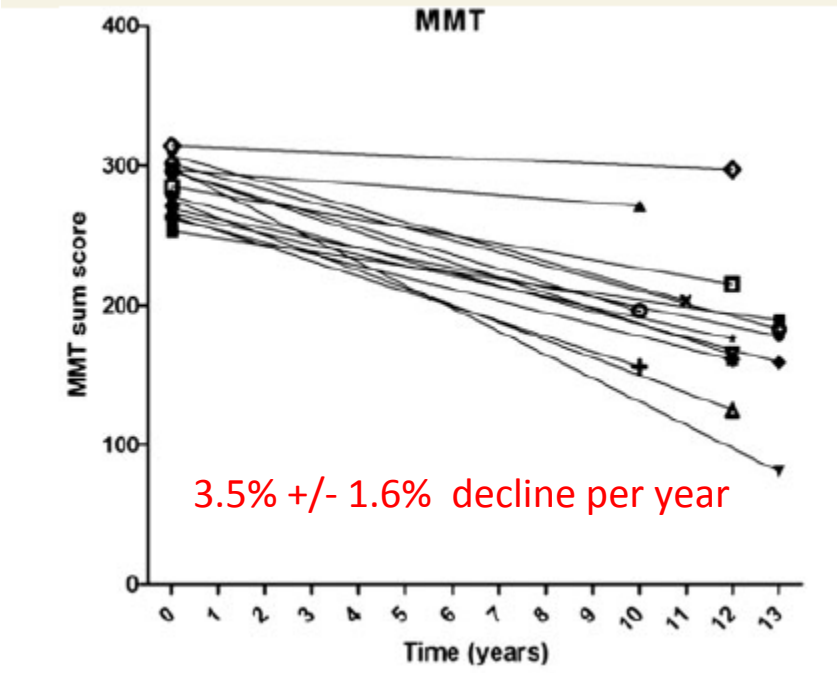


Courtesy of: Benveniste (unpublished)

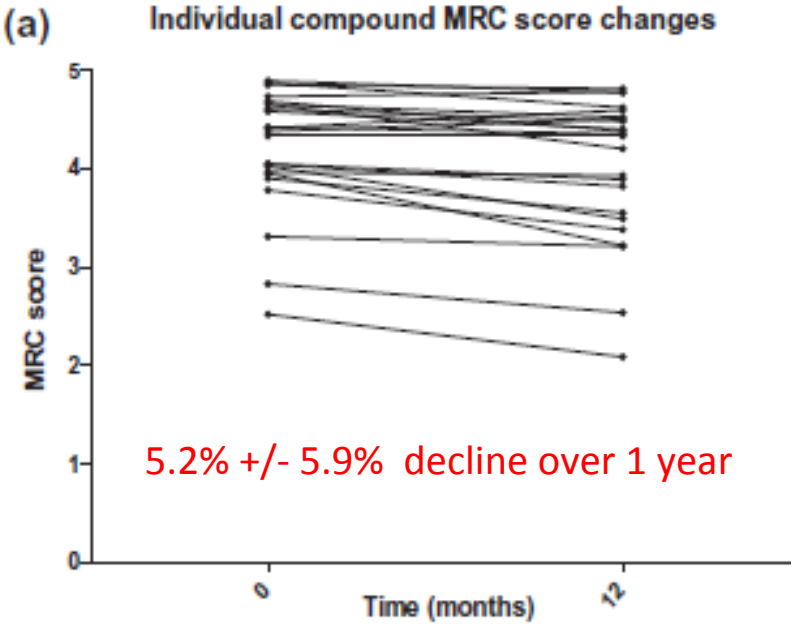
Prognosis/Progression

IBM Prognosis: Slow, gradual progression

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



Cox et al. Brain 2011



Cortese et al. Neuromuscul Disord 2013

UC Irvine Health
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Life Expectancy in sIBM: Normal

Survival seems to be <u>similar</u> to the general population

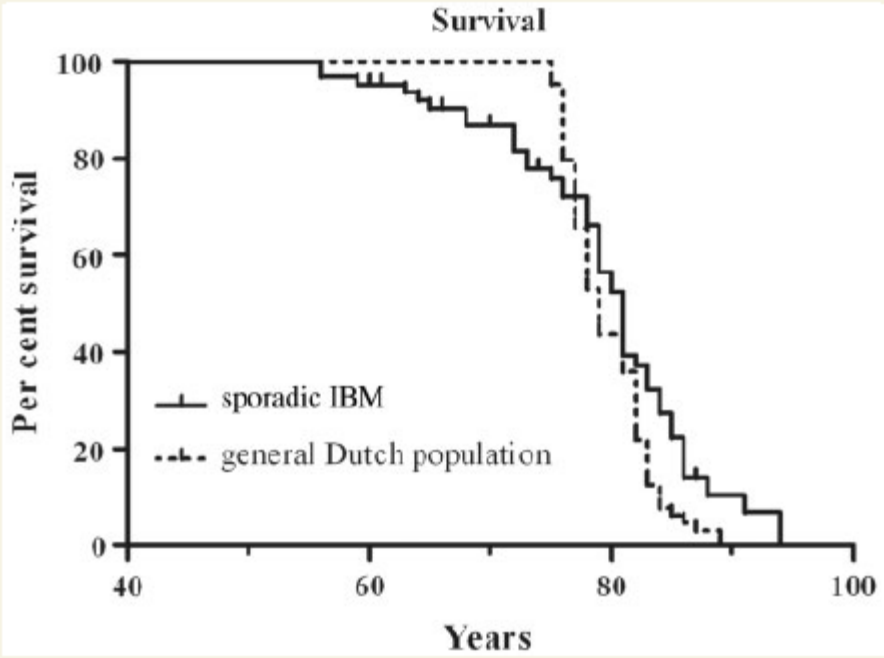

Figure 3 Kaplan-Meier curve showing a comparable survival between sIBM patients and an age- and sex-matched Dutch general population. The curve for the general Dutch population is adjusted for life expectancy for each individual sIBM patient based on the age of onset and gender.

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

Cox et al. Brain 2011

Morbidity & Mortality in sIBM

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

	Dutch population age category 80–84 years (%)	Patients with sporadic IBM (%)	*P*-value	Corrected *P*-value†
Infectious diseases	1.4	2.2	0.66	NS
Neoplasms	23.8	4.3	0.002	0.03*
Diseases of blood/blood-forming organs	0.4	0	0.67	NS
Endocrine/metabolic diseases	3.6	0	0.19	NS
Mental and behavioural disorders	5.6	0	0.10	NS
Diseases of the nervous system	2.8	2.2	0.80	NS
Diseases of the circulatory system (myocardial infarction)	37.7 (7.8)	19.6 (4.3)	0.01	0.16
Diseases of the respiratory system (pneumonia)	11.5 (4.4)	41.3 (28.3)	0.0001*	0.001*
Diseases of the digestive system	4.2	0	0.16	NS
Diseases of the skin	0.3	0	0.71	NS
Diseases of the bone/connective tissue	0.7	0	0.57	NS
Diseases of the genitourinary system	2.8	0	0.25	NS
Cachexia	0.1	6.5	0.0001*	0.001*
External causes of injury and poisoning	2.1	6.5	0.04	0.51
Other/uncertain	3.0	17.4		

†Corrected *P*-value is calculated with a Bonferroni correction of 14. *Significant value.

Cox et al. Brain 2011

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