Myositis 101 for IBM patients

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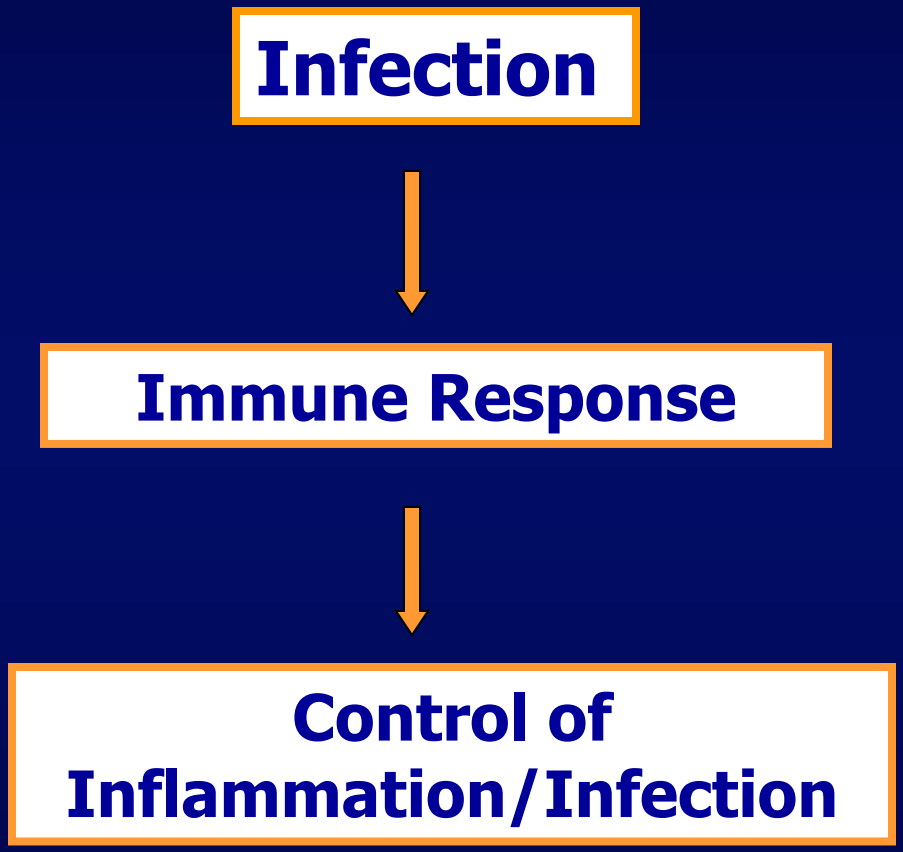
THE MYOSITIS ASSOCIATION

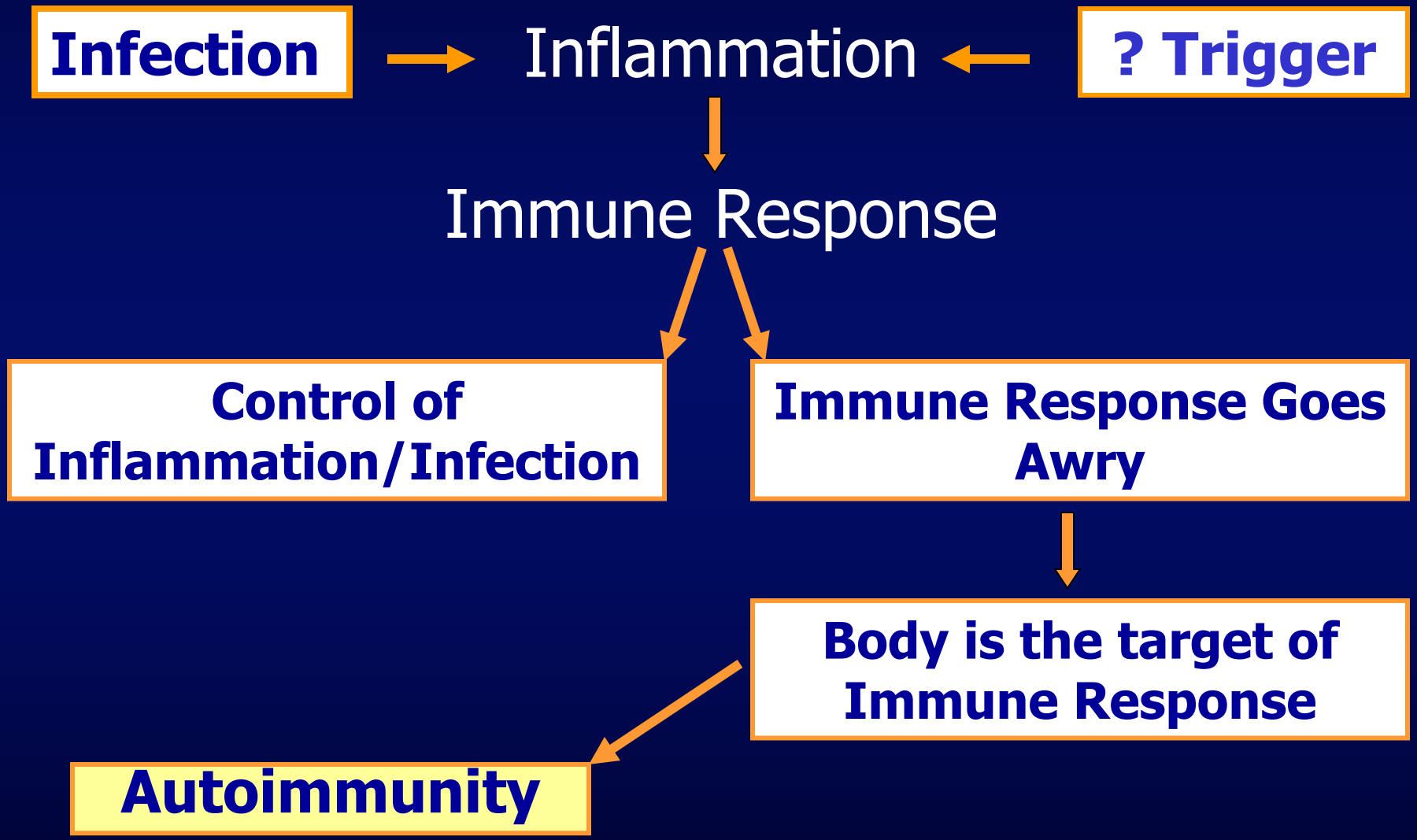
What is Myositis?

- myo = muscle; -itis = inflammation
- "Idiopathic inflammatory myopathy" is medical term (IIM)
  - "idiopathic" = unknown cuase
- Heterogeneous group of autoimmune syndromes; IBM often considered separately
- Muscle weakness is due to inflammation in the muscle tissue for acute (early) myositis.
- Muscle weakness mainly due to atrophy (muscle loss) in long-standing IBM.
- Systemic complications (e.g. lung, joints, skin) are NOT typically seen in IBM, but are common in other IIM.

Understanding the Immune System



Understanding Autoimmunity



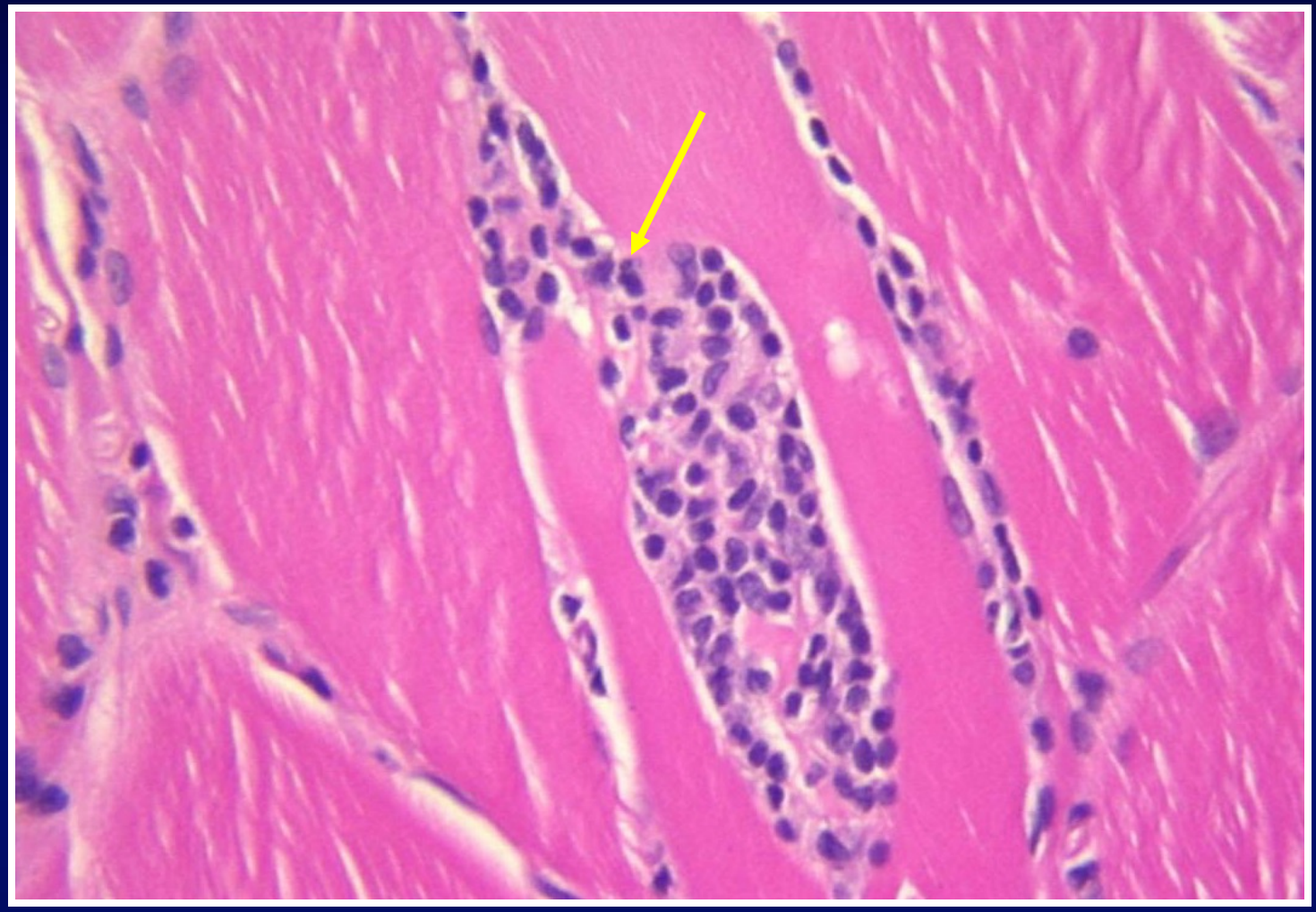
Autoimmunity

- Immune response against *self*
  - loss of tolerance
- Unknown cause
  - susceptibility factors (genetic)
  - environmental triggers
    - e.g. infection / exposures / aging
- Multiple diseases and "syndromes"
  - which sometimes run in families

Autoimmune Diseases

Disease	Target
Rheumatoid Arthritis	Joints (synovium)
Sjogren's Disease	Tear/saliva glands – causes dry eyes/ mouth, can be present in IBM.
Scleroderma	Skin
Multiple Sclerosis	Nervous system
Myositis	Muscle

Most AI diseases have **multiple** targets!



Immune cells (lymphocytes) “attacking” normal muscle tissue in a patient with myositis

Conventional Classification of Myositis

- Inclusion body myositis (IBM)
- Polymyositis (PM)
- Immune-mediated necrotizing myopathy (IMNM)
- Dermatomyositis (DM)
- Juvenile myositis (DM >> PM)
- Malignancy-associated myositis
- Myositis in overlap with another rheumatic disease

There are many other types of myositis that are much more uncommon

How Does a Doctor Diagnose Myositis ?

- Careful history and physical examination including tests for muscle weakness
- Blood tests for increased muscle enzymes: CK (also called CPK or Creatine Phosphokinase), aldolase
  - LDH and Liver Enzymes (ALT/SGPT or AST/SGOT) are also present in muscle and may be elevated in most muscle diseases.
- EMG (electromyography): needle study of muscles
- Muscle biopsy: looking for characteristic pathologic changes in the muscle fibers and blood vessels
  - "immune cells" including lymphocytes
  - vacuoles or inclusions in IBM
- Other diagnostic tests: autoantibody testing in blood; MRI; more specialized testing to rule out other diseases that might mimic myositis

Inclusion Body Myositis

- Most common acquired muscle disease over the age of 50
- Sporadic IBM (sIBM) = IBM
- Hereditary IBM (hIBM) is very rare
- Affects men > women at 2-3:1
- Average time from symptom onset to diagnosis is ~ 5 years

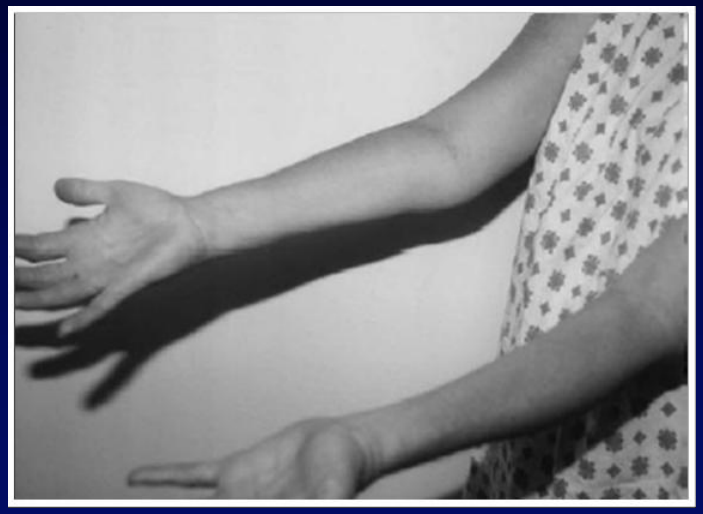
Clinical Features of IBM

- IBM often considered in patients diagnosed with PM who do not respond to treatment
- Insidious (very slow) onset of painless muscle weakness with slow progression
- Early involvement of specific distal (away from the trunk muscles) and asymmetric muscle involvement
  - knee extension (quads)
  - grip weakness (finger flexors)
  - "foot drop"
- Difficulty swallowing
- Characteristic pattern of muscle atrophy and weakness
  - forearm flexors, thigh (quadriceps)

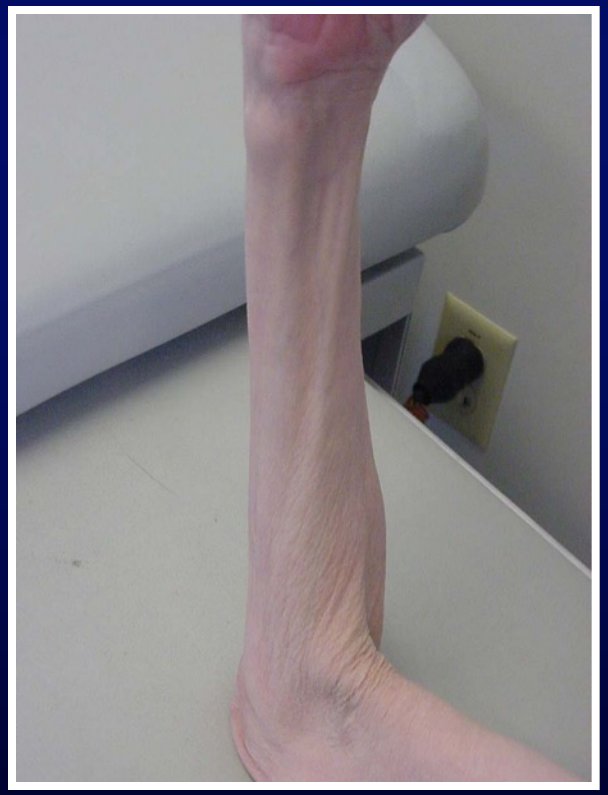
Finger flexion weakness

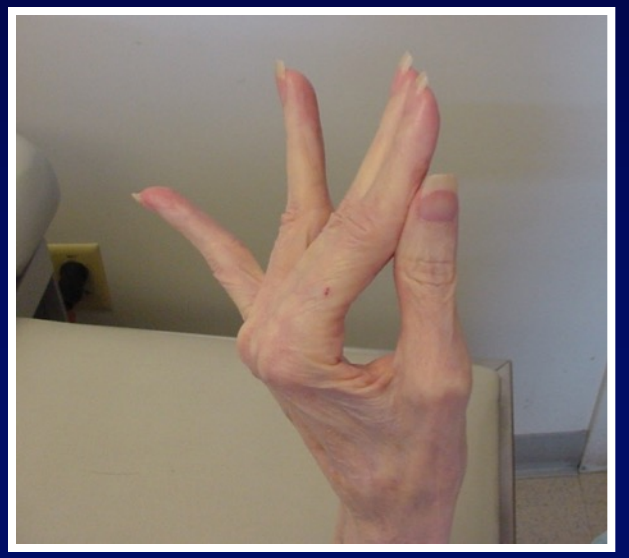
“fist sign”

Inclusion Body Myositis



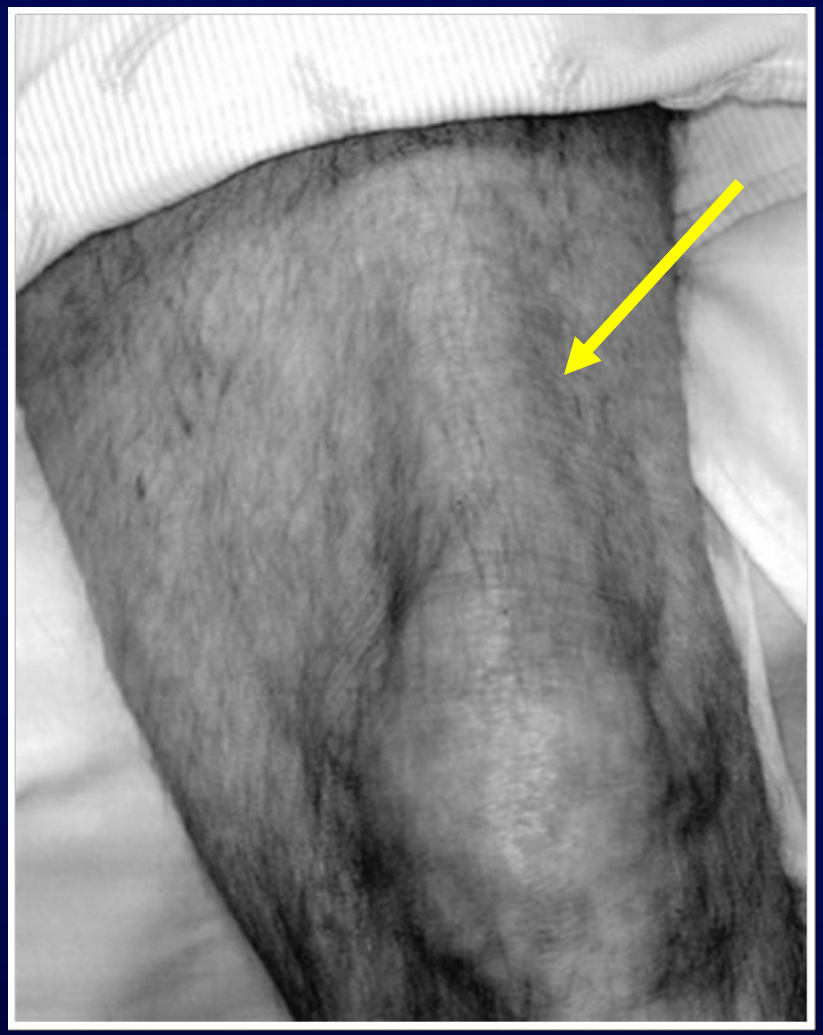
"scooped out" forearm





"teardrop sign"

IBM: Quadriceps Atrophy



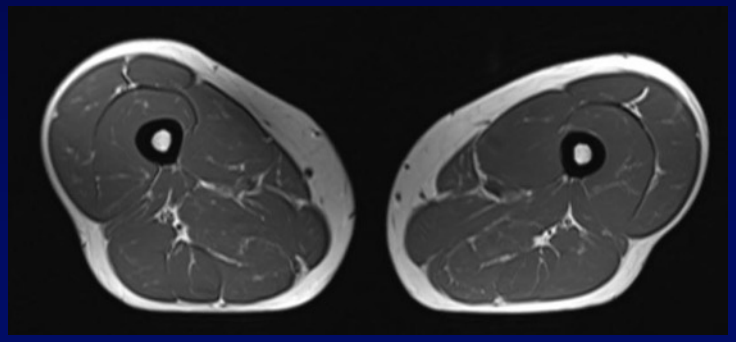
Felice, Medicine, 2001

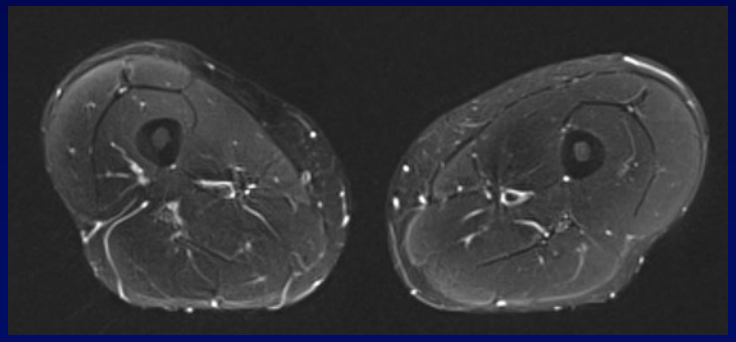
Muscle MRI

T1
Fat = bright
Muscle = dark

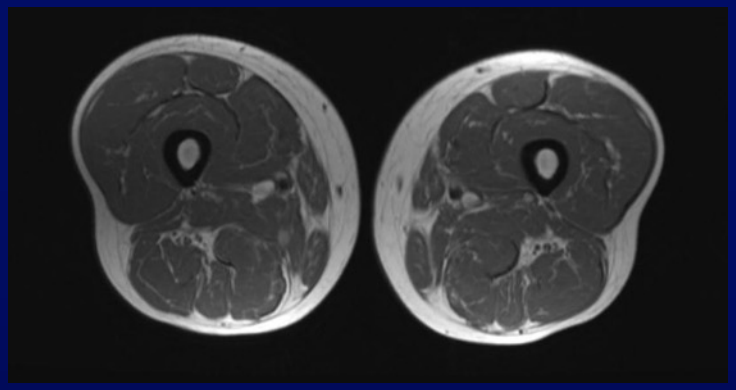
STIR
"Edema" = bright (inflammation)
Normal muscle and fat = dark

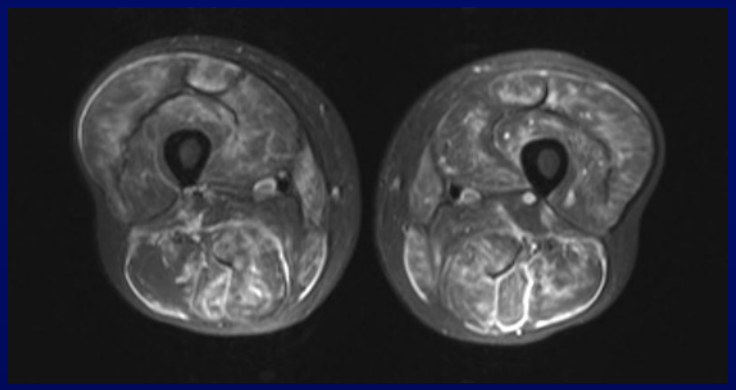
Normal



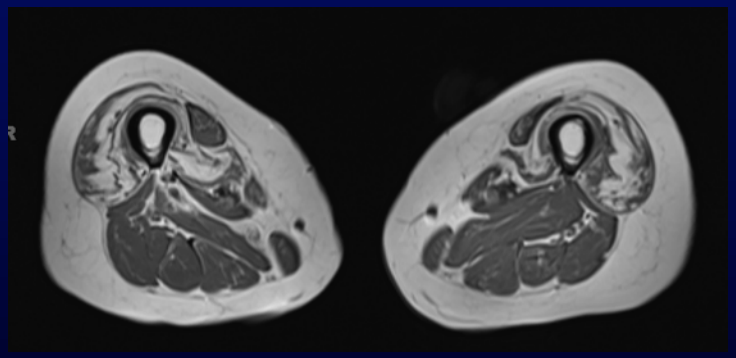


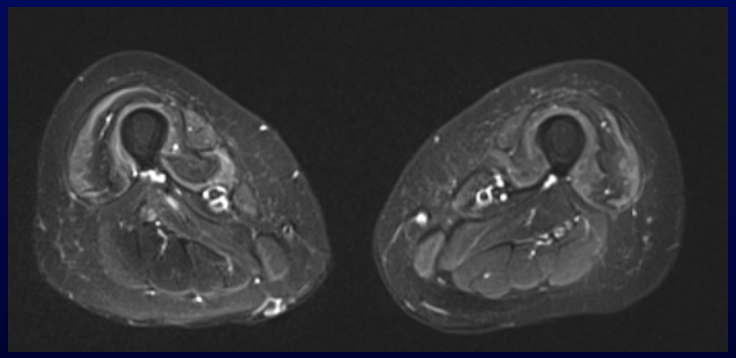
Acute DM
Diffuse muscle edema
No fatty replacement





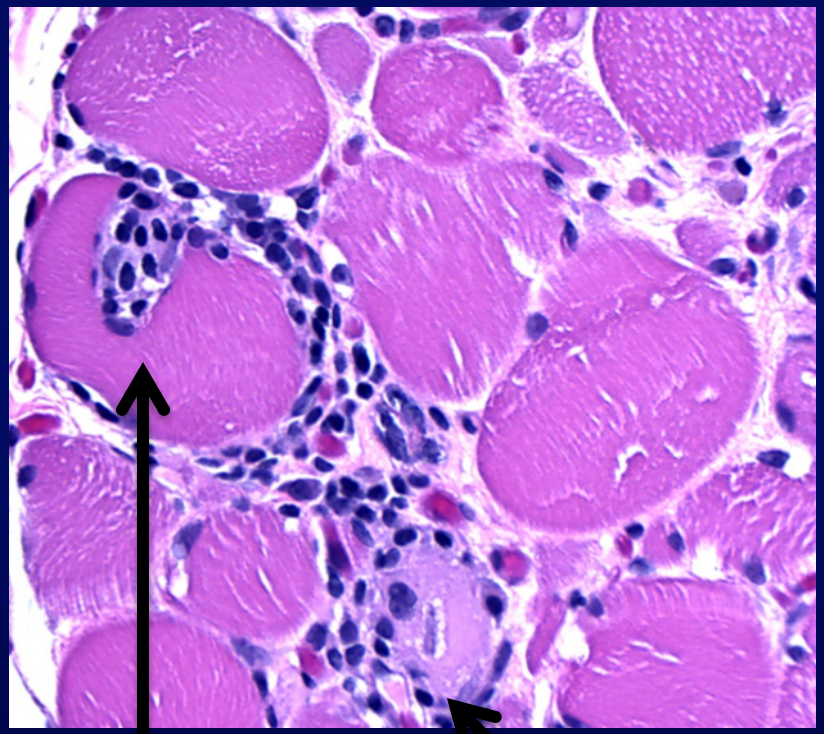
IBM
Fatty replacement
and edema in quads





IBM pathology

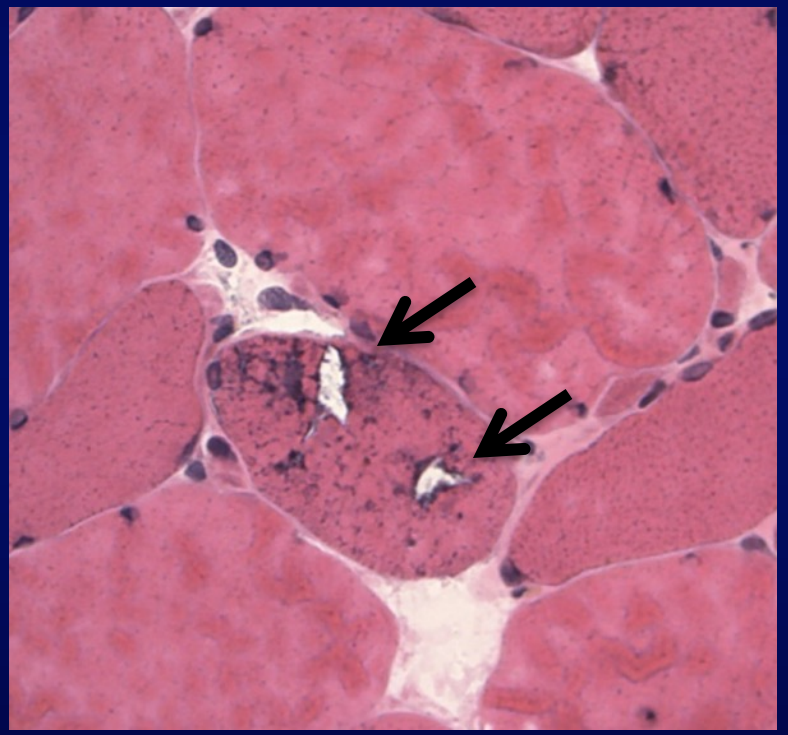
Primary Inflammation



Invasion of T Cells

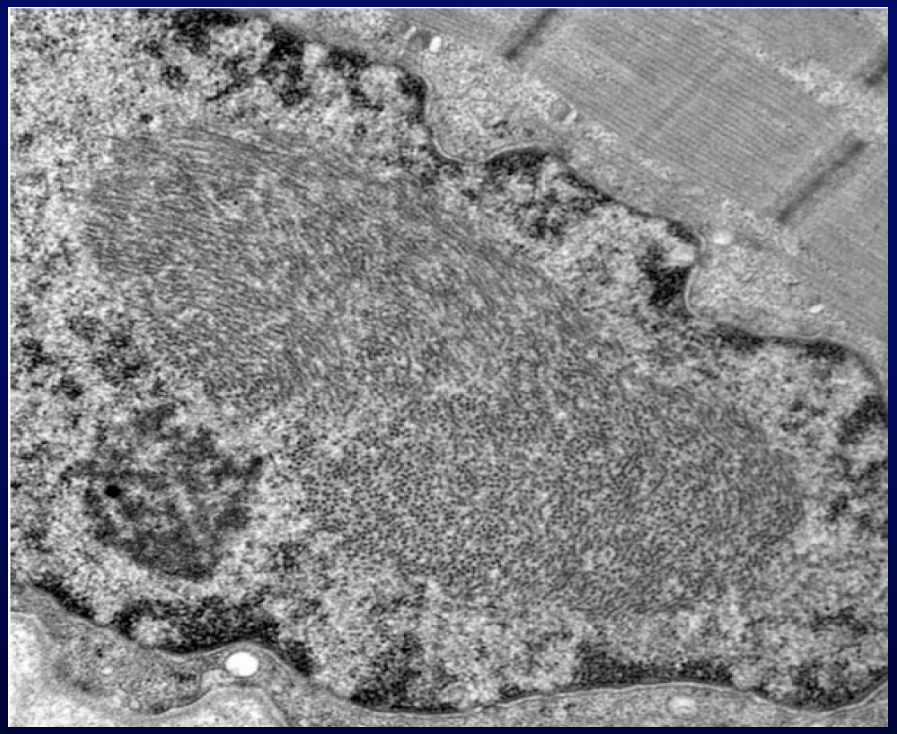
Myofiber Degeneration

Rimmed Vacuoles

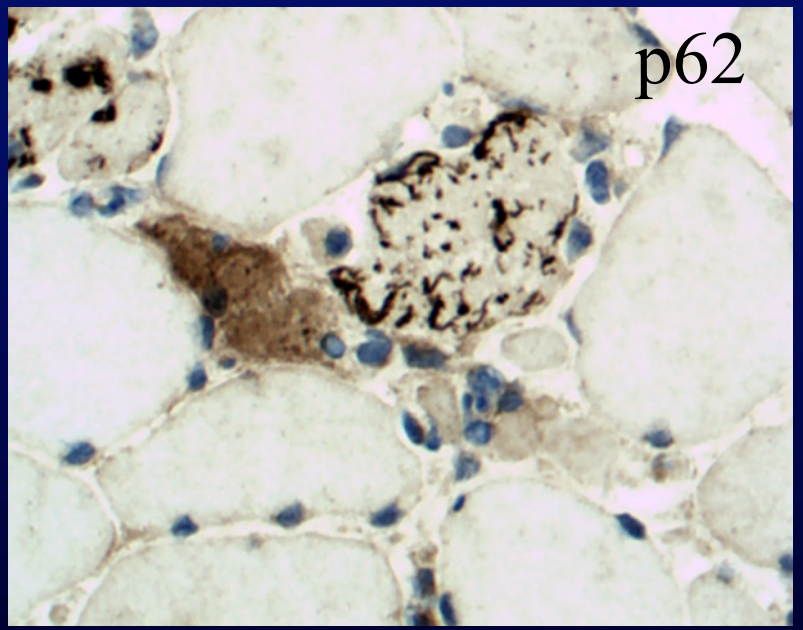


Inclusion Body Myositis: Inclusions

Electron microscope: 15–21-nm tubulofilamentous inclusion



"Amyloid" deposits



How certain is my doctor of the IBM diagnosis?

Study: Machine-based learning applied to 371 patients
"Gold standard": Definite diagnosis of IBM made by specialist

Data-derived Criteria (DDC) for IBM
All 3 of the following features:
1. Finger flexion OR knee extension weakness
2. Endomysial Inflammation
3. Invasion of non-necrotic fibers OR rimmed vacuoles

90% sensitivity and 96% specificity

Lloyd TE, et al, Neurology 2014; 83:426-33

Is the IBM autoantibody a useful diagnostic test?

- Autoantibody recognizes cytosolic 5'-nucleotidase 1A (NT5c1a or CN1a)
  - 72% sensitive
  - 92% specific
  - Recent studies show variable sensitivity (37-76%) → If negative, **NOT helpful**
  - Larman, et al. Ann Neurol, 2013
- Our study (Lloyd et al., Arthritis Care Research 2016)
  - 71 (61%) of 117 patients with IBM,
  - 2 (5%) of 42 patients with PM or healthy volunteers
  - 10 (23%) of 44 patients with Sjögren's syndrome
    - Multiple other studies: range 0-36%.
  - 13 (14%) of 96 patients with Lupus (SLE):
    - Multiple other studies: range 0-20%.
  - <u>Thus, even if antibody positive, not entirely specific for IBM.</u>
- Conclusion: cN1a antibody testing <u>may</u> be helpful in atypical cases
  - Rimmed Vacuoles present in 83% of ab-negative patients; 62% of ab-positive
  - Thus vacuoles less like-likely to be testing in ab-positive patients

IBM "mimics"

- Polymyositis
  - Patients often treated aggressively with immunosuppressive medications, leading to complications
- Rimmed Vacuole Myopathies
  - Inherited Myopathies
    - Hereditary IBM (clinically usually distinct)
    - Oculopharyngeal Muscular Dystrophy (OPMD)
    - Limb Girdle Muscular Dystrophy (LGMD)
      - Dysferlinopathy, ANO5
    - Fascioscapulohumeral dystrophy (FSHD)
  - Colchicine, chloroquine, hydroxychloroquine? (toxic)
  - Denervation (eg ALS)

My doctor says there's no treatment for IBM, is that true?

No! While there's no cure, there are many things you can do to manage the disease.

Where to get information on different therapies?

- Reliable Websites
  - Myositis.org
  - Cureibm.org

  (Kevin Dooley MD)
  - MDA website
  - For doctors:
    - **Uptodate**
    - **Pubmed**
- Be cautious
  - Patientslikeme
  - Facebook
  - Blogs
  - Google

Asked what he would like others to learn from his experience, Mr. Gass said, "Don't trust anecdotes."

His sister-in-law had a different reply: "If something sounds too good to be true, it is."

Management of inclusion body myositis

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INTRODUCTION

Sporadic inclusion body myositis (IBM) is classified along with polymyositis, dermatomyositis, and autoimmune necrotizing myopathy as one of the idiopathic inflammatory myopathies. However, despite some histologic similarities, the clinicopathologic manifestations, treatment, and prognosis of IBM are clearly distinct from the other disorders (table 1). (See "Clinical manifestations of dermatomyositis and polymyositis in adults" and "Initial treatment of dermatomyositis and polymyositis in adults" and "Treatment of recurrent and resistant dermatomyositis and polymyositis in adults".)

The treatment and prognosis of IBM will be reviewed here. The clinical manifestations and diagnosis are presented separately. (See "Clinical manifestations and diagnosis of inclusion body myositis".)

GOALS OF THERAPY

The primary goal of therapy in inclusion body myositis (IBM) is to optimize muscle strength and function. Given the slowly progressive and variable course of the disease, it can be quite challenging to determine if treatment leads to an objective improvement in or stabilization of muscle strength [1]. It is well known that immunosuppressive medications will lower muscle enzyme levels in IBM patients despite continued progression of weakness, and also that creatine kinase (CK) levels decrease with muscle atrophy [2,3]. Therefore, CK levels cannot be used to monitor response to therapy in this disease. Based on the existing data, we only consider a trial of immunosuppressive medications in IBM patients with an atypical presentation or in patients with another autoimmune disease.

1. Maintain quality of life
2. Avoid complications: falls and choking

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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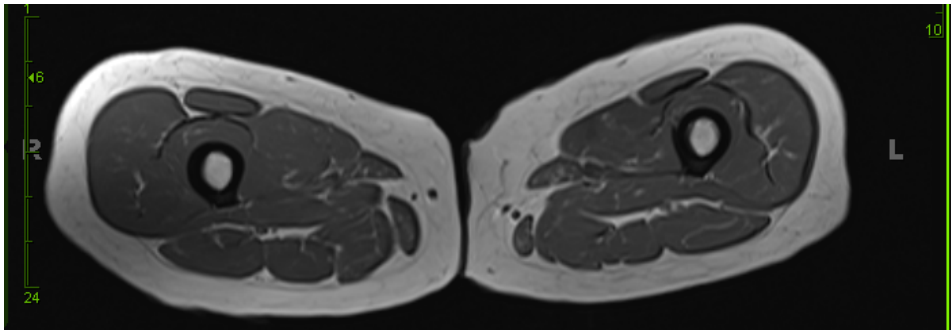
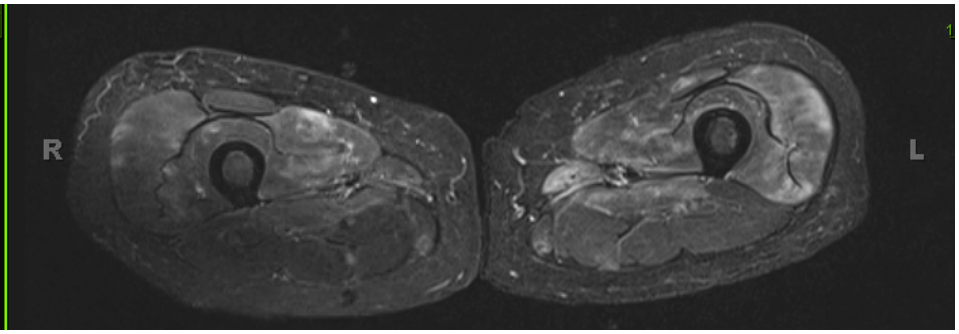
IBM Treatment - Immunosuppressives

- **Do some patients partially respond to immunosuppression?**
  - Some IBM specialists will try methotrexate or other agent but taper if no objective sign of improvement or at least stabilization in strength.
  - CK can NOT be used to measure treatment response.

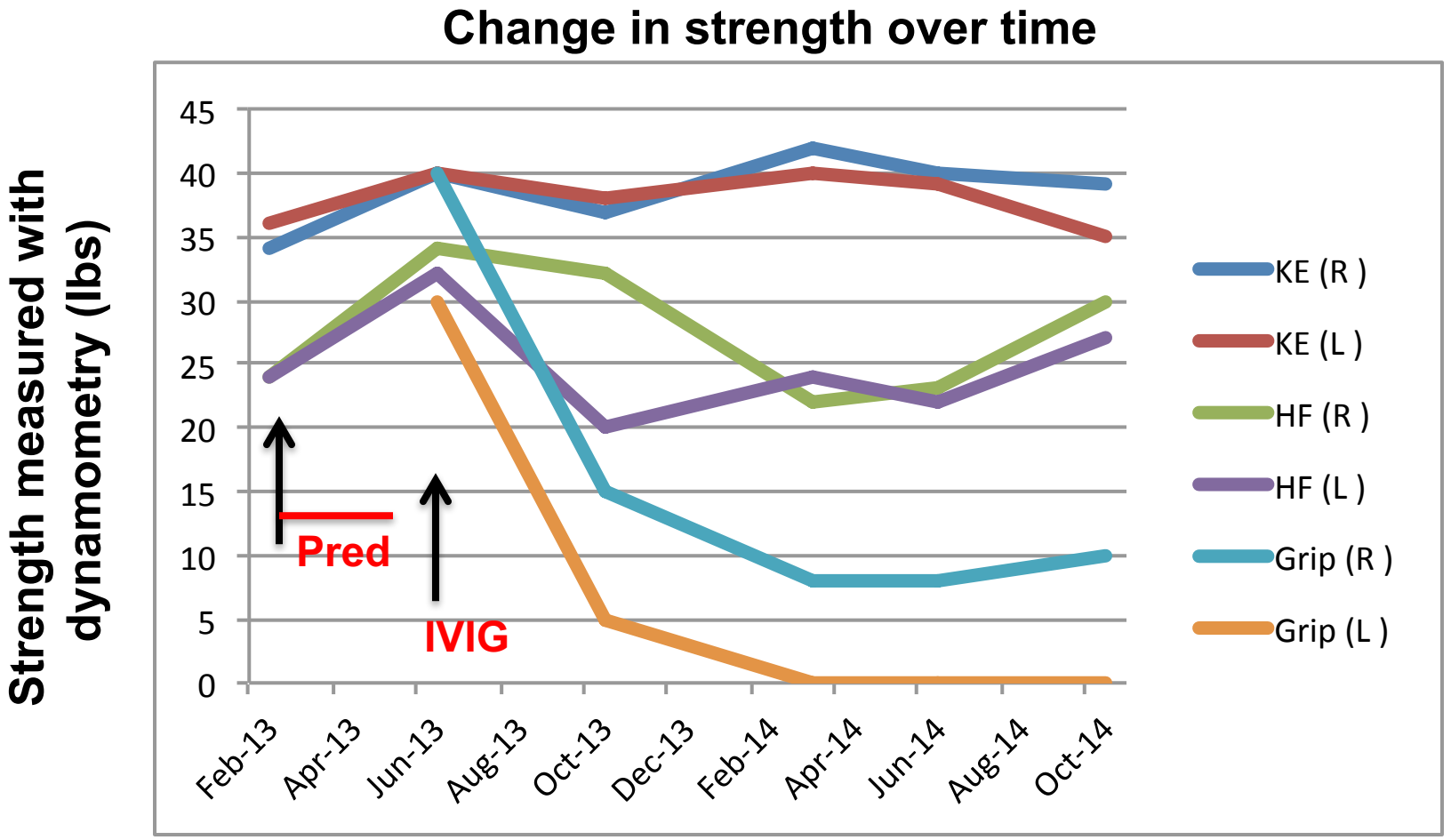
- Case: 68 yo woman 18 mos progressive weakness, starting with left foot drop, progressing to proximal bilateral leg and hand weakness and dysphagia.
  - Exam: typical pattern of weakness, CK ~1000
  - EMG: irritable myopathy
  - Muscle Bx: intense inflammation with rimmed vacuoles



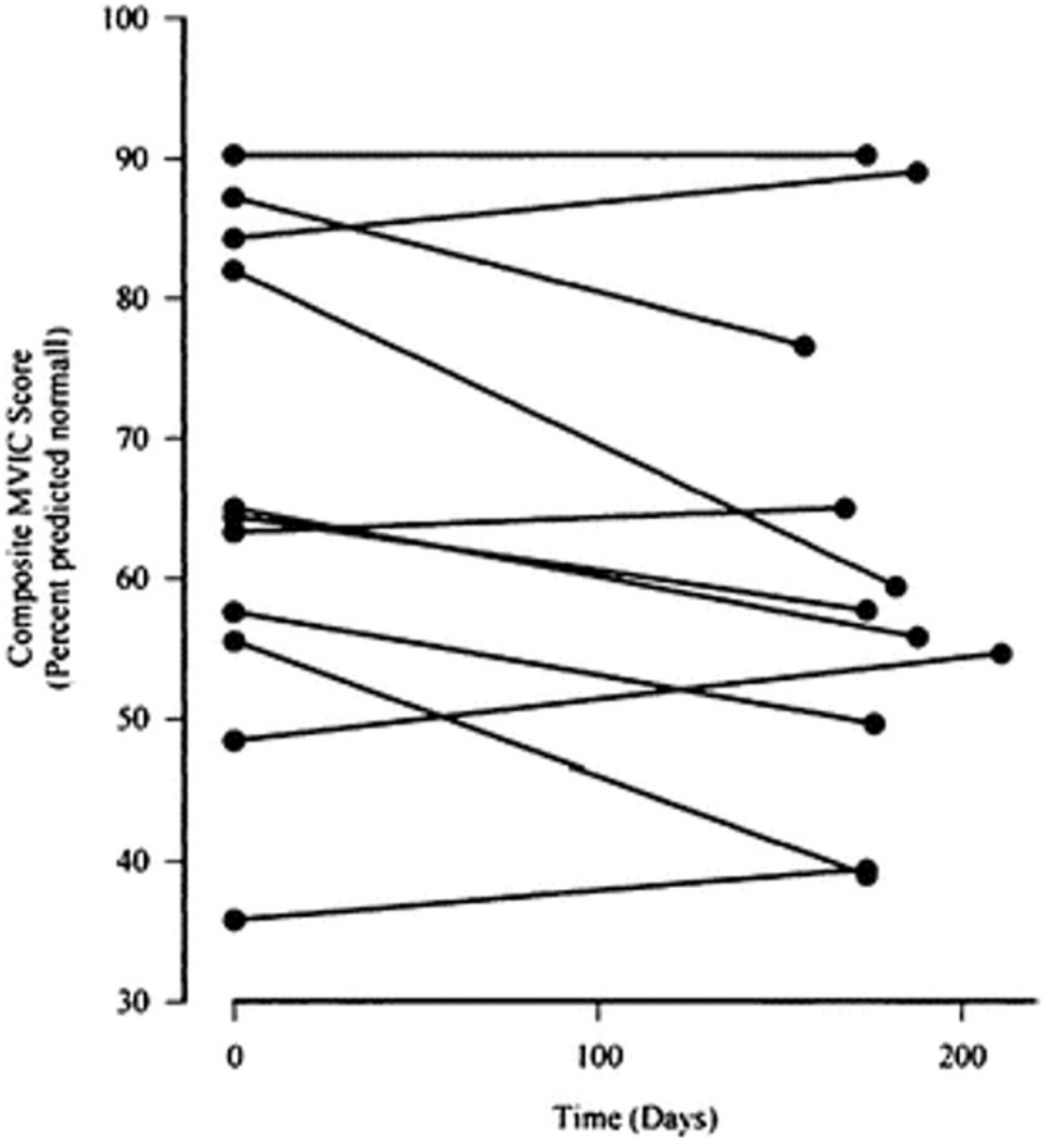


IBM Treatment - Immunosuppressive

- **Do some patients partially respond to immunosuppression?**



Natural History of IBM



Quantitative Myometry

Griggs R C Neurology 2006;66:S30-S32

AMERICAN ACADEMY OF NEUROLOGY®

Table 1 | **IBM clinical trials**

Therapeutic	Year of clinical trial registration	Year of publication	Number of patients	Duration of treatment (months)	Outcome measures: primary (secondary)
Blinded placebo-controlled studies					
IVIG	NA	1997	19	3	QMT (MMT)
		2000	22	6	MMT (NSS)
IVIG + prednisone	NA	2001	37	3	QMT (MMT)
Low-dose IFNβ1a	NA	2001	30	6	QMT (MMT)
High-dose IFNβ1a	NA	2004	30	6	QMT (MMT)
Oxandrolone	NA	2002	19	6	QMT (MMT)
Methotrexate	NA	2002	44	11	QMT (MMT)
Etanercept	2005	NA	20	12	QMT (MMT)
Arimoclomol	2008	2016	24	4	Safety (QMT)
Bimagrumab	2011	2014	14	6	MRI (QMT)
	2013	NA	240	12	6MWD (sIFA)
Rapamycin	2015	NA	44	12	QMT (grip QMT) of quadriceps
Arimoclomol	2016	NA	150	20	IBMFRS (MMT)

6MWD, 6-minute walking distance; DEXA, dual-energy X-ray absorptiometry; IBMFRS, inclusion body myositis functional rating scale; IVIG, intravenous immunoglobulin; MMT, manual muscle testing; NA, not applicable; NSS, neuromuscular symptom score; QMT, quantitative muscle testing; sIFA, sIBM functional assessment.

EBM (Evidence Based Medicine) for IBM

Conventional treatments

- *Diet*
- *Medications*
  - Immunosuppressive meds
  - Muscle growth promoting meds
  - Mainstream supplements
- *Devices*
  - Walking aids
  - Ankle-foot orthoses
- *Therapies*
  - Physical therapy / exercise
  - Occupational therapy
- *Procedures*
  - Esophageal dilation
  - Cricopharyngeal myotomy

"Alternative" treatments

- *Diet*
- *Medications*
  - "Antiinflammatory" supplements
  - "Bodybuilding" supplements
  - Other nutriceuticals
- *Devices*
  - Exoskeleton
  - E-stim (electrical stimulation)
- *Therapies*
  - Massage
  - Accupuncture
- *Procedures*
  - Stem cell injection
  - Hyperbaric oxygen chamber

Clinical Trials

Why so few clinical trials in sIBM?

1. Pathogenesis poorly understood!
   - Good drug targets are unknown.
   - Lack of preclinical animals models
2. Trials are expensive.
   - Pharma will fund clinical trials for rare diseases if can patent.
   - Better surrogate biomarkers need to be developed.
   - “Humanized” mouse models may help.

Therapy - Overview

Speech therapy (SLP)

- SLP referral for dysphagia
- Problems diagnosed by Video Fluoroscopy Swallow Study with SLP Guidance

Physical therapy (PT) and Exercise:

- Stretching to maintain flexibility/avoid contractures
- Exercise: Low impact (eg water aerobics), high frequency, endurance exercises

Occupational therapy

- Mild: “Hand Helper” device to maintain strength and flexibility
- Moderate: Occupational/Hand therapy
  - Exercises
  - Bracing, interphalyngeal (IP) fusion

Dysphagia in IBM

- Usually caused by constriction of upper esophageal sphincter (UES) due to cricopharyngeus involvement
- Diagnosis:
  - Video Fluoroscopy Swallow Study with SLP Guidance
- Management:
  - Mild:
    - Heimlich maneuver training
    - SLP referral - exercises
  - Moderate:
    - GI referral for esophageal dilation
  - Severe/Refractory:
    - ENT referral for surgery (cricopharyngeal myotomy)
    - Consider feeding (PEG) tube if weight loss.

Ankle-foot orthoses

$45

Ossur "Foot-up"

$26

AFO

$260

Carbon Fiber AFO

Carbon Fiber GRAFO "ground reaction"

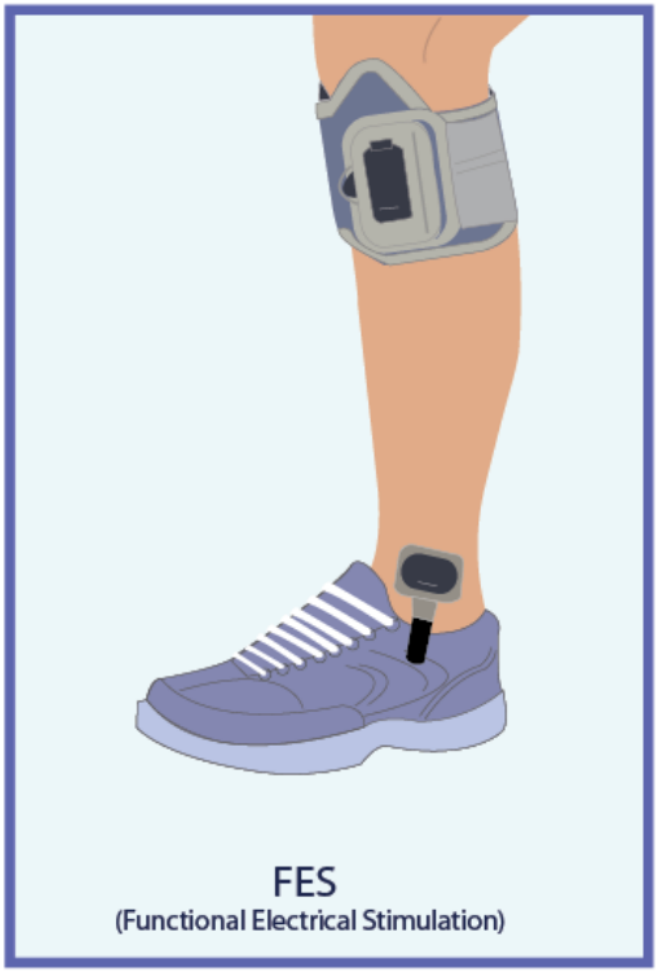
Stance Control Orthosis

COMBO

Custom fitted carbon fiber ground reaction AFO with removable custom fabricated knee orthosis addition to control genu recurvatum

“Alternative” Devices

b-temia
HUMAN AUGMENTATION



Journal of
CLINICAL
NEUROMUSCULAR
DISEASE

Volume 10, Number 4
June 2009

Improvement in Aerobic Capacity After an Exercise Program in Sporadic Inclusion Body Myositis

Liam G. Johnson, BSc(Sp Sci)Hons, Kelly E. Collier, BSc(Sp Sci)Hons,† Dylan J. Edwards, PhD,* Danielle L. Philippe,‡ Peter R. Eastwood, PhD,‡§¶ Susan E. Walters, BAppSci (Physio),* Gary W. Thickbroom, PhD,* and Frank L. Mastaglia, MD**

Results:
Aerobic capacity of the group increased significantly by 38%, and significant strength improvements were observed in 4 of the muscle groups tested ($P < 0.05$). The exercise program was well tolerated, and there was no significant change in the serum creatine kinase level after the exercise period.

Conclusions:
An aerobic exercise program can be safely tolerated by patients with sporadic IBM and can improve aerobic capacity and muscle strength when combined with resistance training. These findings indicate that aerobic and functional muscle strengthening exercise should be considered in the management of patients with IBM.

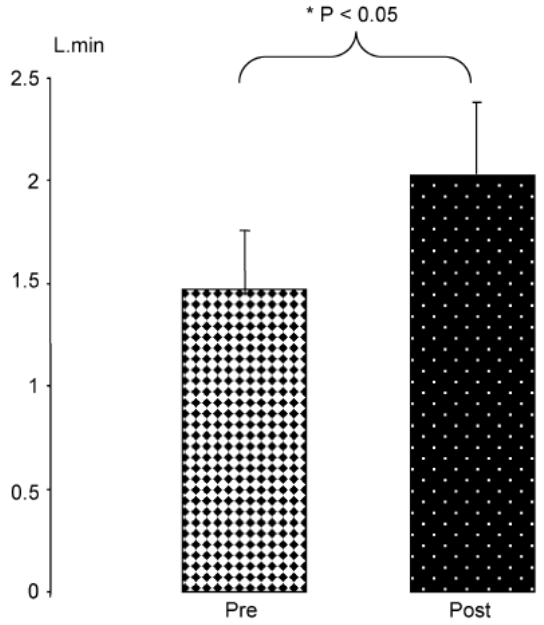


FIGURE 1. Mean (±SE) change in absolute aerobic capacity (L/min) across participants (n = 7), showing a significant improvement after the exercise regimen. *$P < 0.05$.

Improvement in Aerobic Capacity After an Exercise Program in Sporadic Inclusion Body Myositis

Journal of Clinical Neuromuscular Disease. 10(4):178-184, JUN 2009

Liam G Johnson; Kelly E Collier; Dylan J Edwards; Danielle L Philippe; Peter R Eastwood; Susan E Walters; Gary W Thickbroom; Frank L Mastaglia show less

TABLE 3. Mean (±SE) Pre- and Post-Training Muscle Strength Values of the Participants (n = 7)

Muscle	Mean ± SE		P
	Pre-Training	Post-Training	
Untrained			
Grip strength (mm Hg)	150.2 ± 49.9	138.3 ± 55.3	0.122
Shoulder external rotation (kgf)	7.4 ± 0.0	7.6 ± 0.9	0.652
Trained (kgf)			
Knee extension	7.3 ± 0.2	6.6 ± 0.1	0.805
Wrist extension	9.8 ± 0.4	9.1 ± 0.5	0.271
Elbow extension	7.4 ± 0.5	6.8 ± 0.3	0.067
Elbow flexion	10.9 ± 0.5	11.0 ± 0.3	0.402
Shoulder abduction	12.3 ± 0.6	17.2 ± 0.5	0.000**
Hip flexion	11.5 ± 1.2	15.6 ± 0.7	0.008*
Hip abduction	9.0 ± 0.4	10.5 ± 0.2	0.041*
Knee flexion	10.4 ± 0.4	11.5 ± 0.3	0.027*

*$P < 0.05$. **$P < 0.001$.

Massage, Accupuncture

- Little scientific evidence that it is helpful
- Essentially impossible to conduct placebo-controlled trial
- Minimal risk
- Placebo effect is real and can be beneficial!
- So, if it works for you that's great!

Medications

Conventional treatments

- Immunosuppressive meds (SE)
  - IVIG
  - Methotrexate
  - *Statins*
- Muscle growth meds (SE)
  - Oxandrolone / testosterone
  - Bimagrumab*(research only)
  - AAV-Follistatin*(research only)
  - Growth Hormone
- Mainstream supplements
  - Creatine (cheap)
  - CoenzymeQ10 (can be pricey)

"Alternative" treatments

- "Anti-inflammatory" supplements / diet
- "Bodybuilding" supplements
  - Myo-X

Myostatin Inhibitor Hype and Failure

Vantage August 30, 2018

Pfizer bows out of myostatin inhibition in Duchenne muscular dystrophy

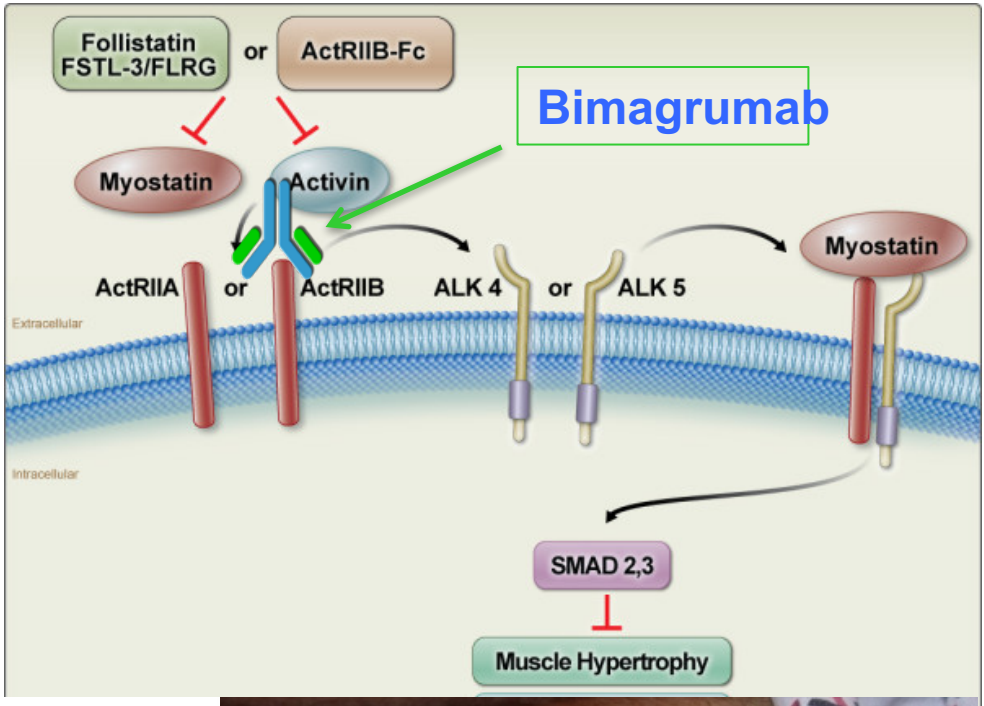
> *MYO-X supplement helped me with my workouts thanks Carlon Colker*
> *— Justin Bieber (@justinbieber) January 7, 2015*

SUMMARY

- For alternative/off-label treatments (AOTs) consider risks/costs vs benefits
  - If plausible mechanism, evidence of efficacy in other muscle diseases, and low risk/cost – **I recommend.**
    - **Exercise**
    - **Creatine**
    - **Consider: CoenzymeQ10**
    - **If doctor recommends statin, I recommend rosuvastatin lowest dose.**
  - If lack of clear mechanism or efficacy but negligible side effects – **I am neutral/supportive.**
    - **Massage**
    - **Accupuncture**
    - **Placebo! -- the power of positive thinking.**

Monoclonal antibodies to ligands or receptors

- Follistatin gene therapy trial
  - Jerry Mendell at Nationwide
  - 3 low dose, 3 medium dose, 3 high dose
  - Bilateral quad injections



Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Follistatin Gene Therapy for Sporadic Inclusion Body Myositis Improves Functional Outcomes

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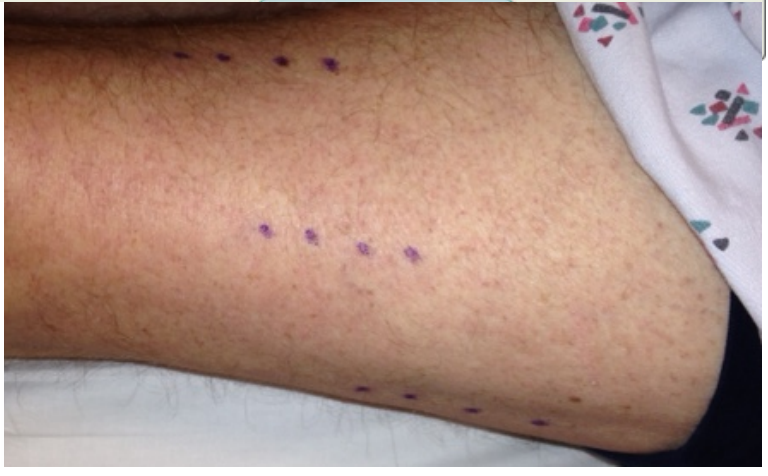

Safety and efficacy of intravenous bimagrumab in inclusion body myositis (RESILIENT): a randomised, double-blind, placebo-controlled phase 2b trial

*Michael G Hanna, Umesh A Badrising, Olivier Benveniste, Thomas E Lloyd, Merrilee Needham, Hector Chinoy, Masashi Aoki, Pedro M Machado, Christina Liang, Katrina A Reardon, Marianne de Visser, Dana P Ascherman, Richard J Barohn, Mazen M Dimachkie, James A L Miller, John T Kissel, Björn Oskarsson, Nanette C Joyce, Peter Van den Bergh, Jonathan Baets, Jan L De Bleecker, Chafic Karam, William S David, Massimiliano Mirabella, Sharon P Nations, Hans H Jung, Elena Pegoraro, Lorenzo Maggi, Carmelo Rodolico, Massimiliano Filosto, Aziz I Shaibani, Kumaraswamy Sivakumar, Namita A Goyal, Madoka Mori-Yoshimura, Satoshi Yamashita, Naoki Suzuki, Masahisa Katsuno, Kenya Murata, Hiroyuki Nodera, Ichizo Nishino, Carla D Romano, Valerie S L Williams, John Vissing, Lixin Zhang Auberson, Min Wu, Ana de Vera, Dimitris A Papanicolaou, Anthony A Amato, and the RESILIENT Study Group**

Funding Novartis Pharma.

Lancet Neurol 2019; 18: 834–44

See Comment page 807

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Summary

Background Inclusion body myositis is an idiopathic inflammatory myopathy and the most common myopathy affecting people older than 50 years. To date, there are no effective drug treatments. We aimed to assess the safety, efficacy, and tolerability of bimagrumab—a fully human monoclonal antibody—in individuals with inclusion body myositis.

Methods We did a multicentre, double-blind, placebo-controlled study (RESILIENT) at 38 academic clinical sites in Australia, Europe, Japan, and the USA. Individuals (aged 36–85 years) were eligible for the study if they met modified 2010 Medical Research Council criteria for inclusion body myositis. We randomly assigned participants (1:1:1:1) using a blocked randomisation schedule (block size of four) to either bimagrumab (10 mg/kg, 3 mg/kg, or 1 mg/kg) or placebo matched in appearance to bimagrumab, administered as intravenous infusions every 4 weeks for at least 48 weeks. All study participants, the funder, investigators, site personnel, and people doing assessments were masked to treatment assignment. The primary outcome measure was 6-min walking distance (6MWD), which was assessed at week 52 in the primary analysis population and analysed by intention-to-treat principles. We used a multivariate normal repeated measures model to analyse data for 6MWD. Safety was assessed by recording adverse events and by electrocardiography, echocardiography, haematological testing, urinalysis, and blood chemistry. This trial is registered with ClinicalTrials.gov, number NCT01925209; this report represents the final analysis.

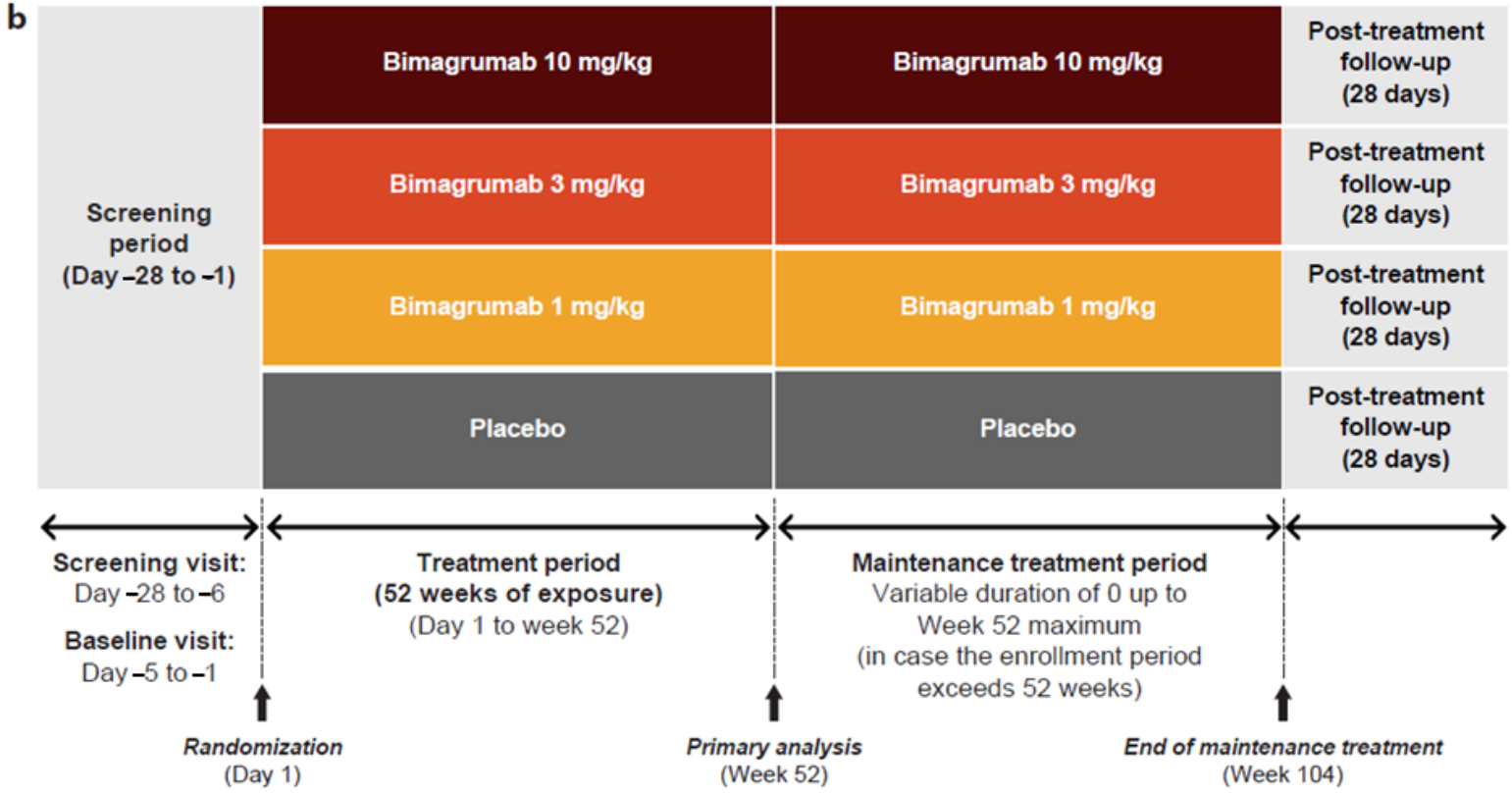
Interpretation Bimagrumab showed a good safety profile, relative to placebo, in individuals with inclusion body myositis but did not improve 6MWD. The strengths of our study are that, to the best of our knowledge, it is the largest randomised controlled trial done in people with inclusion body myositis, and it provides important natural history data over 12 months.

RESILIENT Study: A Phase IIb/III, Randomised, Double-Blind, Placebo-Controlled Study of Bimagrumab in Inclusion Body Myositis

Patients:

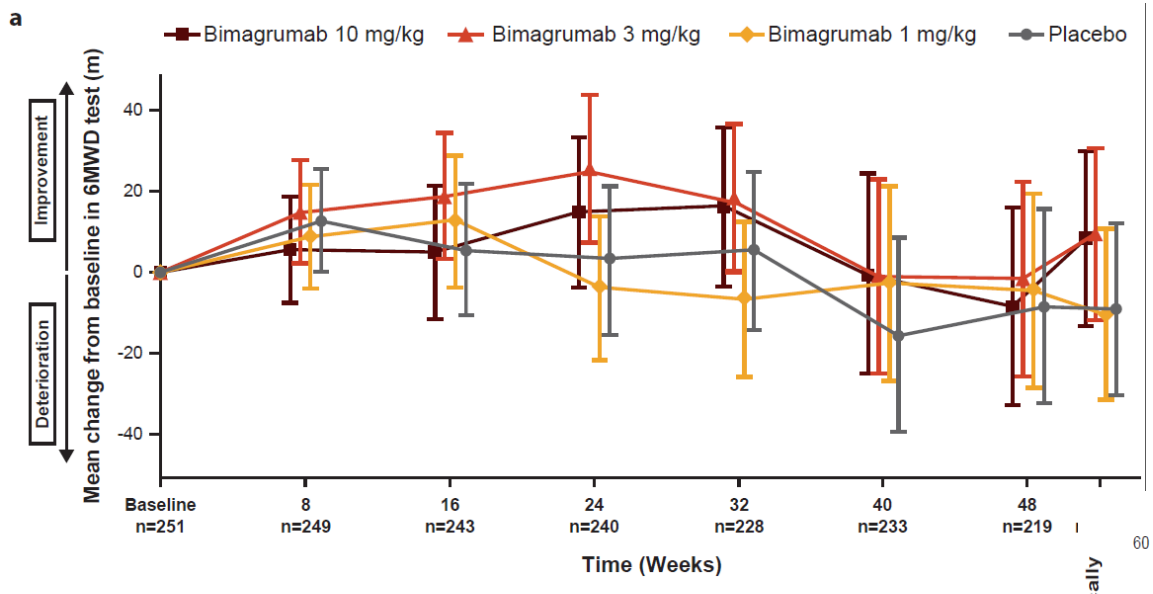
240 men and women (aged 36-85)

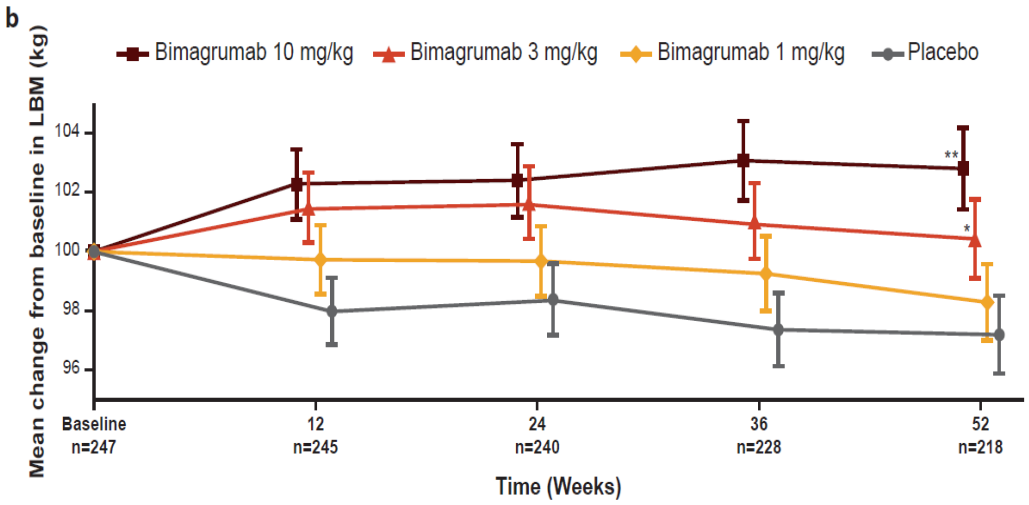
24 sites internationally; 12 in US



Hanna MG, Badrising UA, Benveniste, O, Lloyd TE, et al (Lancet Neurology) in press.

Negative primary outcome but promising secondary outcome measures



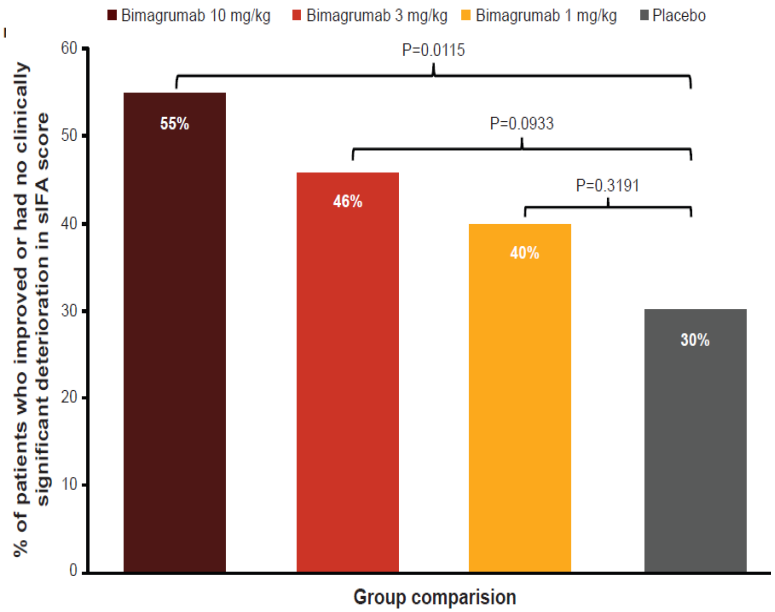


Primary: 6 minute walk distance

- no significant difference
- High variability

Dexa – dose-dependent increase in muscle mas

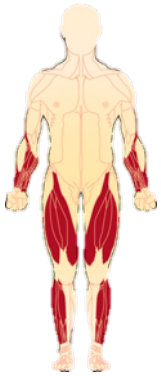
sIFA – dose-dependent improvement in PROs.



What is primary cause of disease?

- **Autoimmune?**
  - Invasion of healthy myofibers by CD8+ T cells
  - Increased prevalence of other autoimmune diseases
    - Association with Sjögren's, Sarcoid
  - Increased association w/ specific HLA haplotypes (HLA-DR3)
  - Early HIV-myositis looks autoimmune, but evolves into IBM-like phenotype (Lloyd et al, Neurology, 2017).
- **Degenerative?**
  - A disease of aging (typically over 50 yo)
  - Accumulation of amyloid, aggregates, autophagosomes
  - Not responsive to immunosuppression
  - IBMPFD (rare genetic form of IBM with Paget's disease and Frontotemporal dementia).
    - Same mutations in VCP gene also cause ALS / FTD.
    - Reports of pathogenic VCP mutations in patients with clinical features of sporadic IBM

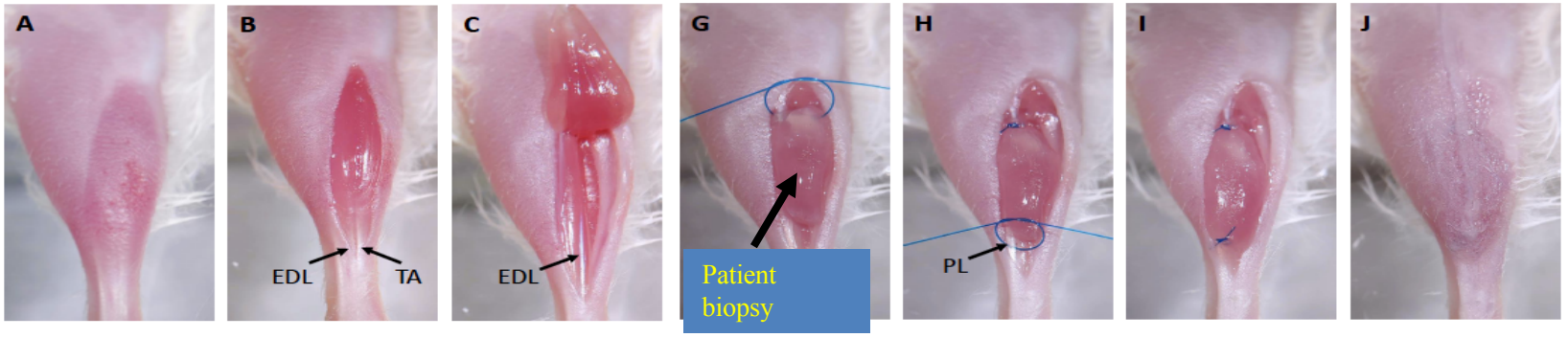
A New Xenograft Model of IBM to study the disease and develop new treatments



(1) Muscle Biopsy Sample

(2) Donor muscle dissected into small pieces

(3) Xenografts are transplanted into host mice

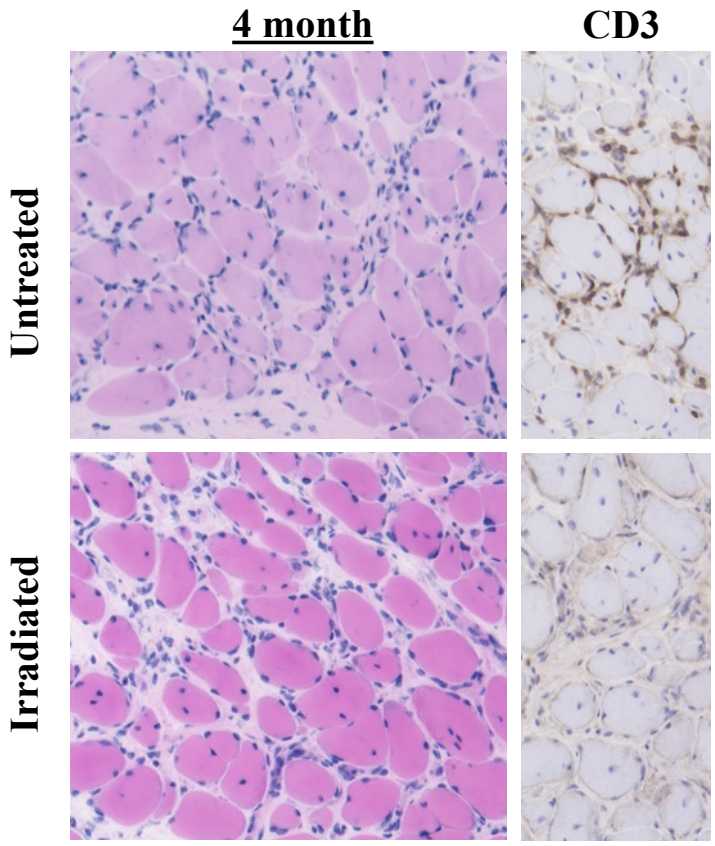


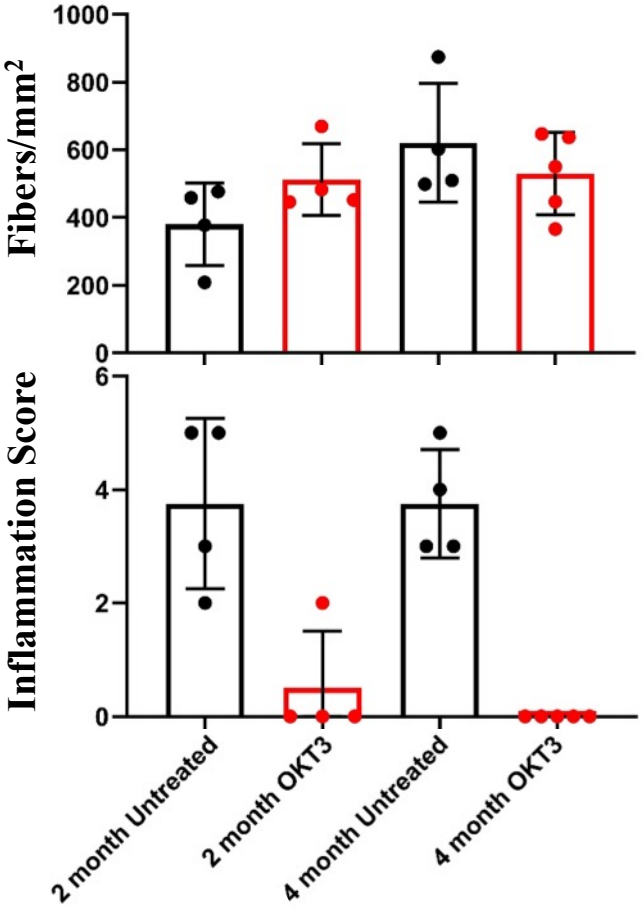
NOD-*Rag1*^{null} *IL2rγ*^{null}

Mice do not make mature B or T cells

Britson et al JOVE– Wagner Lab

OKT3 treatment dramatically reduces number of inflamm cells – what about muscle degeneration?





Acknowledgements

Lloyd Lab
Kyla Britson
Nicole Reed
Will Tsao MD, PhD
Kai Ruan, Ph.D.
Ke Zhang, Ph.D.
Mark Wilhelm
Kathleen Cunningham
Hyun Sung, Ph.D.
Saksham Gupta
Brian Woolums
Andrew Cheng

Hopkins Neuromuscular
Kathryn Wagner MD PhD
Andy Mammen MD PhD
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Ben Larman Lab
Janelle Montagne
Xuwen (Alice) Zheng

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