

Inclusion body myositis clinical features, diagnosis and management

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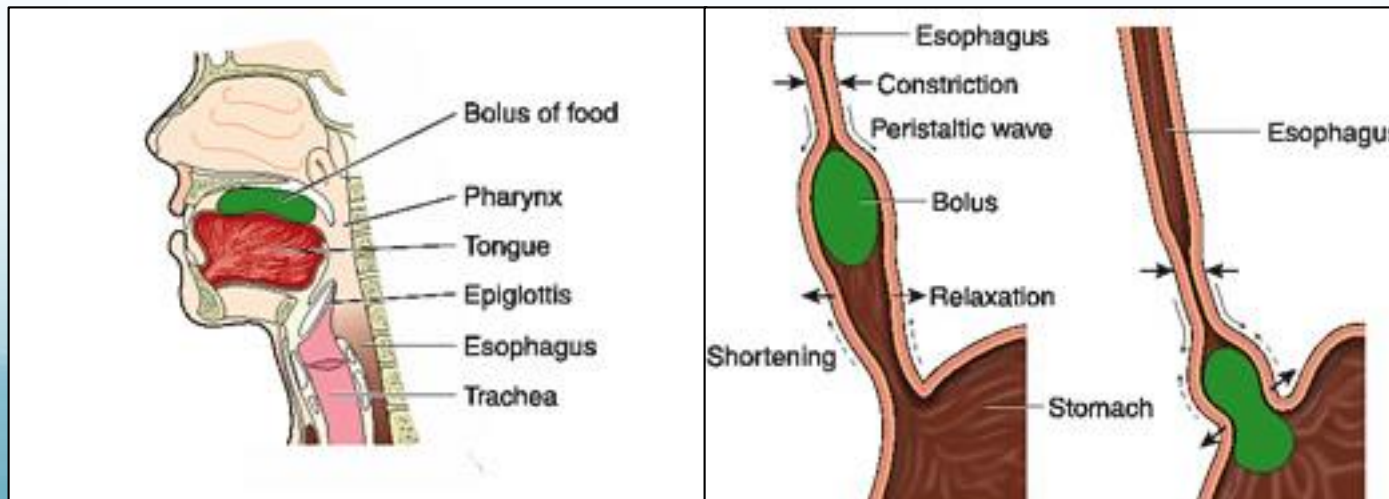
Inclusion body myositis

- Most frequent myopathy > 50 years.
- Males > females
- Prevalence:
 - 1.1 per million in Turkey
 - 4.9 per million in the Netherlands
 - 9.8 per million in Japan
 - 10.7 per million in the USA
 - 14.9 per million in Western Australia
 - 33 per million in Norway
 - 50.5 per million in South Australia

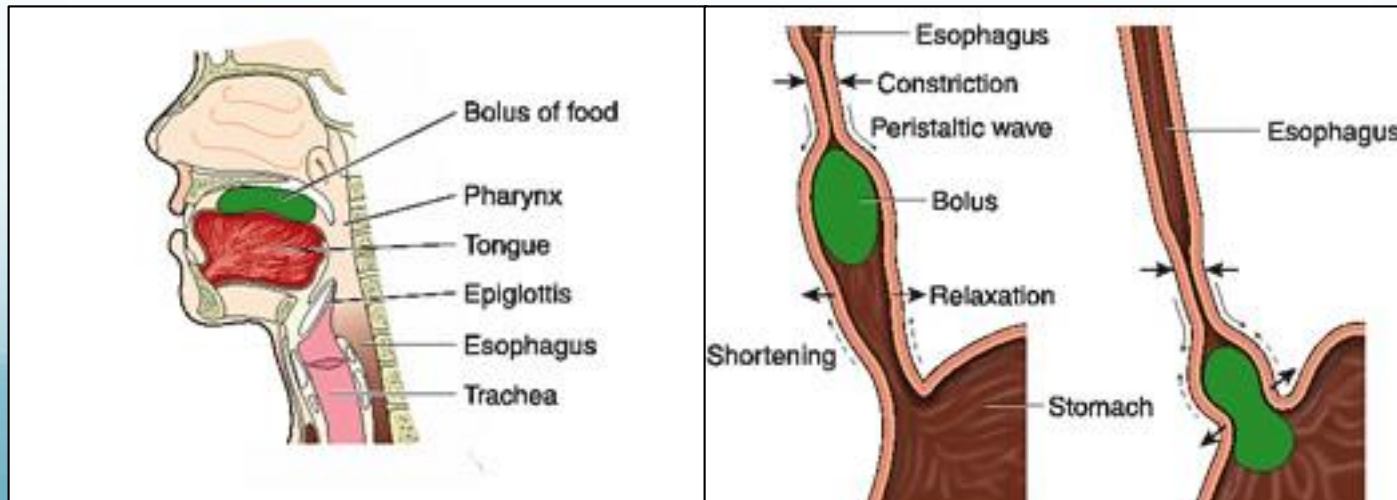
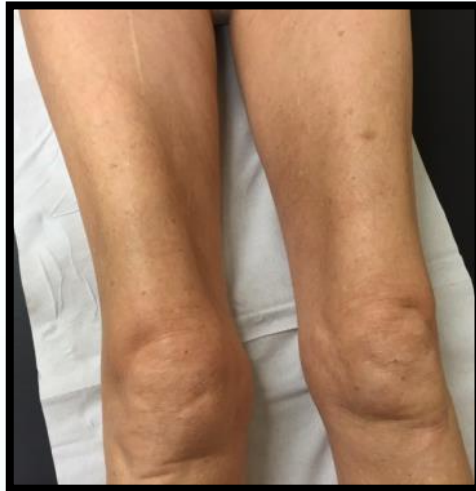
Clinical presentation

- 35% falls and difficulty standing
- Decreased dexterity, swallowing difficulty
- Slowly progressive muscle weakness, often asymmetrical
- Characteristic distribution
 - Thigh muscles (quadriceps)
 - Finger flexors
 - Oesophageal muscles (swallowing)
 - (Facial weakness)
- Usually no muscle pain

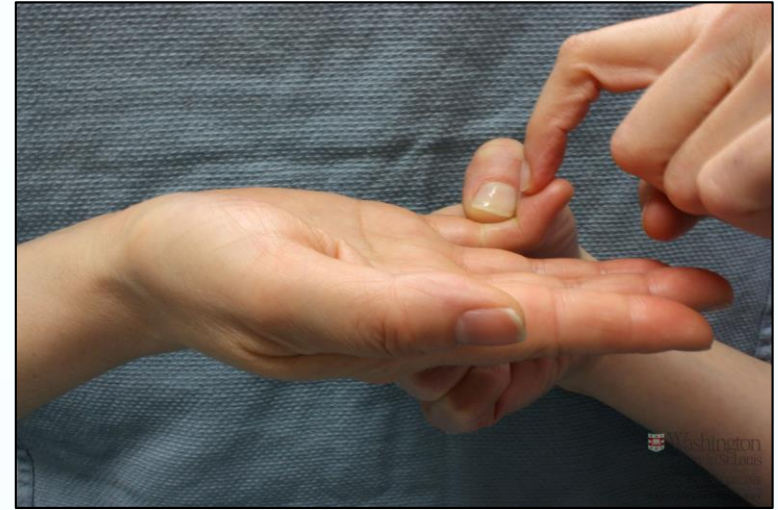
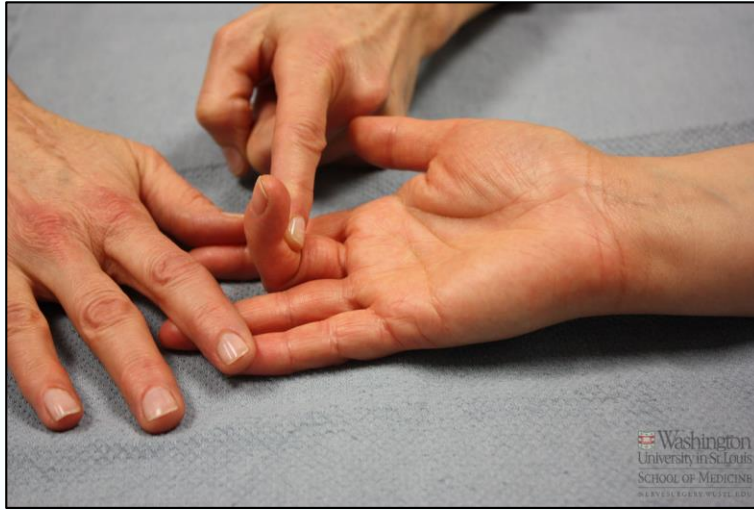
Clinical features



Clinical features



Finger flexor weakness



Swallowing difficulty

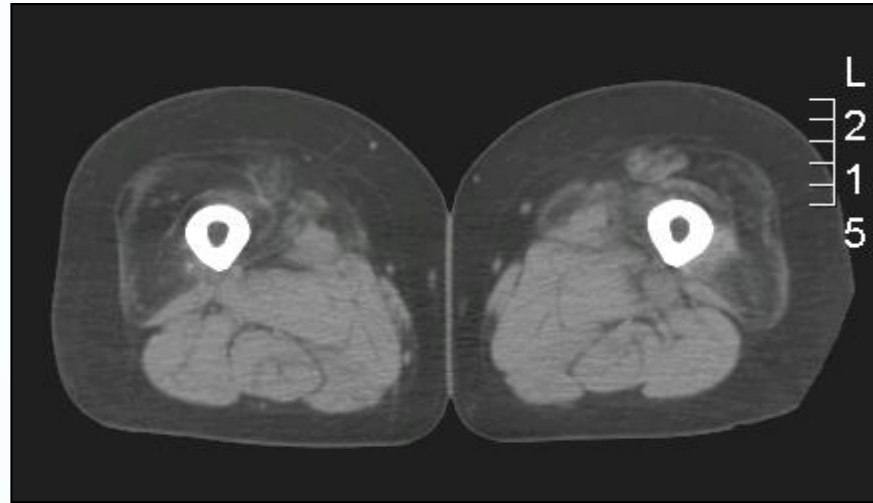
- Male, 65 year old
- Progressive, exists since about one year
- In particular solid food
- Needs to take small bites
- Coughs while eating
- Choking occurs
- Sometimes food comes through the nose
- Lost 7 kg over the past year
- No problems with drinking
- Referral to ENT and gastro-enterologist

Referral to neurology and follow-up

Videofluoroscopy

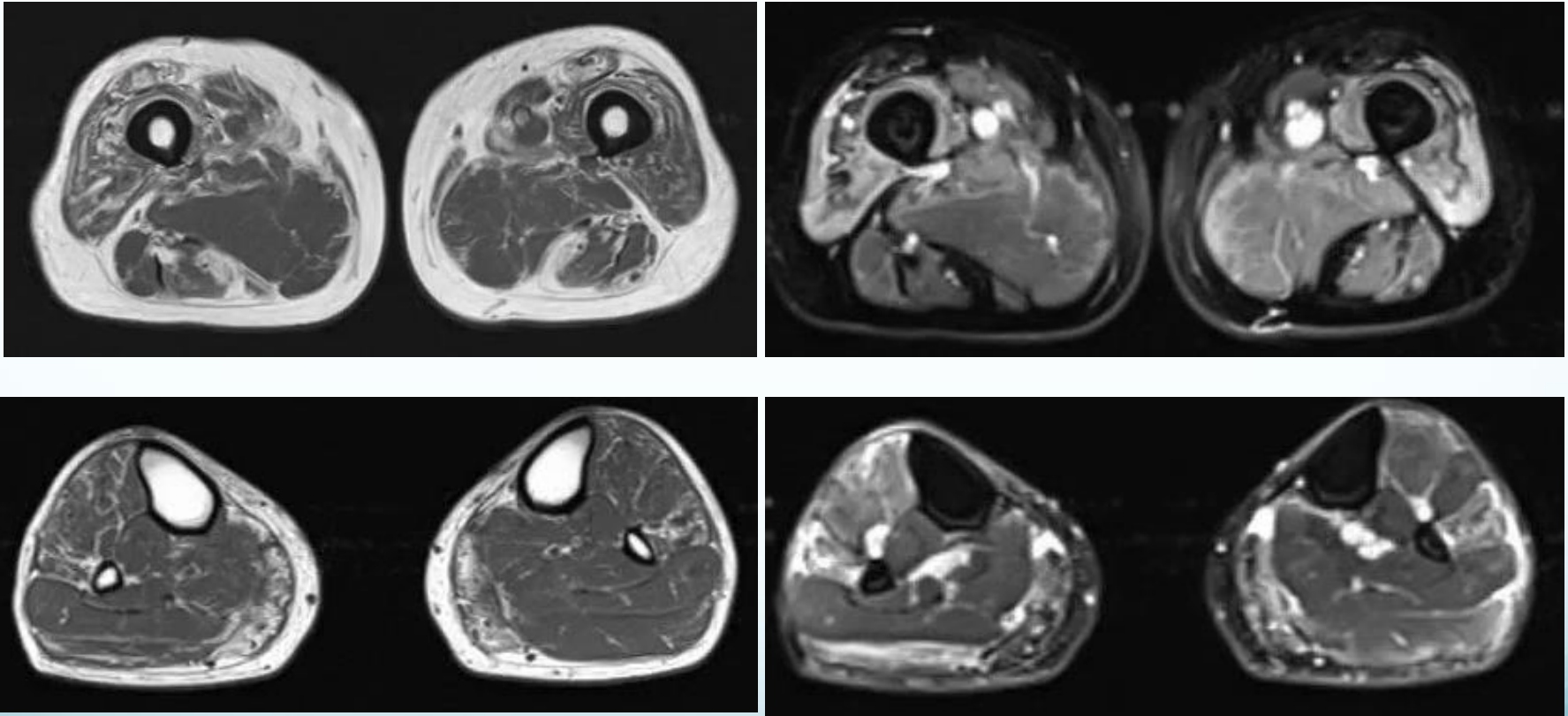
- Hypertrophy of m. cricopharyngeus
- Stasis of contrast
- Reflux from stomach to oesophagus
- Treatment with botox > effective for about one year
- Complains about fatigue in the legs
- 'Feels like I have walked the marathon'
- MRI conducted

Muscle imaging prior to muscle biopsy



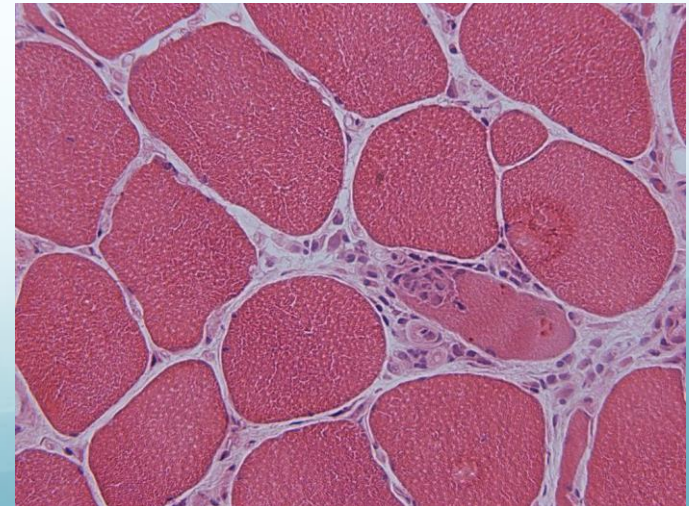
If a muscle biopsy is performed, select the most suitable site for a muscle biopsy on MRI.

MRI pictures in (other) IBM patient



Referral to neurology and follow-up

- Botox effective for about one year
- Complains about fatigue in the legs
- 'Feels like I have walked the marathon'
- MRI: not contributory
- Muscle biopsy consistent with IBM



Inclusion body myositis associated with antibodies and CTDs

- Anti-cN1A IgG autoantibodies is present in 35-70% of IBM patients
- These antibodies also found in connective tissue disorders: SLE and Sjögren syndrome without myositis. Also found in dermatomyositis.
- IBM is associated with Sjögren syndrome and rheumatoid arthritis

Study on clinical features

Age ranges of living and deceased patients under the care of 13 physicians from seven countries

Age range	Number of living patients (<i>N</i> = 585)	Number of deceased patients (<i>N</i> = 149)
<40 years	2	0
41–50 years	19	4
51–60 years	80	19
61–70 years	202	34
71–80 years	204	55
>80 years	78	37

Clinical features cont'd

Typical clinical characteristics of patients with sIBM based on the experience of 13 physicians from seven countries

Characteristics

Time from diagnosis to using an ambulatory aid, mean, years

Cane	3.9
Walker	6.4
Regular wheelchair	10.5
Motorized wheelchair	12.8

Patients using a caregiver^c, mean proportion of patients, %

Professional caregiver/service	29.0
Unpaid caregiver ^d	75.0

Clinical characteristics of sIBM that patients have experienced over the course of illness, mean proportion of patients, % (range)

Dysphagia	60.2 (25–90)
Injurious falls ^e	44.3 (10–100)

Injuries typically sustained by the patients who have experienced an injurious fall, number of physicians selecting

Broken arm or leg	10
Broken hip	9
Sprains	7
Bruises	12
Head trauma	8

Survey amongst IBM patients

Demographic category	Respondents <i>n</i> = 916	Responding yes (%)
Age		
< 40	3	0.33
40-49	27	2.9
50-59	157	17.1
60-69	303	33.1
70-79	292	31.9
≥ 80	134	14.6
Gender	916	
Men	613	66.9

DAILY LIVING AND AMBULATION

Patient characteristic	Respondents (n)	Responding Yes (%)
Swallowing	905	
Normal	332	36.7
Choking	399	44.1
Dietary consistency changes	31	3.4
Frequent choking	109	12.0
Needs tube feeding	34	3.8
Handwriting	914	
Normal	409	44.7
Slow or sloppy	329	36.0
Not all words legible	107	11.7
Able to grip pen but unable to write	26	2.8
Unable to grip pen	41	4.5
Not applicable	2	0.2
Cutting Food and Handling Utensils	894	
Normal	219	24.5
Somewhat slow and clumsy, but no help needed	323	36.1
Can cut most foods, although slow and clumsy; some help needed	200	22.4
Food must be cut by someone, but can still feed slowly	130	14.5
Needs to be fed	22	2.5

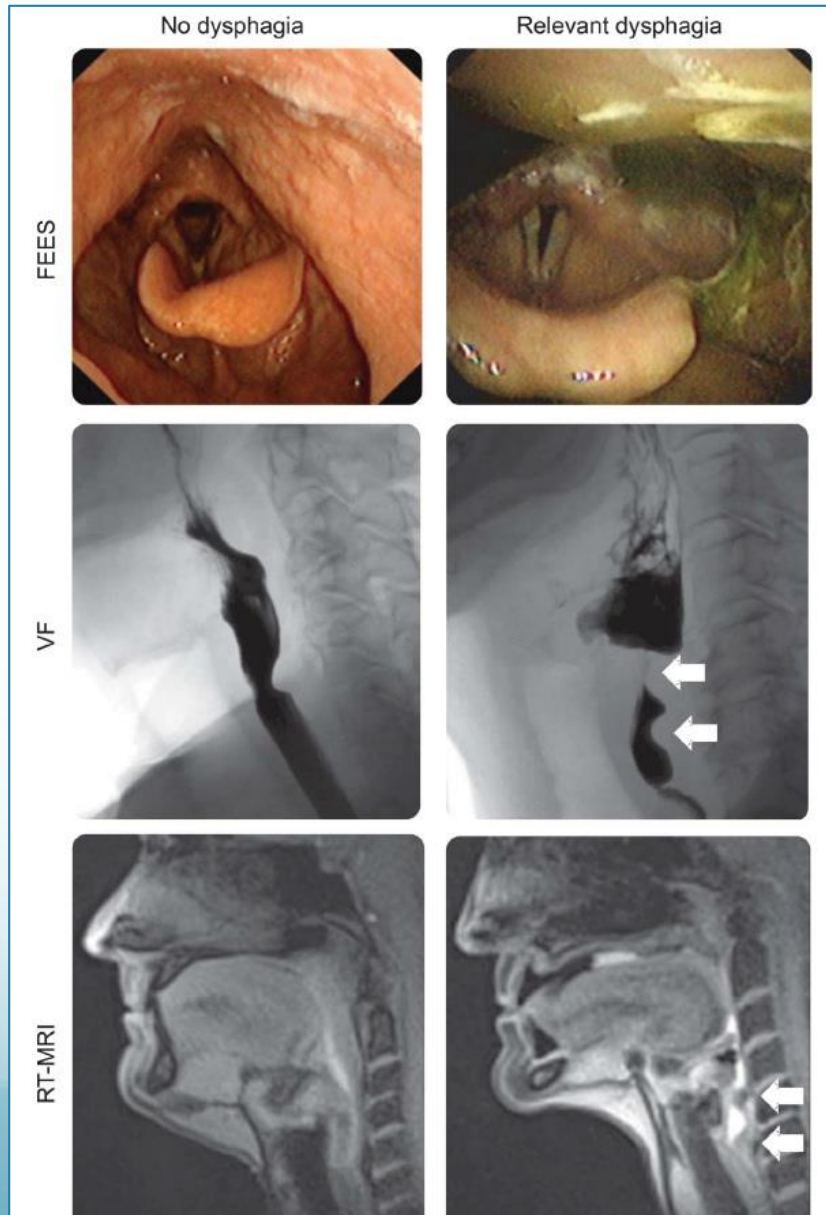
Sit to Stand	913	
Independent (without use of arms)	26	2.8
Performs with substitute motions (leaning forward, rocking) but without use of arms	35	3.8
Requires use of arms	406	44.5
Requires assistance from a device or person	312	34.2
Unable to stand	133	14.6
Not applicable	1	0.1
Walking	914	
Normal	52	5.7
Slow or mild unsteadiness	155	17.0
Intermittent use of an assistive device (ankle-foot orthotic device or AFO, cane, walker, etc.)	237	25.9
Dependent on assistive device	225	24.6
Wheelchair dependent	243	26.6
Not applicable	2	0.2
Amount that IBM Interfered with Normal Work (including work outside the home and housework)	864	
Not at all	20	2.3
Slightly	40	4.6
Somewhat	144	16.7
Extremely	356	41.2
Considerably	282	32.6
Not applicable	22	2.5

DIAGNOSIS

Respondents (n) Responding Yes (%)

Symptoms That Compelled Doctors Visit		
Trouble swallowing	211	23.0
Impaired use of arms and legs	489	53.4
Weakness	640	69.9
Fatigue	293	32.0
Falls	520	56.8
Difficulty climbing stairs	546	59.6
Other	187	20.4
Time Span Between First Observed Symptoms and First Doctor's Diagnosis	909	
1-3 months	60	6.6
3-6 months	84	9.2
6-12 months	130	14.3
1-2 years	207	22.8
2 or more years	417	45.9
Other	11	1.2
Nature of First Diagnosis	914	
IBM	465	50.9
Polymyositis	172	18.8
Arthritis	39	4.3
Do not know	53	5.8
Other	185	20.2

Evaluation of dysphagia



FEES: Flexible
endoscopic evaluation
of swallowing
Videofluoroscopy
Real time-MRI

Management

- Monitoring/treatment of dysphagia: cricopharyngeal myotomy, or repeated injections of botulinum toxin injections
- Monitoring of leg and hand weakness
- Multidisciplinary team
- Physiotherapy, occupational therapy
- Exercise
- Orthosis
- No effective treatment is currently available.
- Standard regimen with glucocorticosteroids and immunosuppressants or IvIG not effective.

Longterm outcome in sIBM

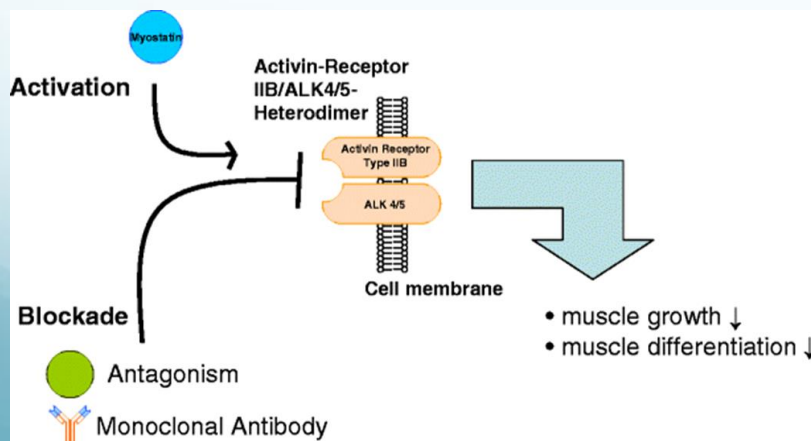
- Patients become wheelchair-dependent approximately 15 years after onset of the disease
- Normal life-expectancy (indirect relationship to disease: significantly more deaths due to pneumonia)

Clinical trials in IBM

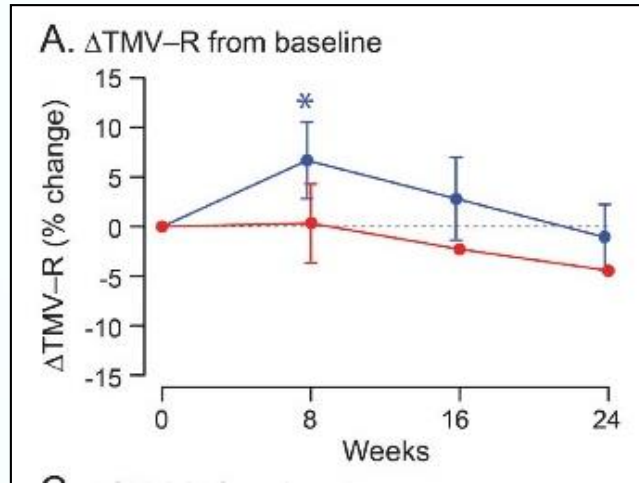
	Not supported	Phase I	Phase II	Phase III	Approved
Immunosuppressants	→ X				
TNF blocking agents	→ X				
Lymphocyte depletion	→ X				
Lithium	→ X				
Anakinra	→ X				
Stem cell transplant	→				
Arimoclomol	→				
Follistatin (FS344)	→				
Bimagrumab	→				

Resilient trial in IBM

- Randomised double-blind placebo-controlled multicenter trial with i.v. BYM338 (bimagrumab) for 52 weeks in IBM.
- Bimagrumab has an inhibitory effect on myostatin leading to muscle hypertrophy and increase in strength

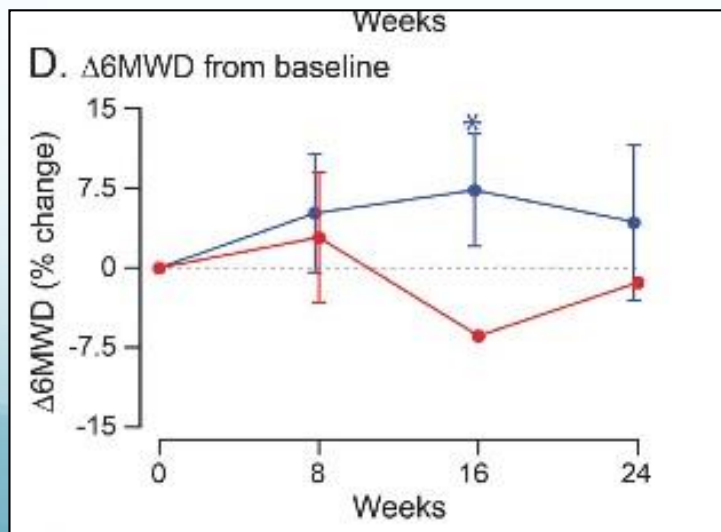


The primary outcome was change in muscle quantity, measured by thigh muscle volume (TMV) using MRI after 8 weeks (Amato et al. Neurology 2014).



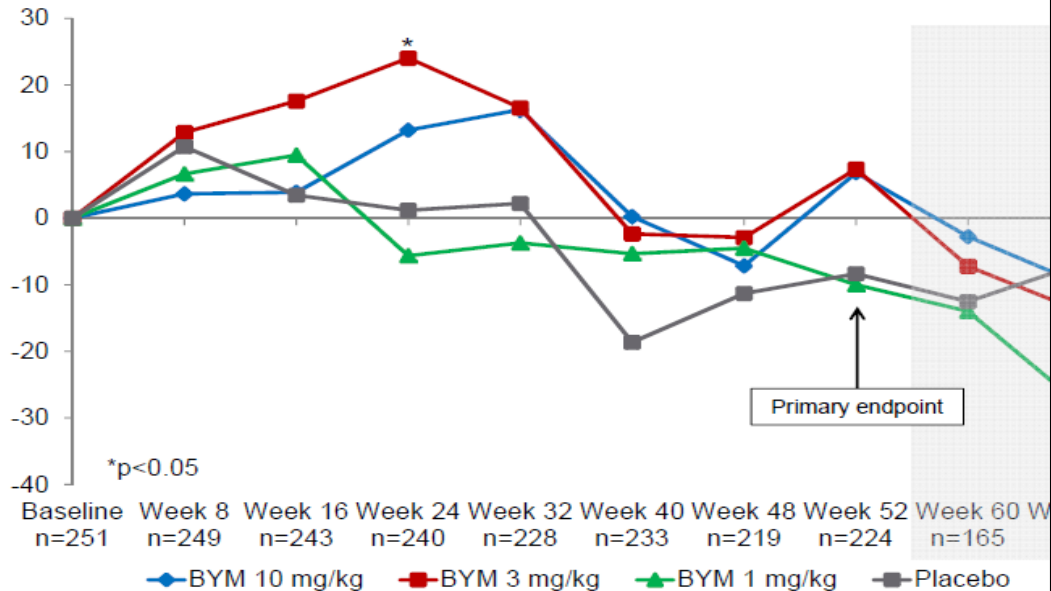
(11 IBM patients, 3 controls)

This study provides evidence that in IBM Bimagrumab increases thigh muscle volume at 8 weeks



RESILIENT: A randomized, double-blind, placebo-controlled, phase IIb/III study to evaluate efficacy, safety and tolerability of intravenous BYM338 at 52 weeks on physical function, muscle strength, and mobility in patients with sporadic inclusion body myositis

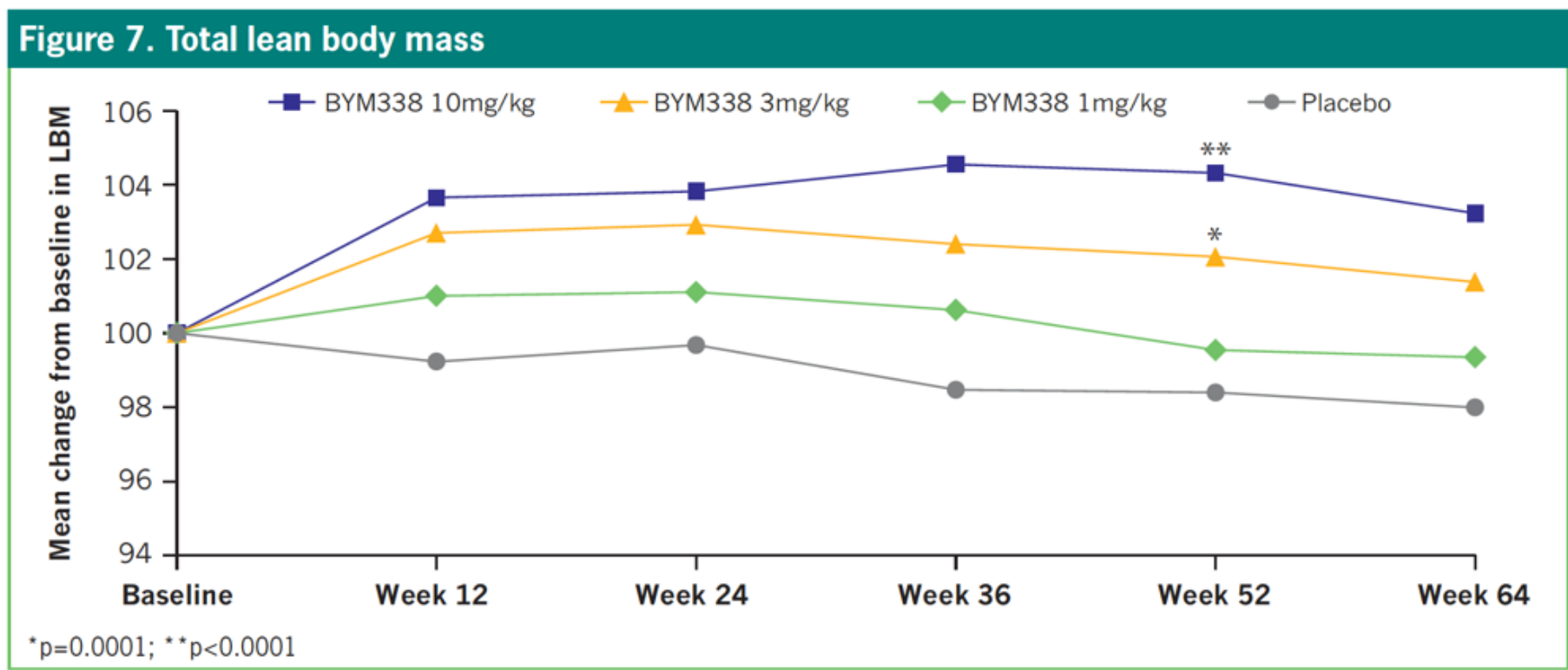
Mean change from baseline in 6MWD
Initial improvement not sustained on long term treatment



Study did not achieve primary endpoint

Caution: relevant drop in sample size beyond week 52 and therefore no inferential statistics conducted; very small sample (n<45 total, <15 for any group) for visits beyond week 68 and therefore not shown here

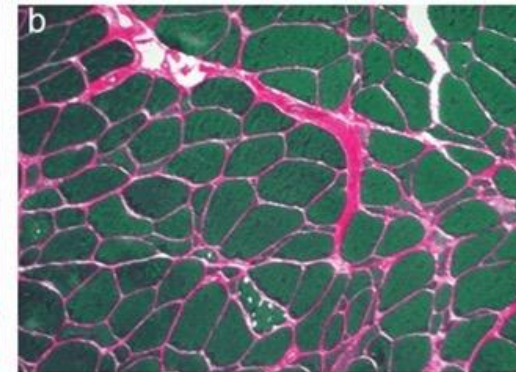
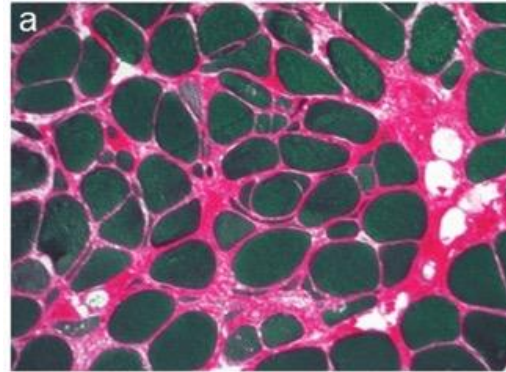
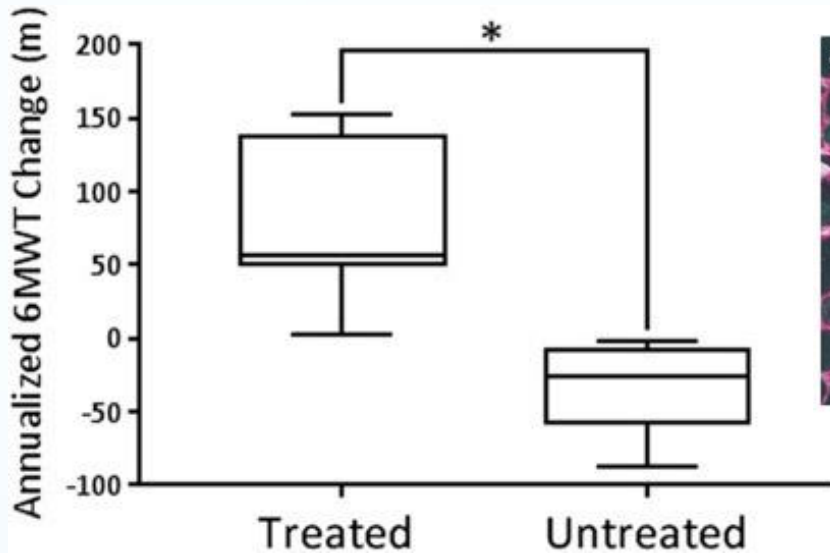
At Week 52, bimagrumab 3 and 10 mg/kg treatments resulted in statistically significant changes in lean body mass compared with placebo



Promising results

- Follistatin (inhibits myostatin) delivered by an adenovirus-mediated gene therapy.
- Arimoclomol (reduces cell stress and accumulation of proteins) was proven to be safe in a small group of IBM patients

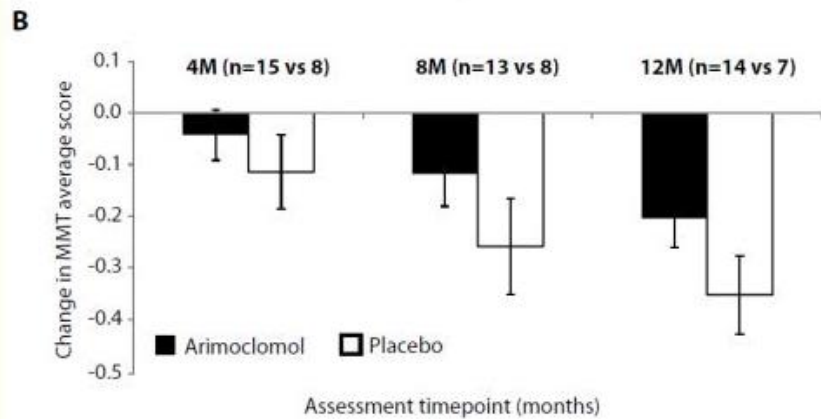
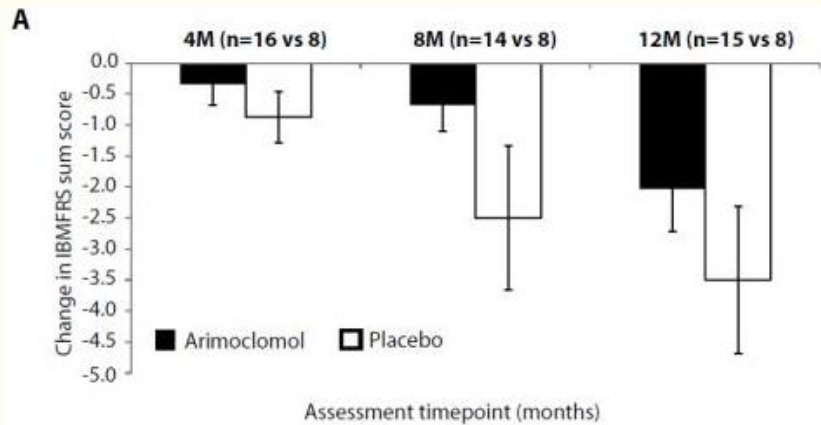
Follistatin Gene Therapy for Sporadic Inclusion Body Myositis Improves Functional Outcomes



rAAV1.CMV.huFS344, 6×10^{11} vg/kg
delivered to R/L quads of 6 sIBM subjects.
Primary outcome : distance travelled for the 6-min walk test

Mechanisms:

- Inhibits inflammation
- Inhibits formation of fibrosis
- Stimulates regeneration of muscle



In mice, which develop IBM treatment with Arimoclomol ameliorated disease pathology and improved muscle function.

Rapamycin vs. Placebo for the Treatment of IBM: Improvement of the 6 Min Walking Distance, a Functional Scale, the FVC and Muscle MRI

Rapamycin (Sirolimus) is used in organ transplantation

- Rapamycin 2 mg/day (n=22) vs PBO (n=22)
- Primary endpoint: stabilization of maximal voluntary quadricep strength
- Secondary endpoints: other muscle strength, 6MWD, pulmonary function tests, qualitative MRI
- Study failed to meet primary endpoint
- Significant improvements vs PBO in
 - 6MWD
 - IBM composite degradation index
 - FVC
 - Fat–muscle replacement (quads and hamstrings)
 - Contractile cross-sectional area (quads)

Change from baseline to Month 12	Rapamycin (n=22)	PBO (n=22)	P-value
1° endpoint: mean relative change in quad strength	–11.07%	12.36%	P=NS
Mean 6MWD, m	–4.1	– 38.5	P=0.035
IBM composite degradation index	–11.91%	–24.26%	P=0.038
Mean % change in FVC	+12.3%	+1.6%	P=0.016
MRI, fat–muscle replacement			
– Quadriceps	1.7%	4.4%	P=0.025
– Hamstrings	0.9%	7.3%	P=0.027
MRI, ↓ contractile cross-sectional area in quadricep (mm ²)	–3.7	–10.7	P=0.005

Promising data on rapamycin use in a disease with a high unmet need

Exercise as therapy

- Mild to moderate intensity nonfatiguing exercise
- Exercise and vascular occlusion (restricting muscle blood flow using tourniquet cuffs)

J Vis Exp. 2010; (40): 1894.

Published online 2010 Jun 5. doi: [10.3791/1894](https://doi.org/10.3791/1894)

PMCID: PMC3153908

PMID: [20548279](https://pubmed.ncbi.nlm.nih.gov/20548279/)

Vascular Occlusion Training for Inclusion Body Myositis: A Novel Therapeutic Approach

Bruno Gualano, Carlos Ugrinowitsch, Manoel Neves Jr., Fernanda R. Lima, Ana Lúcia S. Pinto, Gilberto Laurentino, Valmor A.A. Tricoli, Antonio H. Lancha Jr., and Hamilton Roschel



Requirements for future trials in IBM

- Awareness of the subtypes and their functional decline
- More knowledge about measurement of the functional decline
- Better outcome measures
 - 6MWT not always appropriate
- Patient related outcome measures
- Biomarkers such as MRI studies

