Inflammatory Myopathies – Update

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Objectives

- Review types of inflammatory myopathies
- Approach to diagnosis
- Review 2017 ACR/EULAR classification criteria for adult and juvenile IIM
- Challenging cases (Update in treatment)
- Clinical trials

Idiopathic Inflammatory Myopathies

- Dermatomyositis
- Polymyositis
- Immune mediated necrotizing myopathy (IMNM)
- Inclusion Body Myositis (IBM)

Approach to muscle weakness - History and Exam

- Muscle tenderness
- Disease onset
- Progression
- Pattern of muscle weakness – generalized/proximal/distal
- Family history
- Drug use, Exercise history
- Associated symptoms – skin rash/lungs/swallowing problems/CTD features

Investigations - basic

- CK
- Aldolase, LDH, aminotransferases
- Urine (rhabdomyolysis)
- ANA (if clinically appropriate)
- EMG

Investigations

- Myositis Specific Autoantibodies (if clinically appropriate)
- MRI
- Muscle biopsy
  - when to do?
  - histopathology, immunohistochemical staining, biochemical staining and EM
  - important surgeon familiar with shipping & handling
- Genetic testing

CK

- Standard reference for most labs are too low (0 – 200 IU/L)

✓**CK vary by age and sex**

✓ ? Redefine elevated CK at least 1.5 times above UNL

✓ White women 325 , white men 504, Black women 621, Black men 1,200

- **Physical activity raises CK**
- 4% asymptomatic/min symptoms patients with raised CK have “macro CK”

✓ Enzyme complex with an atypically high molecular mass and reduced clearance

✓ If suspect, check CK electrophoresis

- **Is CK a good biomarker for assessing muscle disease activity?**

Inflammatory muscle disease assessment

Lu T, Ng K, Isenberg D et al

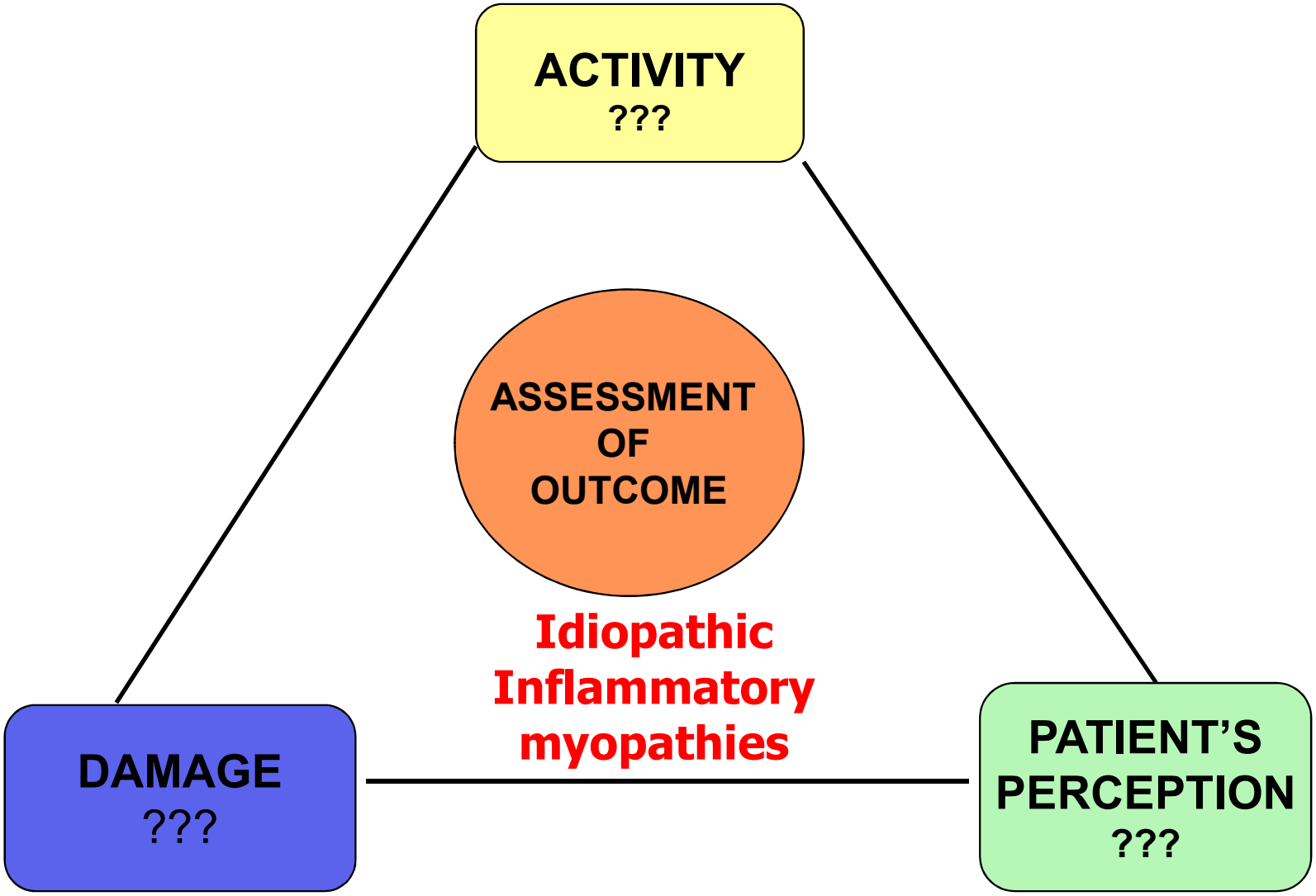
Inflammatory muscle disease assessment

Curr Rheumatol Rep. 2008 Aug;10(4):328-32

Sultan SM, Allen E, Oddis CV et al

Reliability and validity of the myositis disease activity assessment tool

Arthritis Rheum. 2008 Nov;58(11):3593-9.


ACTIVITY
???
ASSESSMENT
OF
OUTCOME
Idiopathic
Inflammatory
myopathies
DAMAGE
???
PATIENT'S
PERCEPTION
???

IMACS IIM
Disease Activity Core Set

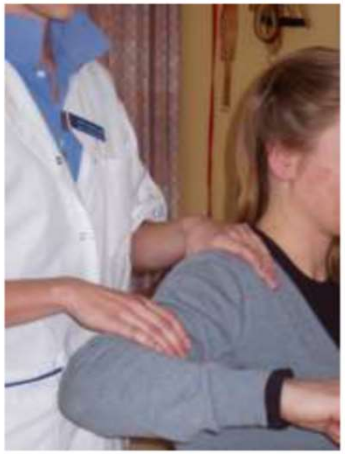
- Global Assessments: Physician and patient/parent - VAS
- Muscle strength: MMT (proximal, distal & axial muscles) MMT8 max score 80
- Physical function: HAQ (CHAQ / CMAS)
- Laboratory: Serum activity of ≥ 2 muscle enzymes (CK, LD, aldolase, AST, ALT)
- Extra-skeletal muscle disease activity
  - Myositis Disease Activity Assessment (MDAAT, MITAX)

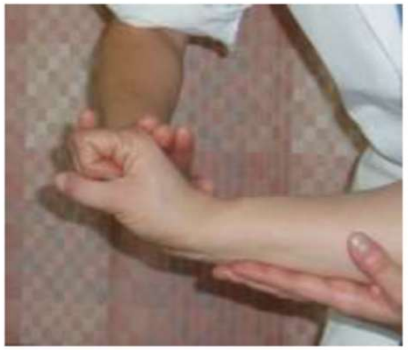
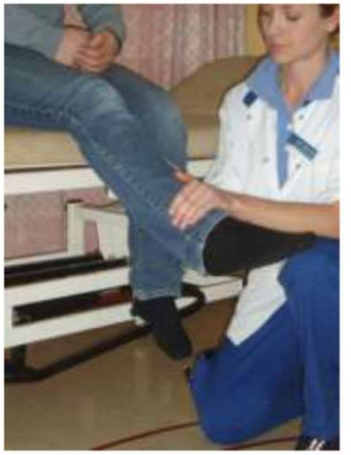
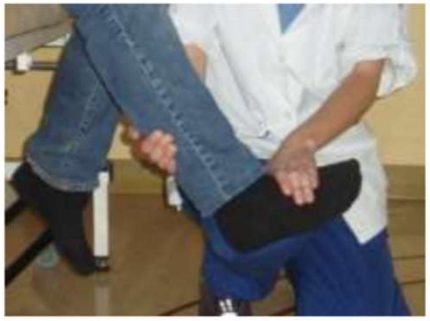
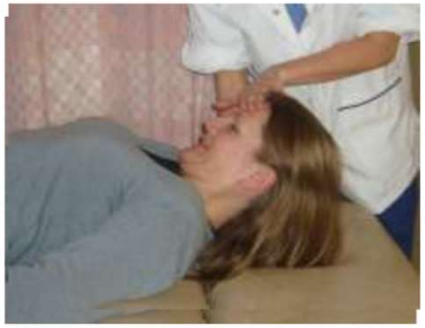
Miller, Rider et al., 2001, Rheum.40:1262-73

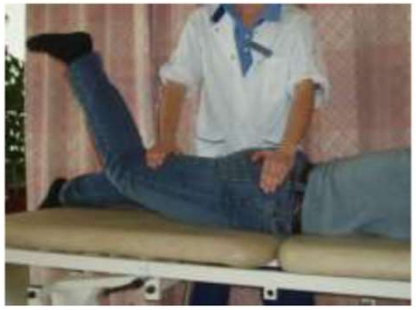
https://dir-apps.niehs.nih.gov/imacs/index.cfm

Manual Muscle Test-8

max. score 80





IMACS WEBSITE: HTTPS://DIR-APPS.NIEHS.NIH.GOV/IMACS/

Myositis Assessment Indices

ACTIVITY (MDAAT)

- MITAX (myositis intention to treat index based on BILAG index)
- MYOACT (series of visual analogue scales)

DAMAGE (MDI)

- Myositis damage index based on SLICC
- MYODAM (series visual analogue scales)

MEDICAL PROGRESS

POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)

ANTHONY BOHAN, M.D., AND JAMES B. PETER, M.D., PH.D.

- 5 main criteria
  1. Symmetric, proximal weakness
  2. Muscle biopsy evidence
  3. Elevated CK, LDH, AST/ALT, aldolase
  4. EMG triad of myopathy
  5. Characteristic rashes of DM

2017 EULAR/ACR criteria for IIM

- Age of onset (>18 but <40); or >40
- Symmetric, progressive, proximal UE/LE weakness
- Neck flexor>extensor
- Skin: Heliotrope, Gottron's papules, Gottron's sign
- Dysphagia, esophageal dysmotility
- Anti-Jo-1
- Elevated CK, or AST, or ALT, or LDH
- Muscle bx features- endomysial infiltration, perimysial and/or perivascular inflammation, perifasicular atrophy, rimmed vacuoles

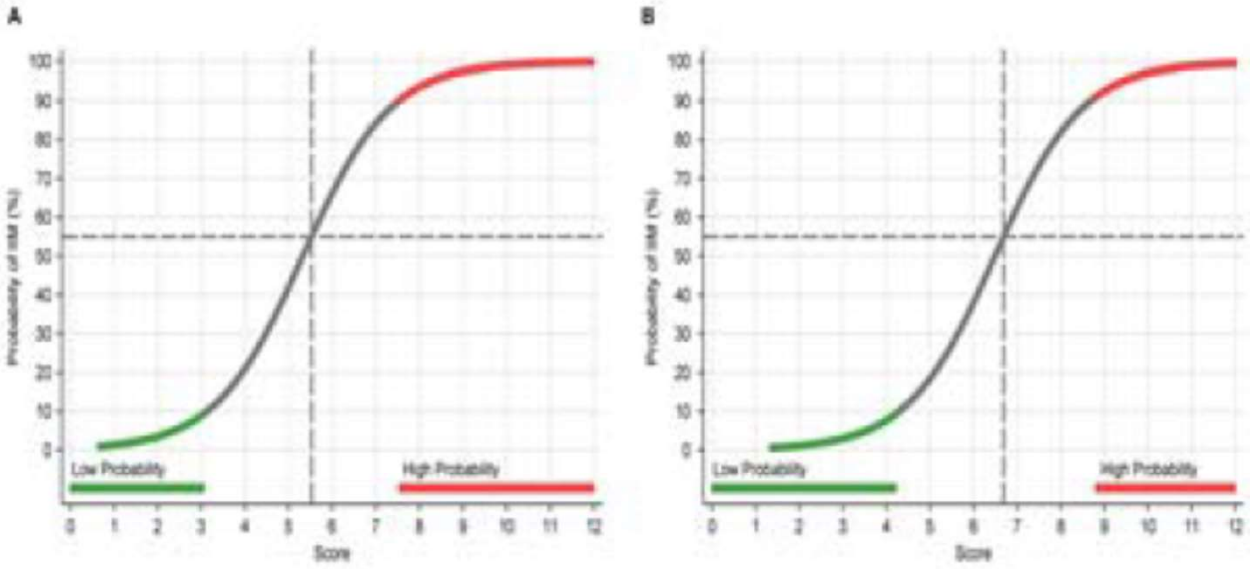
- EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups
  - Data-driven criteria, validated in external cohorts
  - Multidisciplinary study → consensus
  - Easily accessible and well-defined variables
  - Different weights for different variables
  - Flexible model
  - Good performance
  - Easy to use with the calculator for smartphones
  - *Webcalculator:*

http://www.imm.ki.se/biostatistics/calculators/iim/

2017 EULAR/ACR criteria for IIM

- Consensus study design
- Two models- **with or without** muscle biopsy results

Web-based calculator provides ***probability*** of having IIM



Definite IIM; ≥ 90% probability or total aggregate score of ≥ 7.5 (no muscle biopsy) and ≥ 8.7 (with muscle biopsy)

Classification Criteria for Idiopathic Inflammatory Myopathies

Probability (min - max):	0 - 100%

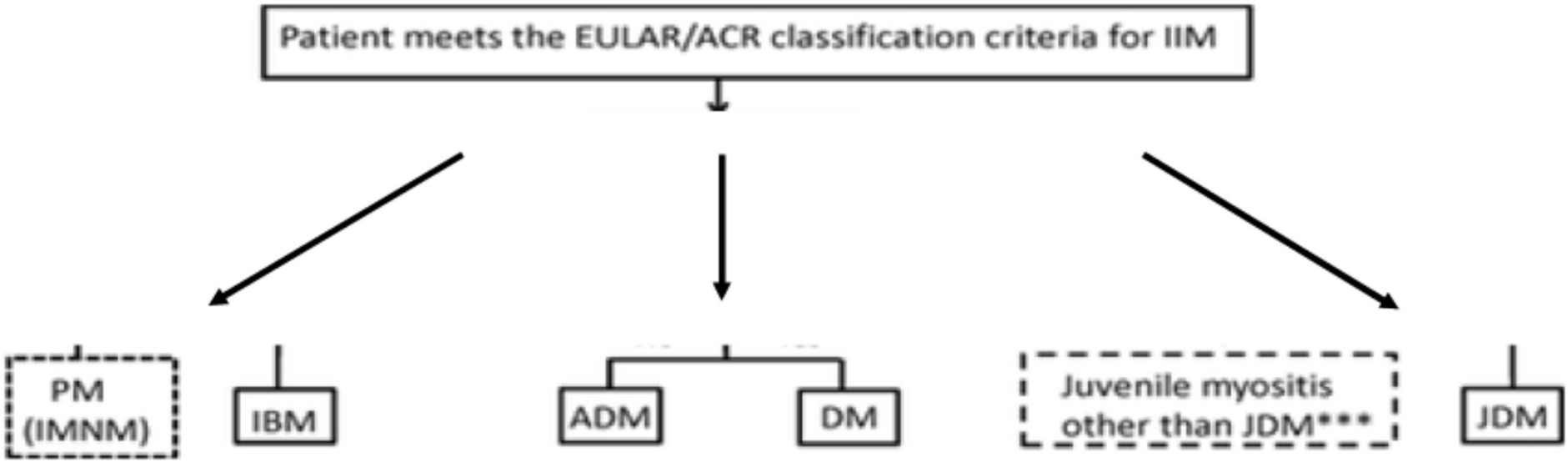
Age of onset of first symptom	☐ 0-17	☐ 18-39	☐ 40+

	Yes	No
Objective symmetric weakness, usually progressive, of the proximal upper extremities	☐	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities	☐	☐
Neck flexors are relatively weaker than neck extensors	☐	☐
In the legs proximal muscles are relatively weaker than distal muscles	☐	☐
Heliotrope rash	☐	☐
Gottron´s papules	☐	☐
Gottron's sign	☐	☐
Dysphagia or esophageal dysmotility	☐	☐
Anti-Jo-1 (anti-His)	☐	☐
Serum creatine kinase activity (CK) activity or Serum lactate dehydrogenase (LDH) activity or Serum aspartate aminotransferase (ASAT/AST/SGOT) activity or Serum alanine aminotransferase (ALAT/ALT/SGPT) activity	☐	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers	☐	☐
Perimysial and/or perivascular infiltration of mononuclear cells	☐	☐
Perifascicular atrophy	☐	☐
Rimmed vacuoles	☐	☐

Webcalculator: www.imm.ki.se/biostatistics/calculators/iim; Excel file with formulas

Correction in formula: *Probability of IIM without muscle biopsy=1/[1+exponential(5.33–score)] or, Probability of IIM including muscle biopsy=1/[1+exponential(6.49–score)]* *Ann Rheum Dis 2018;* 77, (9)

2017 EULAR/ACR criteria for IIM



Limitations of the 2017 criteria for IIM

- Only 1 autoantibody included: anti-Jo1
- Necrotizing myopathy cannot be distinguished from Polymyositis
- Limited MRI and EMG data
- Juvenile PM cases were limited

Myositis autoantibodies

Immunoprecipitant method (Euroimmune line blot), Canterbury Laboratory

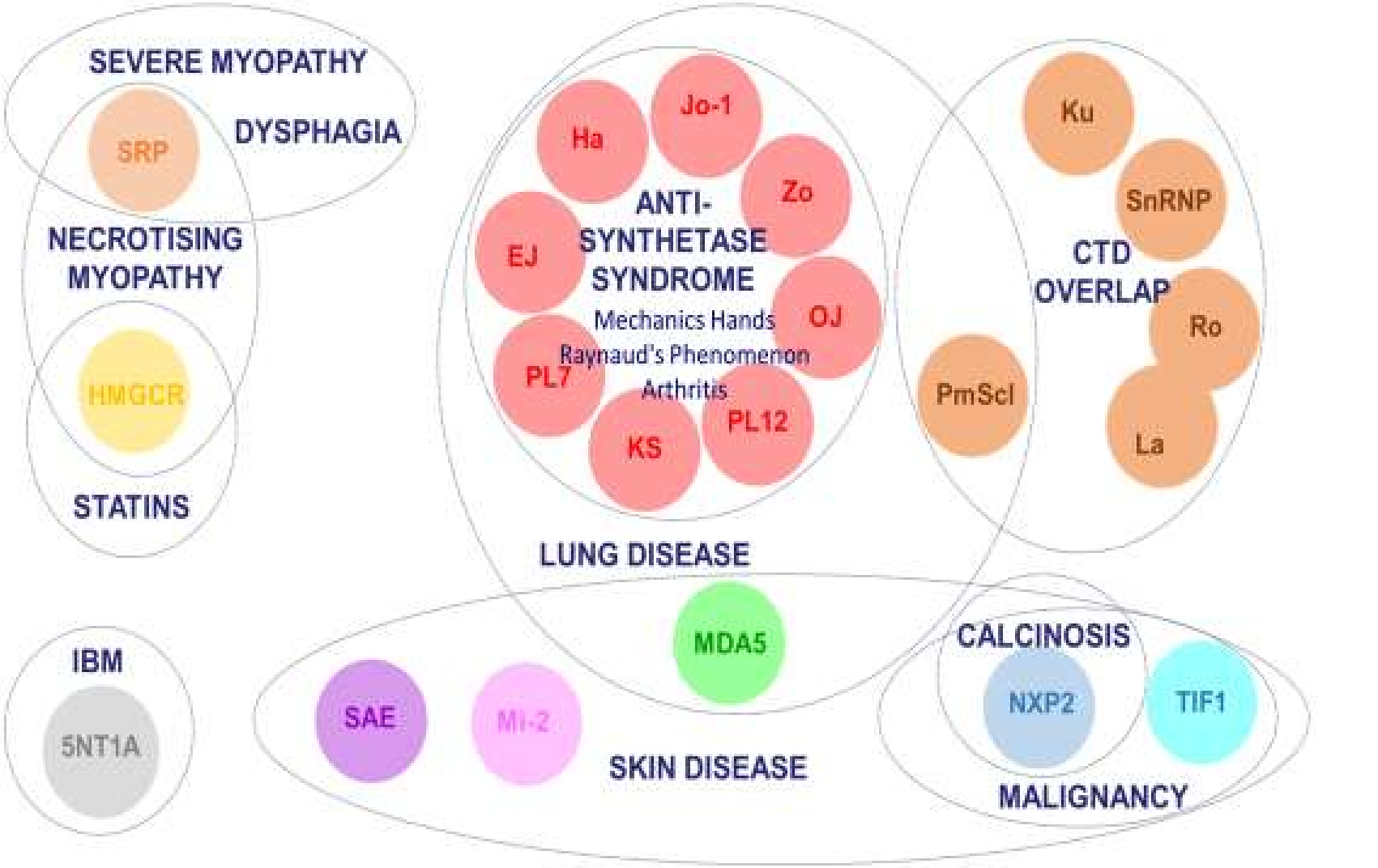
Myositis Specific Antibodies

- Jo-1, PL-7, PL-12, EJ, OJ
- Mi-2, **SAE 1, NXP 2, MDA 5**
- **SRP**
- **HMGCR autoantibodies**
- **TIF1g**

Myositis Associated Antibodies

- Ku
- PM-Scl 100, PM- Scl 75
- Ro-52

MSDA/MAAs and clinical associations in adult myositis



Betteridge and McHugh JIM 2015

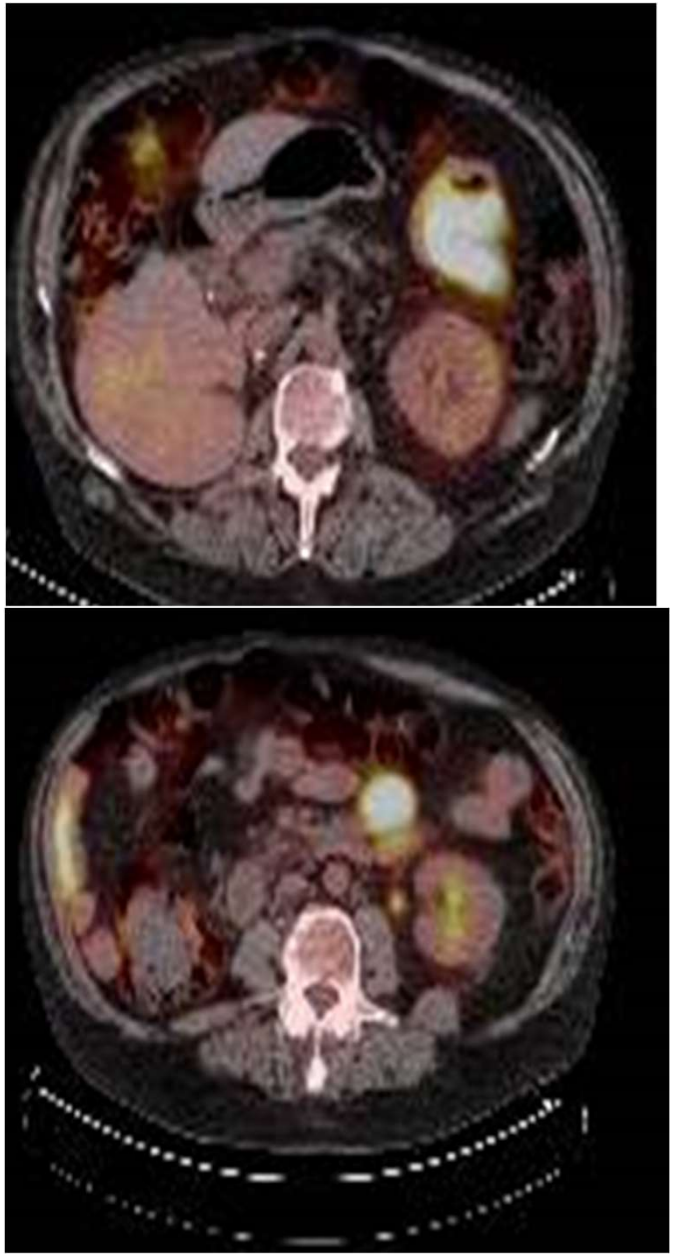
Learning points *(Case 1 – DM with cancer)*

- Pts with anti TIF1γ often have resistant skin disease
- Antibody helpful as high negative predictive value
- Presence of anti-TIF1γ in adult DM requires very careful screening strategy for occult malignancy
- Anti TIF1γ in juvenile DM not associated with cancer but have difficult skin disease and ulceration

Cancer Associated Myositis

- CAM mostly in DM with incidence ratio of 2.4 – 7.7
- Ovary, lung, GI tract, breast and nasopharyngeal
- Presence of anti-TIF1g
  - ✓Specificity 89%
  - ✓Sensitivity 70%
  - ✓Negative predictive value 93%
  - ✓Diagnostic odds ratio 18

Selva-O'Callaghan, Curr Opin Rheum, 2010



TIF-1 gamma dermatomyositis

- More extensive skin disease
- Less likely to have
  - ILD,
  - Raynaud's,
  - Arthritis

Fiorentino DF et.al J Am Acad Dermatol 2015 Mar;72(3):445-66

Refractory disease

- Age appropriate malignancy screening
- CT Chest, abdomen, pelvis, or
- Whole body PET-CT

Tx of dermatomyositis

Methotrexate

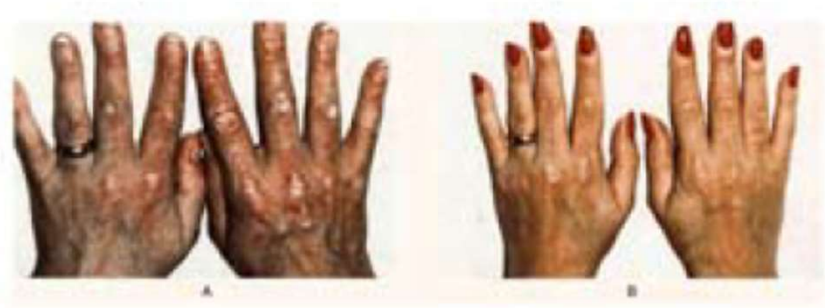
Mycophenolate mofetil

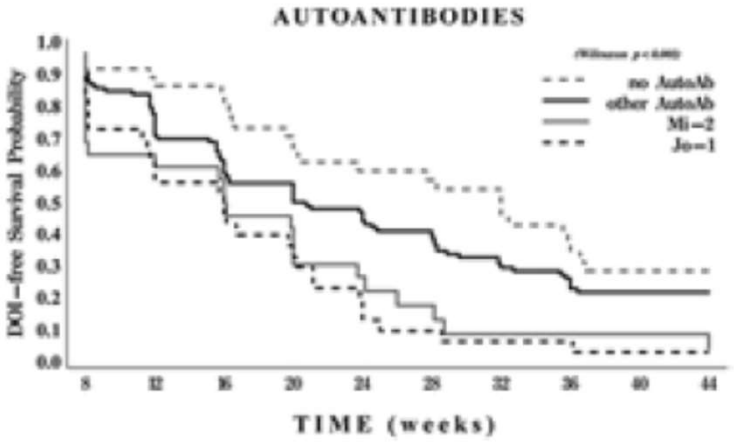
Azathioprine

+/-

IVIG

Rituximab





RIM trial

Dalakas MC et al. N Engl J Med 1993;329:1993-2000.
Aggarwal R, et. al Arthritis and Rheumatology 2014; 66: 3,740-749

Learning points *(Case 2 –Refractory PM, think of other myopathies)*

- Pitfalls in muscle biopsy interpretation

✓Overlap histological features of IIM with IBM and some muscular dystrophies

Ng KP, Smith CR, Isenberg DA. Rheumatology 2007 Oct; 46(10):1618-9

✓**Consider re-biopsy** if patient not responding to treatment

✓Important to liaise with pathologist

✓Advances in immunohistochemical tests will help in accurate diagnosis

Inclusion Body Myositis

- Most common acquired myopathy after age>50
- Progressive, insidious weakness
- Knee extensor weakness>>hip flexion
- Finger flexor weakness
- Asymmetric muscle weakness

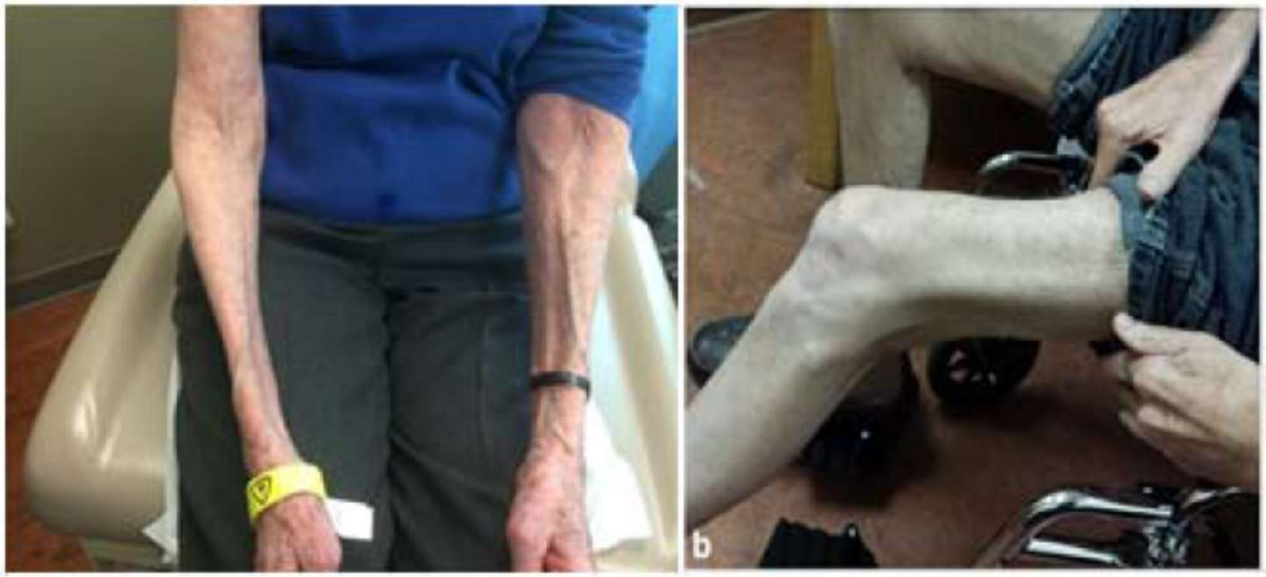


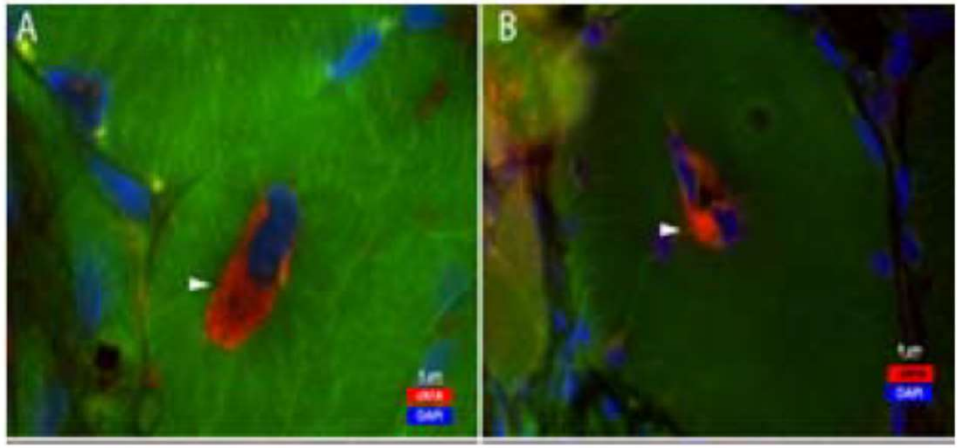
Image courtesy of Myma Albayda

Naddof E et. al Neurotherapeutics 2018

Finger Flexor Weakness

NT5C1-A antibody

- Autoantigen is cytoplasmic 5'nucelotidase 1A (cN1A; NT5C1A)- identified in 2013 .
- cN1A is distributed abnormally in IBM muscle
- Localizes to areas of myonuclear degeneration and rimmed vacuoles



Large accumulations of cN1A immunoreactivity (arrowhead) around stained myonuclei

Larman HB et. al Ann Neurol 2013 Mar; 73(3), 408-418

NT5C1-A antibody

- Commercially available
- 70% sensitive
- 93% specific

- May not be specific for IBM
  - **71 of 117 (61%) of IBM**
  - 2 of 42 (5%) of PM
  - 24 of 159 (15%) of DM
  - 10 of 44 (23%) patients with Sjogrens Syndrome (no muscle)
  - 13 of 96 (14%) patients with SLE (no muscle)

Lloyd T et al Arthritis Care and Research April 2015

The bottom line: resist the urge to immunosuppress IBM

- There are no FDA-approved treatments
- Most experienced clinicians do not believe immunosuppression has a significant sustained positive effect
- Natural history of the disease makes it difficult to interpret intervention in individual patients
- One study of 136 patients followed for 3+ years with half getting immunosuppressive therapy*
  - All progressed
  - Treated patients developed difficulty walking faster

*Benveniste, Brain, 2011

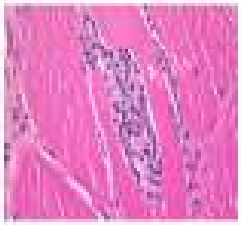
Case 3 learning points *(AntiSynthethase syndrome –PL12)*

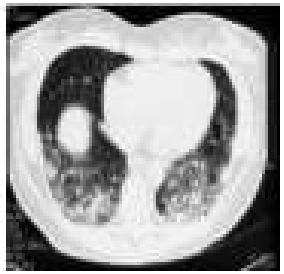
- Not all patients have classic triad: **ILD, arthritis, myositis**
- Ro52 possible worse lung disease
- Anti-PL7 and anti-PL12 - more severe lung disease
- Anti-Jo1 - more severe muscle disease
- ***Treatment***
- **ILD** – follow ILD algorithm
- **Myositis** – follow IIM algorithm
- **Both myositis and ILD** – lung more severe, so defer to lung

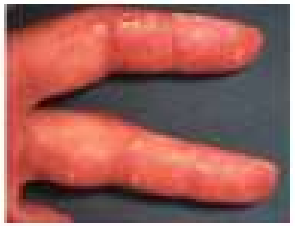
Anti-Synthetase Syndrome

Clinical Features

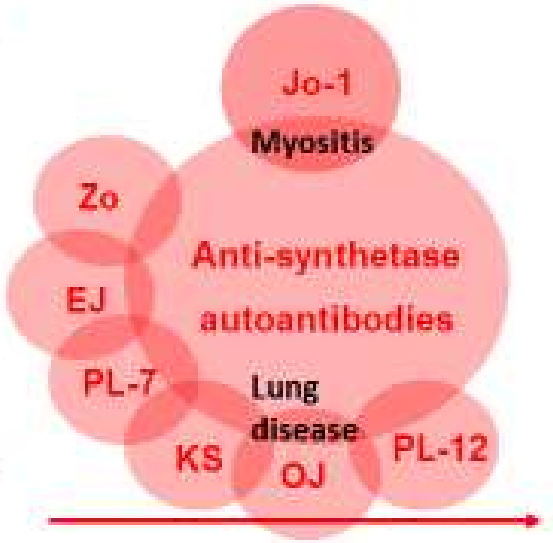
- Myositis
- Interstitial pneumonia (50-80%)
- Arthritis (50-90%)
- Raynaud's (60%)
- Mechanics Hands (70%)
- Fever (80%)

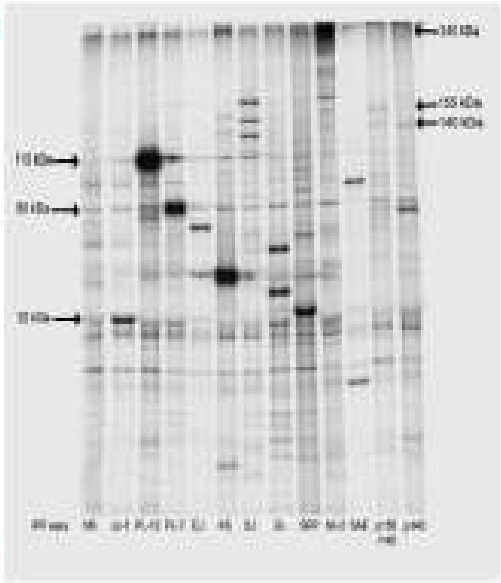




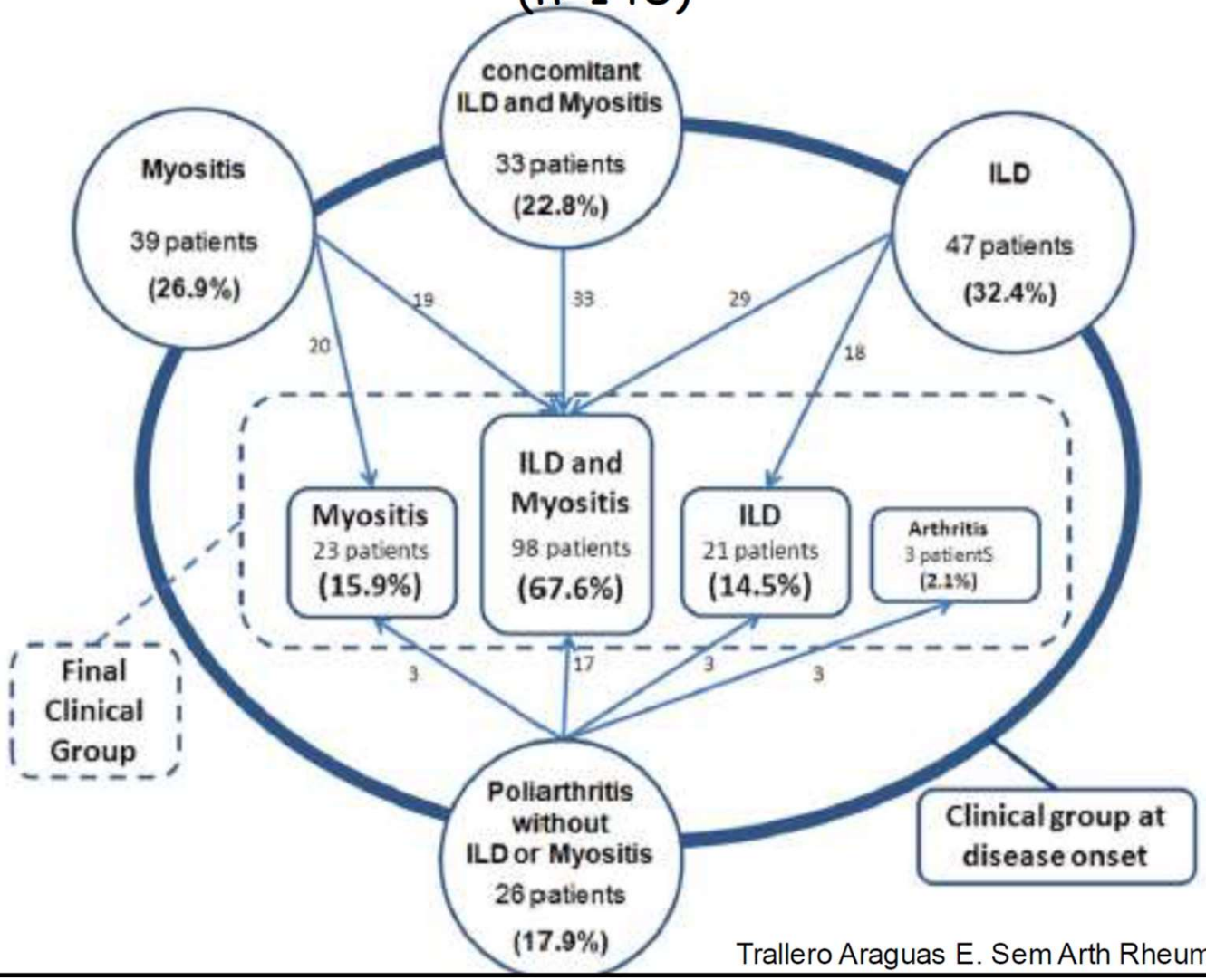


Autoantibody	tRNA synthetase target	Prevalence
Jo-1	Histidine	25-30%
EJ	Glycerine	<2%
PL-7	Threnyine	3-4%
KS	Asparigine	<2%
OJ	Isoleucine	<2%
PL-12	Alanine	3-4%
Zo	Phenylalanine	<2%



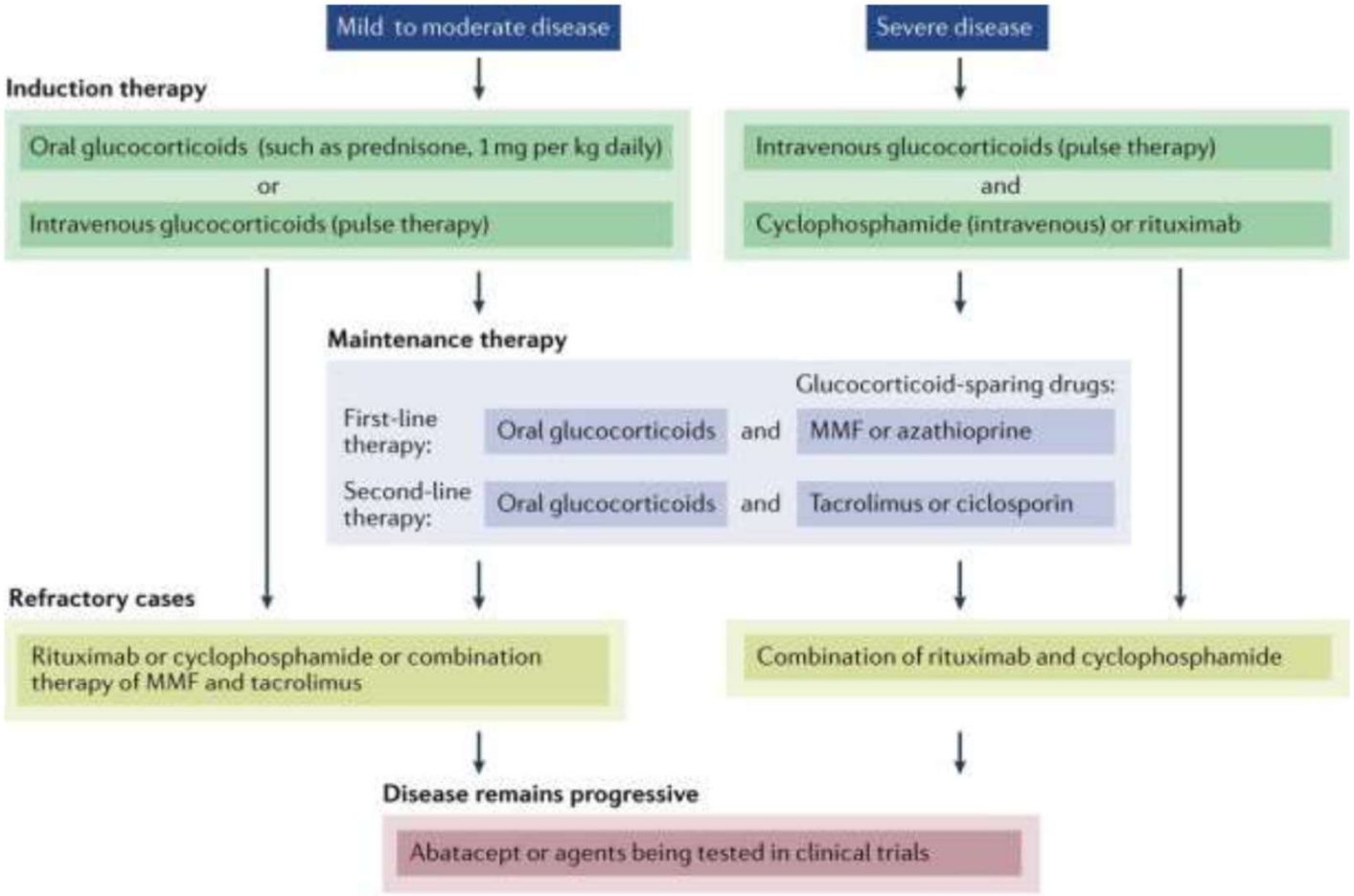


Presentation of anti-Jo-1 pos patients (n=148)



Trallero Araguas E. Sem Arth Rheum, 2016

Proposed approach to treating myositis-associated interstitial lung disease



PJP prophylaxis warrants consideration but no guidelines exist.

Nature Reviews | Rheumatology

Adapted from Moghadam-Kia, S., Oddis, C. V. & Aggarwal, R. Update on the treatment of myositis. *Int. J. Clin. Rheumatol.* **9**, 505–518 (2014).

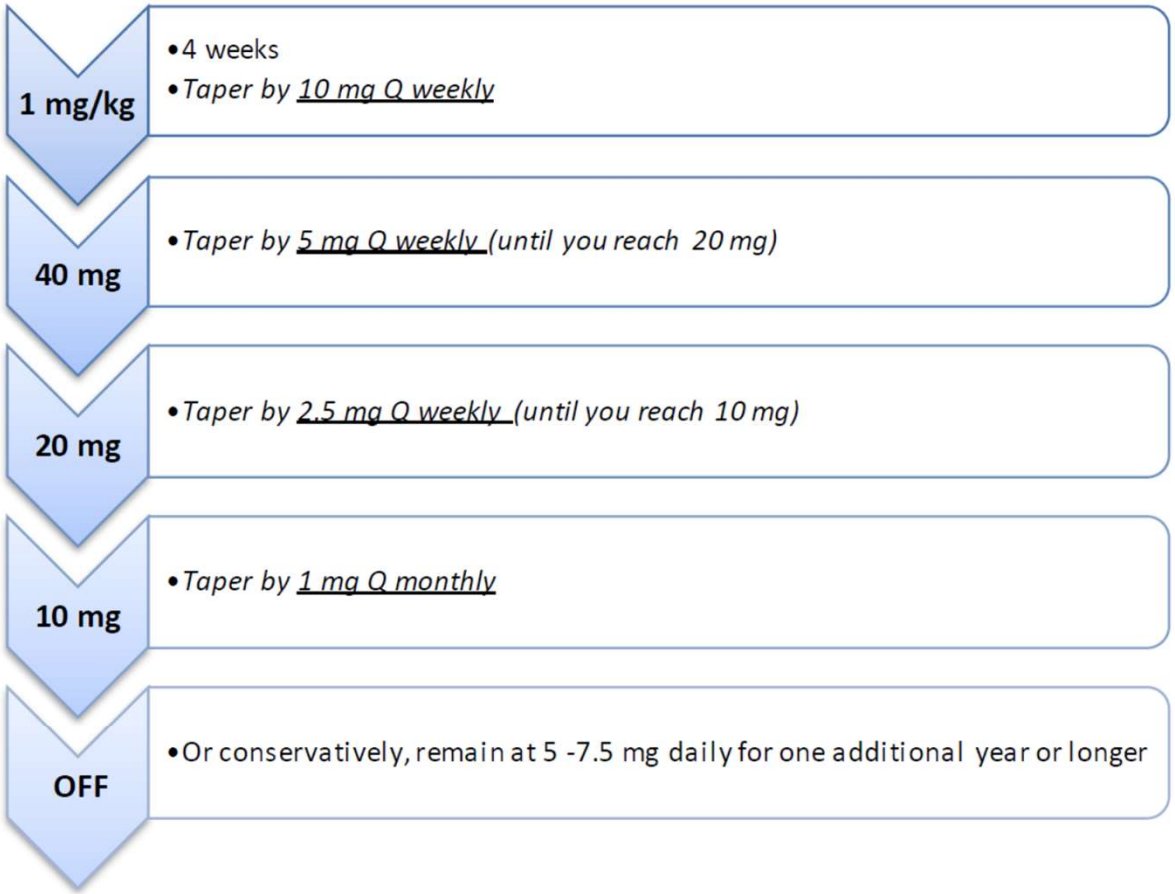
Myositis

- Despite lack of RCTs, **glucocorticoids(GC)** remain the backbone of treatment
- Initial therapy: 1-2 mg/kg/day up to a max of 80-100 mg/day
- If other features such as dysphagia present, IV (GC) therapy warranted
- High dose oral GC maintained for 2-4 weeks then gradually tapered to minimally effective dose (5-7.5 mg daily) – sometimes continued for one year or longer
- In adults, we recommend concomitant glucocorticoid sparing IS therapy within the first two weeks of GC therapy

Cavagna. Autoimmunity Reviews 16(2017) 999–1007

Oddis. Current Opinion in Rheumatology. 1993 5(6):742–748

Corticosteroid Taper example



Some advocate for a one month dose of 1mg/kg followed by a *25% steroid reduction each month* with goal of daily dose of prednisone 5-10 mg within 6 months

Overview of pharmacological therapy in Idiopathic Inflammatory Myopathies (IIM)

First-line therapy:	Glucocorticoids	and	Methotrexate or azathioprine	and/or	IVIG
Second-line therapy:	Glucocorticoids	and	MMF, tacrolimus or ciclosporin or combination therapy of methotrexate and azathioprine	and/or	IVIG
Third-line therapy:	Glucocorticoids	and	Rituximab, cyclophosphamide, RCI or other biologic agents	and/or	IVIG

Nature Reviews | Rheumatology

Oddis, C. V. & Aggarwal, R. (2018) Treatment in myositis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2018.42

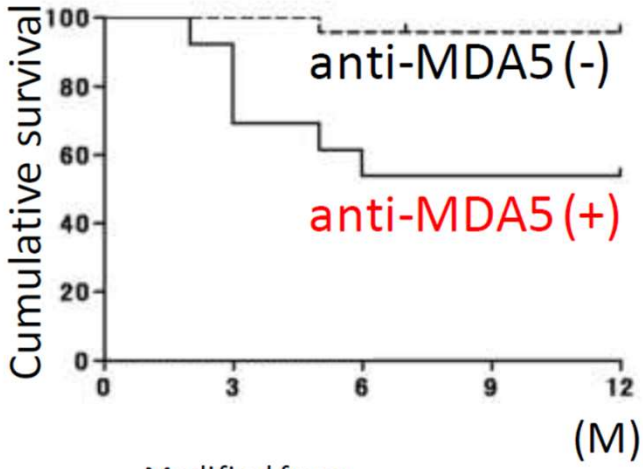
Learning points – *Case 4 Amyopathic DM & MDA5 ab*

- Peri orbital oedema and Gottrons papules pathonomonic
- Skin histology in DM difficult to distinguish from SLE
- Amyopathic DM often misdiagnosed as SLE
- Anti MDA5 - seen in patients with significant skin and lung disease
- Generally poor prognosis especially if have ILD (50% cases)
- Skin rash more severe

Anti-MDA5 (melanoma differentiation associated gene 5)

- Anti-CADM140/MDA5 is detected in clinically amyopathic dermatomyositis (CADM) and a part of DM patients[1)].

- Associated with RP-ILD in DM/CADM.
  Sensitivity, 77%; specificity, 86%[2)]



Modified from
Nakashima R, Mimori T, et al.
Rheumatology 2010

- A prognostic factor for poor survival in Asian patients[3)].

- The levels of anti-MDA5 and serum ferritin are correlated with the activity of RP-ILD[4,5)].

1) Sato S, et al. Arthritis Rheum 2009
2) Chen Z, et al. Arthritis Care Res 2013
3) Nakashima R, Hosono Y, Mimori T. Lupus 2016
4) Sato S, et al. Mod Rheumatol 2013
5) Gono T, et al. Mod Rheumatol 2011

Efficacy and Safety of Combined Immunosuppressive Therapy with High-Dose Glucocorticoid, Tacrolimus, and Cyclophosphamide in Interstitial Lung Disease Accompanied by Anti-MDA5-Positive Dermatomyositis
-A Multicenter Prospective Study -

Hideaki Tsuji[1)], **Ran Nakashima**[1)], Yoshitaka Imura[2)], Masato Yagita[2)], Hajime Yoshifuji[1)], Shintaro Hirata[3)], Takaki Nojima[3)], Eiji Sugiyama[3)], Kazuhiro Hatta[4)], Yoshio Taguchi[5)], Masaki Katayama[6)], Yuji Hosono[1)], Shuji Akizuki[1)], Kosaku Murakami[1)], Motomu Hashimoto[7)], Masao Tanaka[7)], Koichiro Ohmura[1)], and **Tsuneyo Mimori**[1)]

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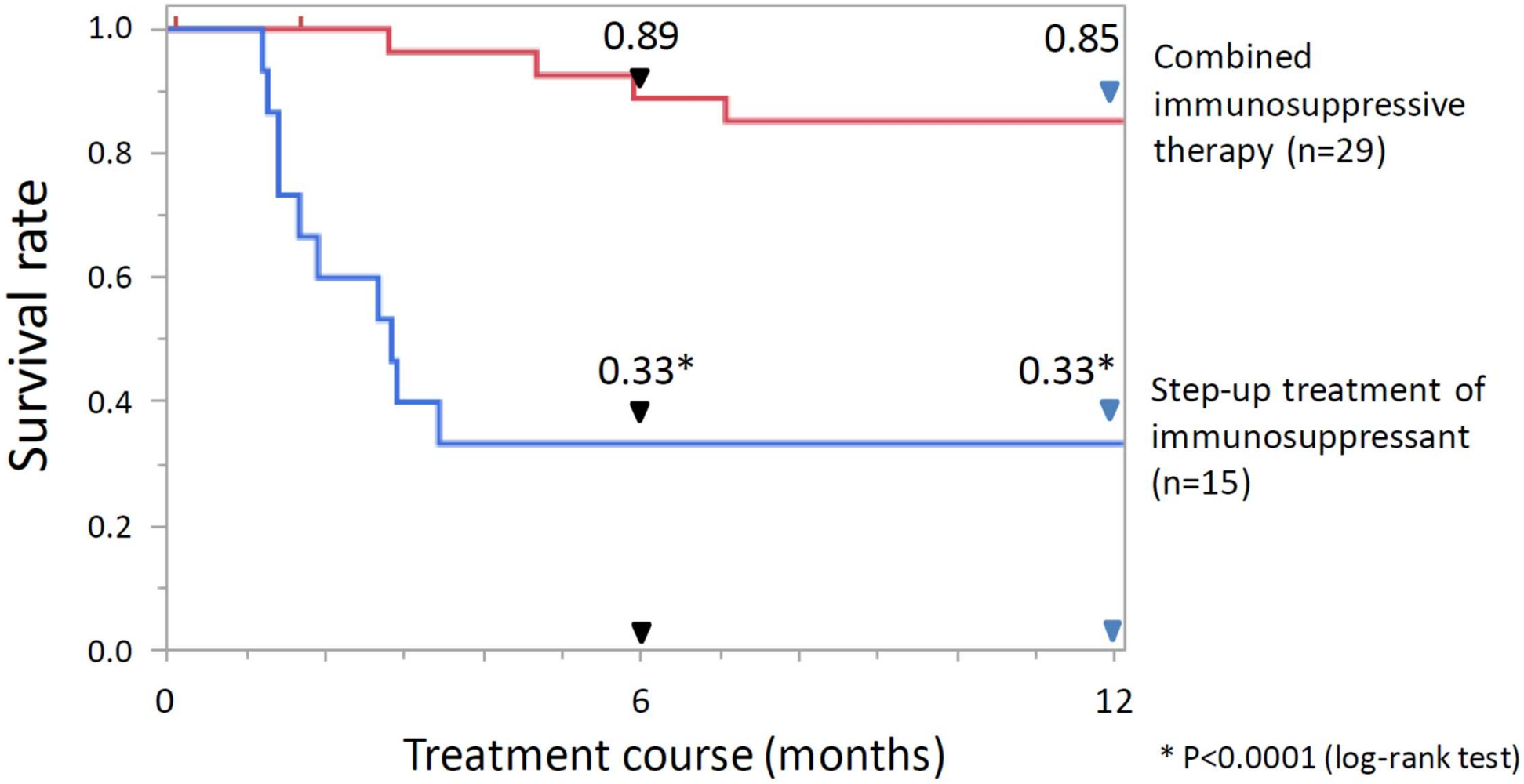
Primary endpoint: survival rate after treatment

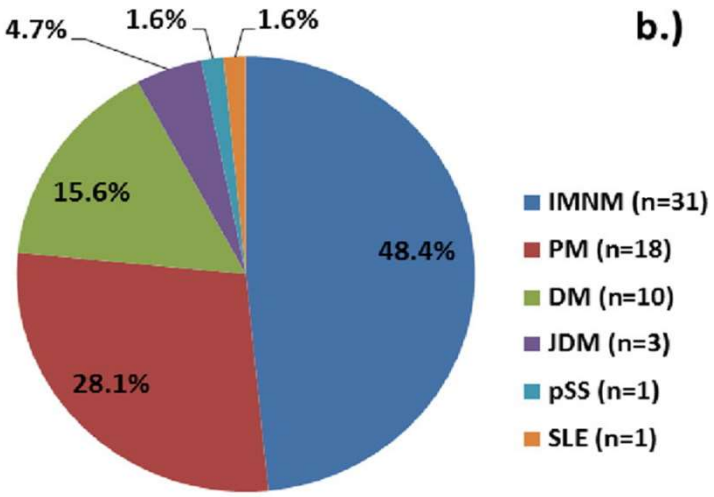


Case 5

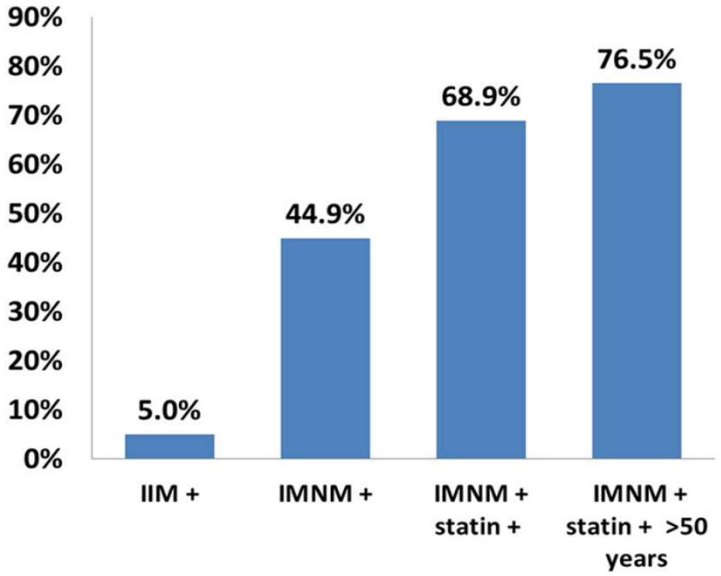
- **Refractory polymyositis**
- **Very high CK > 20,000**
- **Autoimmune necrotizing myopathy**
- *Consider re-biopsy and myositis autoantibodies*
- *Review of past biopsies and discussion with muscle pathologist important*

Immune-mediated necrotising myopathy

- Subacute, insidious progressive muscle weakness
- Anti-signal recognition particle
  - Associated with cardiac involvement



- Cases associated with statin use
  - May progress after statin stopped
  - Associated with anti-HMG CoA-reductase
  - Treatment with immunosuppressive agents and IVIG often required



Musset et al Autoimmunity Reviews 2016

Immune mediated necrotizing myopathy (IMNM)

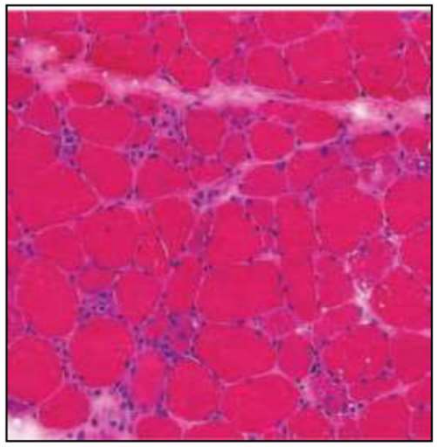
Three subsets based on expert consensus

1) *anti-SRP myopathy*

2) *anti-HMGCR myopathy*

high CK, proximal muscle weakness and anti-SRP or anti-HMGCR antibodies:

3) antibody negative IMNM: high CK, proximal muscle weakness, and muscle biopsy features including:



Scattered necrotic fibers

Different stages of necrosis and myophagocytosis and regeneration

Macrophages but few lymphocytes

Clinico-sero-pathological classification of Immune mediated necrotizing myopathy - ENMC consensus based workshop 2016

Allenbach Y et al. Neuromusc Dis, 2018;28:87-99

Clinical trials in Refractory DM

- Lenabasum – (DM) – upcoming Phase III trial
- Repository corticotropin (PM+DM) – Open label study of 10 pts
- Abatacept- (PM+DM)- Open label pilot of 19 pts
- Tofacitinib – (DM) - Open label trial of 10 pts

Ongoing trials in IBM

- Arimoclomol – co-induces the heat shock response and increases HSP level
  - Early phase pilot trial in patients with IBM showed it was safe
  - Trend at 8 months in favor of arimoclomol
  - Large international phase 2/3 trial is ongoing

- Pioglitazone – upregulate mitochondrial pathways (Hopkins)
  - Open label proof of concept study – 15 patients

Tx of IBM-Degenerative Pathway

- Bimagrumab, Activin receptor II (ARII) inhibitory monoclonal antibody (10 IBM, 4 placebo) – thigh muscle volume evaluated by MRI was increased; NO statistically difference in muscle function. (Phase 3 was not promising, results not published)

- Follistatin gene therapy, a myostatin antagonist→ improvement in 6 min walk test (+concomitant steroids and exercise)