Clinical strategies for the effective diagnosis and management of myositis

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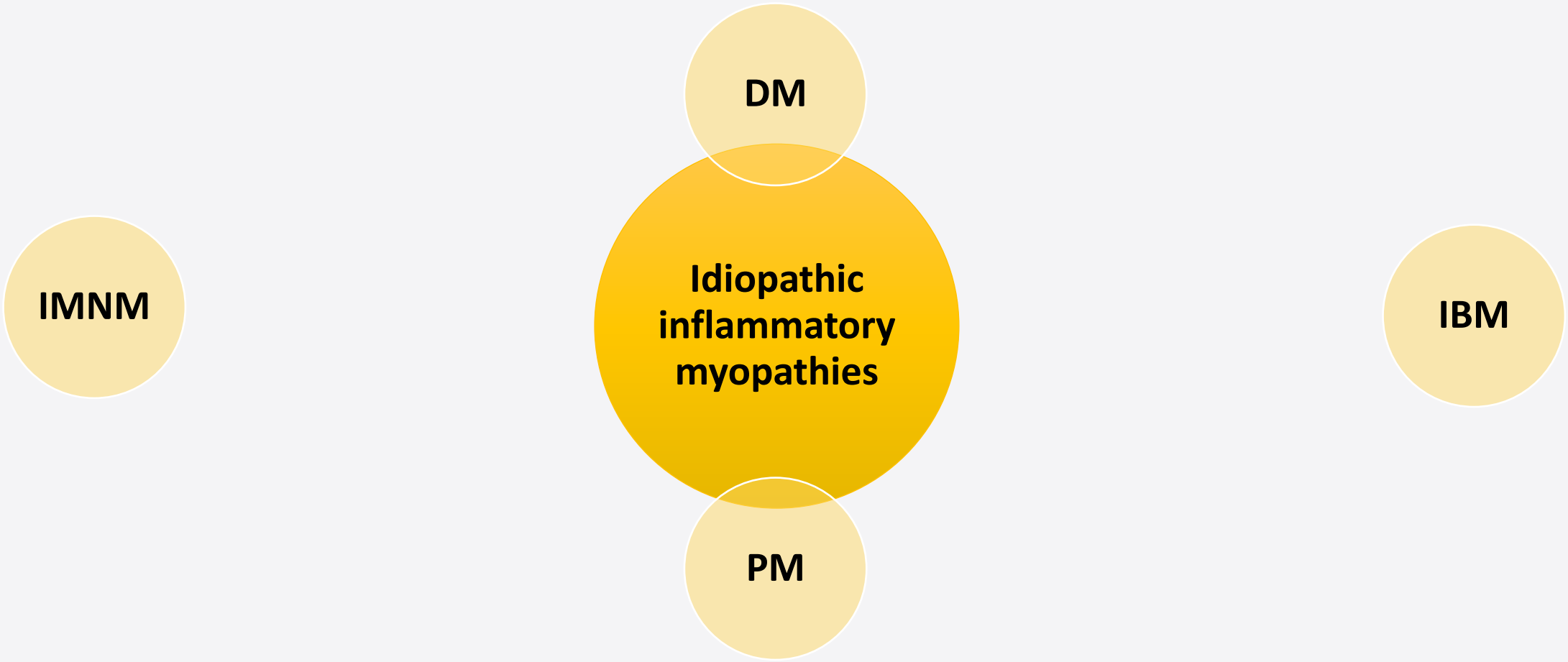
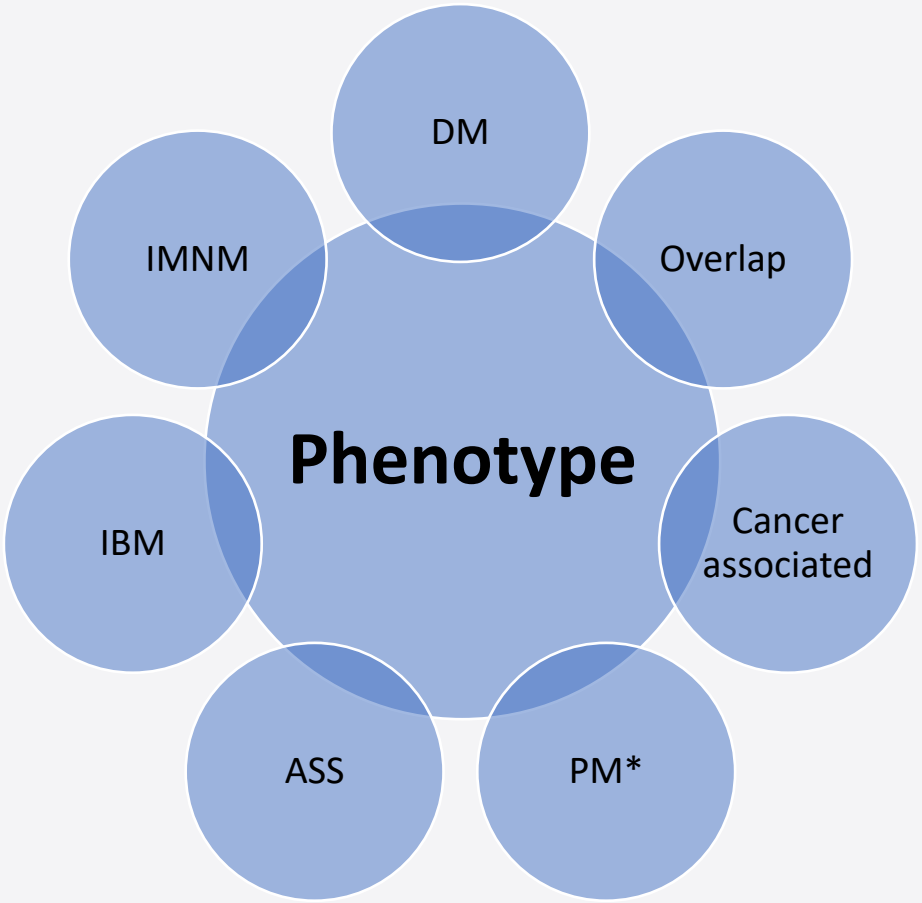
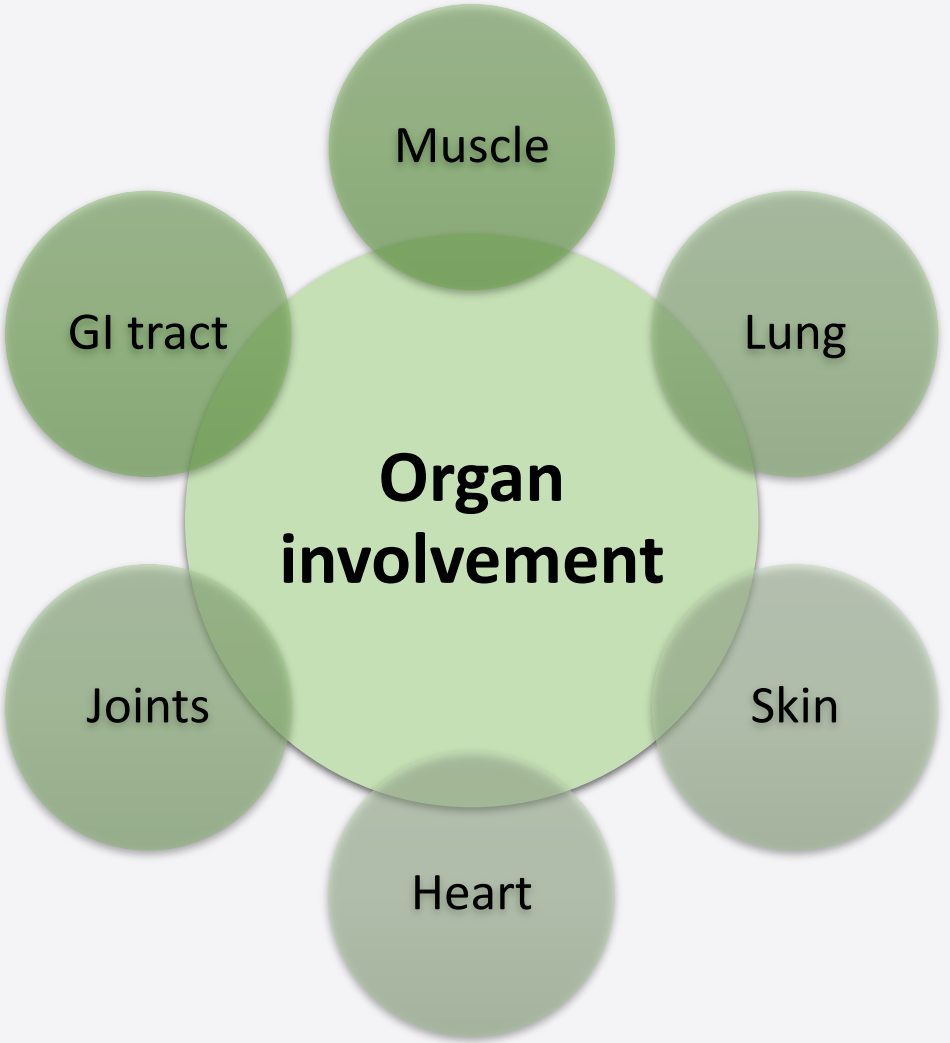
Agenda

1) **Diagnosis**
a) Phenotypes of disease
b) Laboratory markers
c) Cancer screening
d) Clinical evaluation
e) Imaging procedures
f) Biopsy

2) Treatment


DM
IMNM
Idiopathic inflammatory myopathies
IBM
PM


DM
IMNM
Overlap
Phenotype
IBM
Cancer associated
ASS
PM*


Muscle
GI tract
Lung
Organ involvement
Joints
Skin
Heart

Myositis specific (MSA) and associated antibodies (MAA)

- MSA are, generally, **mutually exclusive**.

- Their positivity addresses a clearly defined clinical subtype of disease.

- Their role in the monitoring is **uncertain** (but not for MDA5 and HMGCR)

- Their positivity may be influenced (and impaired) by different laboratory techniques (quantitative, qualitative, semiquantitative), which may display different results:

a) **Blot**:
b) **ELISA**:
c) **IP**
d) **PMAT**

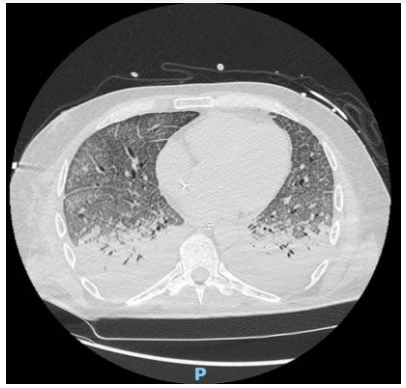
MSA

- **MI-2:** skin and muscle involvement, good overall response to treatment. Seldom ILD.
- **SAE**: severe skin involvement and dysphagia, ILD uncommon, sometimes cancer associated myositis
- **NXP**: calcinosis, high risk of cancer associated myositis
- **SRP, HMGCR:** IMNM
- **cN1A**: IBM, but its clinical relevance is uncertain.
- **JO-1, PL-7, PL-12, EJ, OJ, KS, ZO, HA**: anti-synthetase syndrome (mechanic hands, ILD, myositis, arthralgia/arthritis, fever)
- **MDA5**
- **TIF1ɣ**

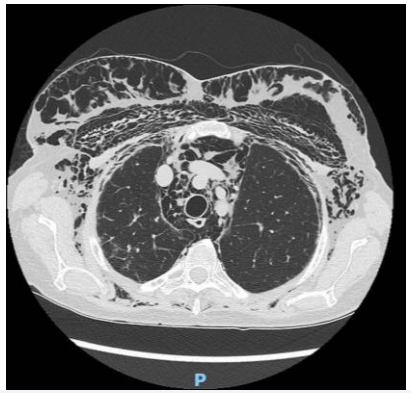
MAA

- **Ro/SSA**: often positive in ASyS, clinical meaning uncertain
- **Pm/SCL**: overlap (scleromyositis)
- **Ku**: overlap
- **RF/ACPA**: sometimes present in ASyS

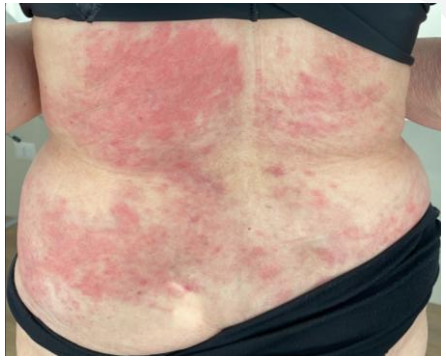
MDA5 syndrome: three clusters of disease



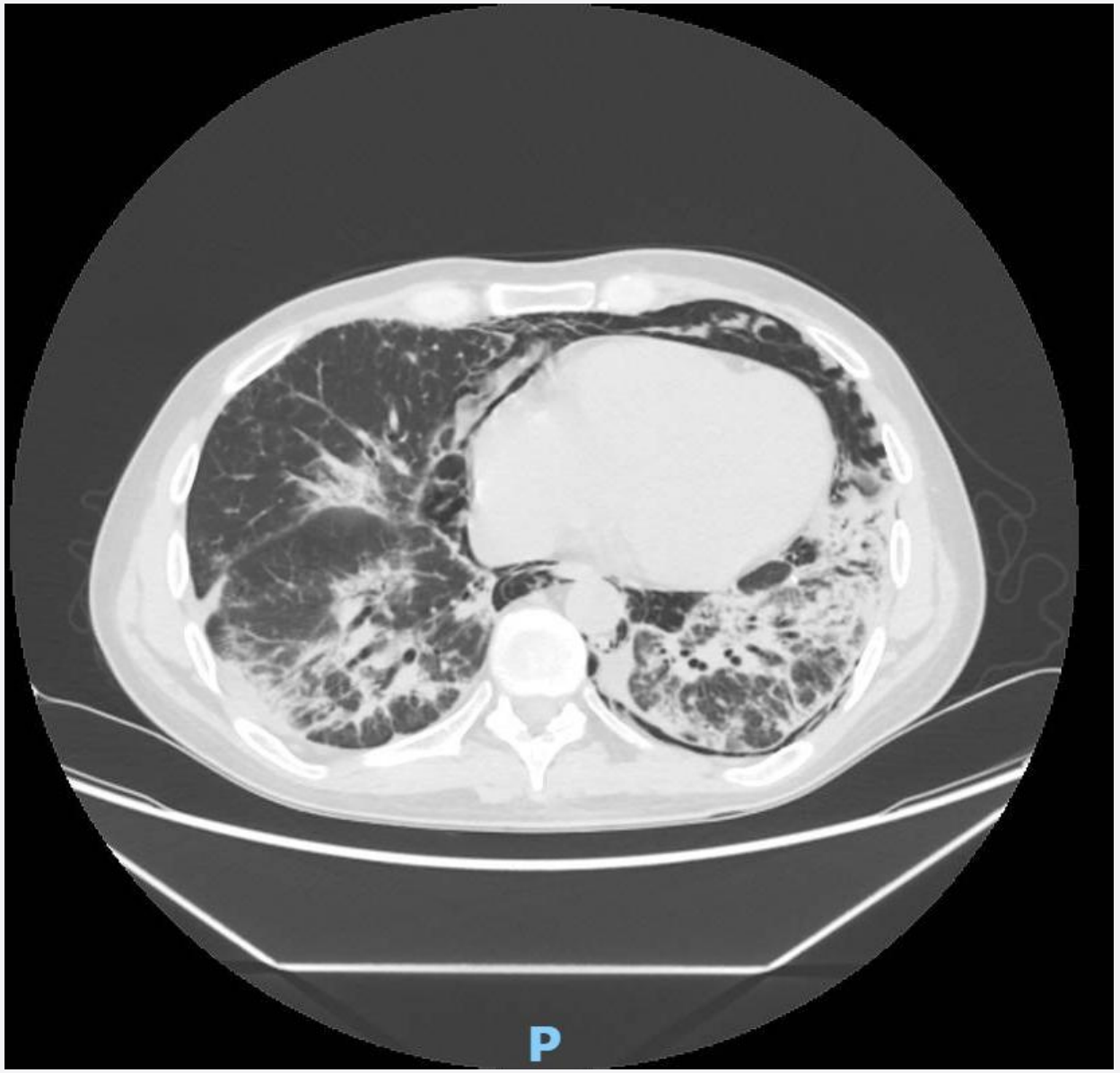
- Rapidly progressive ILD with elevated mortality
- Muscle involvement neglectable



- ILD not progressing into RP-ILD
- Myositis, severe skin disease, dysphagia, dysphonia



- Amyopathic
- ILD absent
- Severe skin disease and arthritis


P

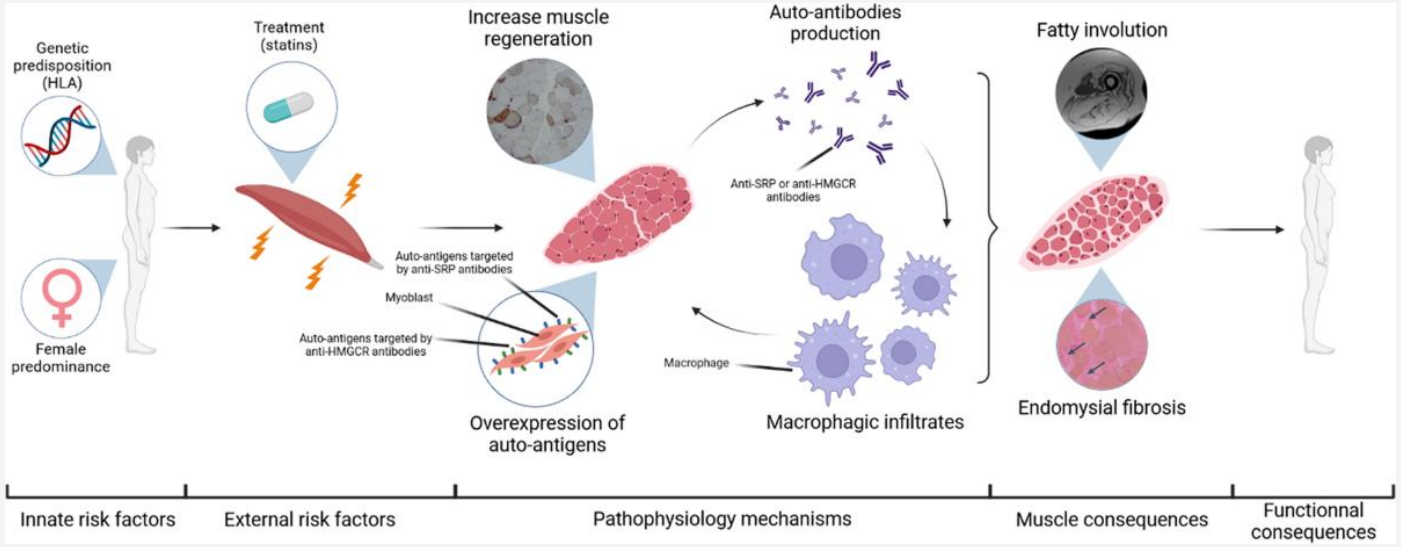
TIF1γ dermatomyositis

Younger than 40

- **Cancer associated myositis** in >90% of cases
- ILD uncommon
- **Dysphagia** poor prognostic factor
- Very severe skin disease

Older than 40

- Amyopathic
- Difficult-to-treat skin disease
- **Not associated to cancer**



Dallevet et al., *Curr Opin Rheumatol*, 2023; Allenbach et al., *Neuromuscular Disorders*, 2018

A — Anti-SRP-Myopathy

	Non-severe	Severe*
Initial treatment	• ± **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d	• **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d

At the same time or within 1 month, start 2nd or 3rd agent
- **Oral/sc Methotrexate°** (0.3 mg/kg/w, max 15 & 25 mg/w in child & adult, respectively)
- **Rituximab**[£,§] 750 mg/m² (max 1g) D1 + D7-D15

eventually
- **IVIG** 2 g/kg/m, 3-6 times

If no adequate response within 6m: reconsider **Rituximab** (*if not started*) and keep giving other treatments.

B — Anti-HMGCR-Myopathy

	Non-severe	Severe*
Initial treatment	• ± **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d	• **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d

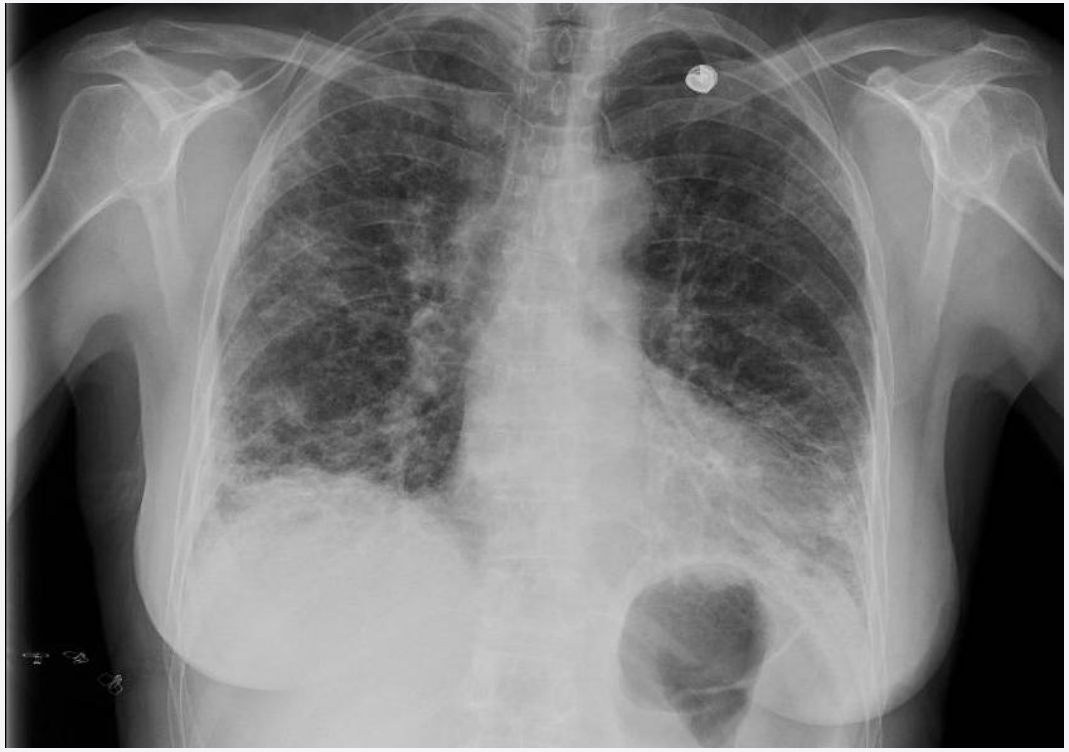
At the same time or within 1 month, start 2nd or 3rd agent
- **Oral/sc Methotrexate°** (0.3 mg/kg/w, max 15 & 25 mg/w in child & adult, respectively)
- **IVIG** 2 g/kg/m, 3-6 times *(possibly alone in case of steroids contraindication or intolerance)*

eventually
- **Rituximab**[£] 750 mg/m² (max 1g) D1 + D7-D15

If no adequate response within 6m: reconsider **Rituximab** (*if not started*) and keep giving other treatments.

Anti-SRP & anti-HMGCR-Myopathy

Maintenance treatment
- Taper **oral steroids** to the lowest dose as tolareted or as soon as possible (regarding the maximum benefit)
- Continue **Methotrexate** at least 2 years of well-controlled disease (slowly tapered later: 2.5 mg/w each month)
- Continue **Rituximab** every 6 months, at least 2 years of well-controlled disease
- If started **IVIG** are stopped or tapered, as tolerated.Nota bene: many HMGCR+patients may required IVIG



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https://doi.org/10.1007/s12026-023-09387-z

ORIGINAL ARTICLE

Prevalence of myositis specific and associated antibodies in a cohort of patients affected by idiopathic NSIP and no hint of inflammatory myopathies

Edoardo Conticini[1] · Miriana d'Alessandro[2] · Paolo Cameli[2] · Laura Bergantini[2] · Elena Pordon[2] · Lucia Cassai[2] · Luca Cantarini[1] · Elena Bargagli[2] · Bruno Frediani[1] · Brunetta Porcelli[3,4]

- Six out of 16 idiopathic NSIP (37,5%) had significant MSA and/or MAA positivity: one displayed positivity of anti-PL-7, one of anti-Zo, anti-TIF1γ and anti-Pm-Scl 75, one of anti-Ro52, one of anti-Mi2β, one of anti-Pm-Scl 75 and the latter of both anti-EJ and anti-Ro52.
- Among the patients who displayed any MSA and or MAA positivity, **3 fulfilled** Connors and Lega **criteria for ASS**, while none satisfied Solomon and EULAR/ACR ones.

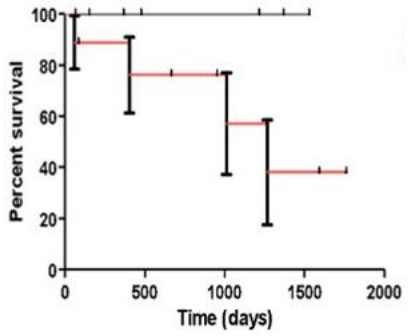


Figure 1. Survival comparison between seropositive and seronegati
Kaplan-Meier curves (log rank test chi square 3.358; p=0.0328).

Parameter	Total population	Seropositive patients	Seronegative patients	*p* value
N°	16	7	9	
Female gender (%)	8 (50)	5 (71.4)	3 (33.3)	0.3147
Age (years)	72 ± 6.1	72 ± 6.6	72.2 ± 5.5	0.9096
Therapy				
Oral steroids (%)	16 (100)	7 (100)	9 (100)	1.0000
Mycophenolate (%)	4 (25)	1 (14.2)	3 (33.3)	0.5846
Azathioprine (%)	2 (12.5)	1 (14.2)	1 (11.1)	1.0000
Nintedanib (%)	5 (31.2)	1 (14.2)	4 (44.4)	0.3077
Serological testing				
CRP (mg/dl)	0.73 ± 1.07	0.96 ± 1.2	0.21 ± 1	0.2573
AST (UI/l)	22.5 ± 9.1	24.1 ± 9.5	16.6 ± 4.4	0.2129
ALT (UI/l)	21.6 ± 14.9	24.8 ± 16.7	12.8 ± 2.7	0.0534
LDH (UI/l)	195 ± 4.2	187.4 ± 6.4	197.1 ± 3.5	0.5986
CPK (UI/l)	44.5 ± 0.7	46.5 ± 3.4	42.1 ± 1.5	0.4968
Myoglobin (UI/l)	44.5 ± 2.1	47.1 ± 3.6	43.6 ± 3.6	0.8569
Aldolase (UI/l)	4.5 ± 1.9	4.4 ± 1.1	4.5 ± 1.3	0.8796
ANA titre				0.1296
- Negative (< 1:160)	11 (68.7)	3 (42.8)	8 (88.8)	
- 1:160–1:320	4 (25)	3 (42.8)	1 (11.1)	
-> 1:320	1 (6.2)	1 (14.2)	0 (0)	
Lung function tests				
FVC ml	2308.1 ± 962	2224.2 ± 1079	2373.3 ± 922.5	0.3510
FVC (%)	79 ± 18.7	83.1 ± 13.6	75.9 ± 22.2	0.7340
FEV1 ml	1865 ± 668.6	1774.2 ± 644.3	1935.5 ± 703.2	0.6806
FEV1 (%)	81.1 ± 16.9	84.2 ± 12.5	78.5 ± 20.3	0.6504
FEV1/FVC	82.6 ± 8.6	82.1 ± 10.7	83.1 ± 7.2	0.8371
DLCO (%)	59.1 ± 30.9	62 ± 10.6	57.1 ± 39.3	0.2977
KCO (%)	86.7 ± 34.6	94.1 ± 17.9	79.6 ± 42.6	0.5035
Outcomes				
Δ FVC ml	− 200.6 ± 280.9	− 61.4 ± 165.4	− 322.5 ± 313	0.1520
Δ FVC %	− 8.1 ± 11.5	− 3.3 ± 8.9	− 12.3 ± 12.4	0.1236
Δ DLCO ml/min/mmHg	− 2.9 ± 12.5	1.3 ± 2.4	− 6.4 ± 16.6	0.3602
Δ DLCO %	− 6.4 ± 8.5	− 4.7 ± 6.7	− 7.1 ± 9.4	0.5255
Death (%)	4 (25)	0 (0)	4 (44.4)	0.2335

Patients suspected of Anti-synthetase syndrome

↓

Classification Criteria for Anti-synthetase syndrome

- ✓ Within each clinical/serological domain, only count the highest weight for calculating the total score
- ✓ Not present/not assessed/not available in any clinical/serological variables has score of 0

Clinical domain	Weight	Other clinical features	Weight
Joint involvement		***Mechanic's hands/Hiker's feet***	1.5
Inflammatory arthralgia or arthritis	1.0	***Raynaud's phenomenon***	0.5
Muscle involvement		***Inflammatory rashes*** (Gottron's, heliotrope, V-sign, shawl sign, malar rash)	0.5
Subclinical evidence of myositis (muscle enzyme/EMG/MRI)	1.0	***Unexplained fever***	0.5
Clinical evidence of myositis	1.5	**Serological domain**	**Weight**
Biopsy-supported myositis	2.0	***Anti-ARS antibodies***	
Interstitial lung disease		Non-Jo-1 positive by non-IP methods	3.0
UIP or other/unclassifiable pattern	1.5	Jo-1 positive by any methods or non-Jo-1 positive by IP	3.5
Predominant NSIP and/or OP pattern	2.5		
		ANA with cytoplasmic pattern	1.5
		Anti-Ro52 or anti-SSA antibodies	1.0

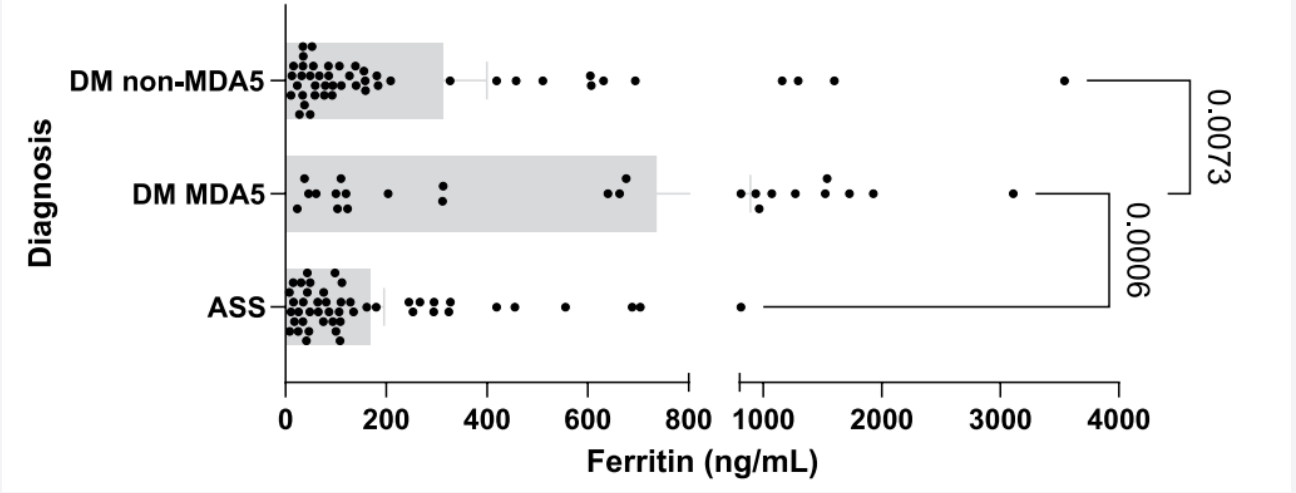
Zanframundo et al., *ACR convergence* 2024

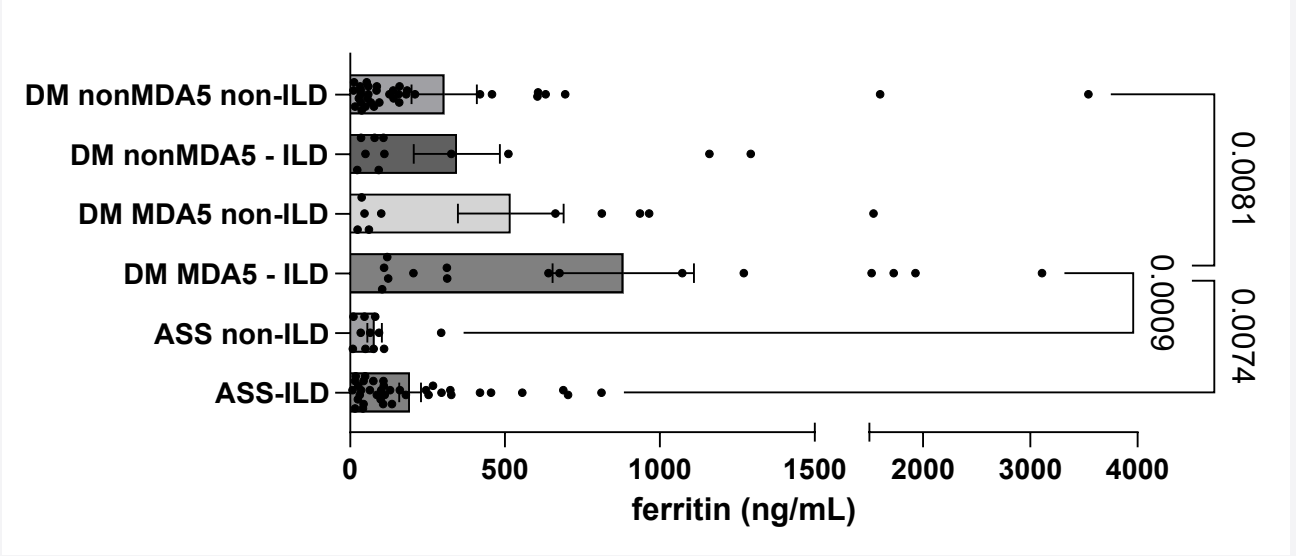
Biomarkers other than CK, aldolase, myoglobin and transaminase: ferritin

Parameters	DM MDA5	ASS	DM nonMDA5	p values
Ferritin (ng/mL)	736.84±773.18	167.27±195.19	313.26±593.954	**0.0007**
Age at 1st diagnosis (years)	40.95±17.31	51.20±12.65	44.83±22.21	0.1379
PHGA	3.32±2.04	2.60±2.51	2.91±2.73	0.2243
Number of organs involved	2.72±0.79	2.63±0.96	2.45±0.97	0.2940
ESR (mm/hr)	41.07±33.46	29.03±25.78	31.84±28.71	0.3330
CPK (µg/L)	243.48±281.92	457.98±711.08	1630.91±4701.49	0.3683
CRP (mg/dL)	8.13±12.91	3.66±5.62	6.14±12.02	0.3907
MDI	5.19±2.99	4.17±3.69	3.33±3.39	0.1090

Comparison of clinical and serological findings according to autoimmune profile

ASS anti-synthetase syndrome, *DM* dermatomyositis, *ESR* erythrocyte sedimentation rate, *MDI* myositis damage index, *PhGA* physician global assessment, *CPK* creatine phosphokinase, *CRP* C-reactive protein, *DM* dermatomyositis, *PM* polymyositis, *SD* standard deviation





Conticini et al., *Rheumatol Int,* 2025.

Clinical evaluation: CDASI (cutaneous DM disease area and severity index)

To evaluate **disease activity** and **damage** in **15 anatomical areas**

CDASI evaluates disease activity through examination of:

- **Erythema**
- **Scale**
- **Erosion or ulceration**

Gottron's – Hands

Examine patient's hands and double score if papules are present		Ulceration
0-absent 1-pink; faint erythema 2-red erythema 3-dark red		

Periungual

Periungual changes (examine)	
0-absent 1-pink/red erythema/microscopic telangiectasias 2-visible telangiectasias	

Alopecia

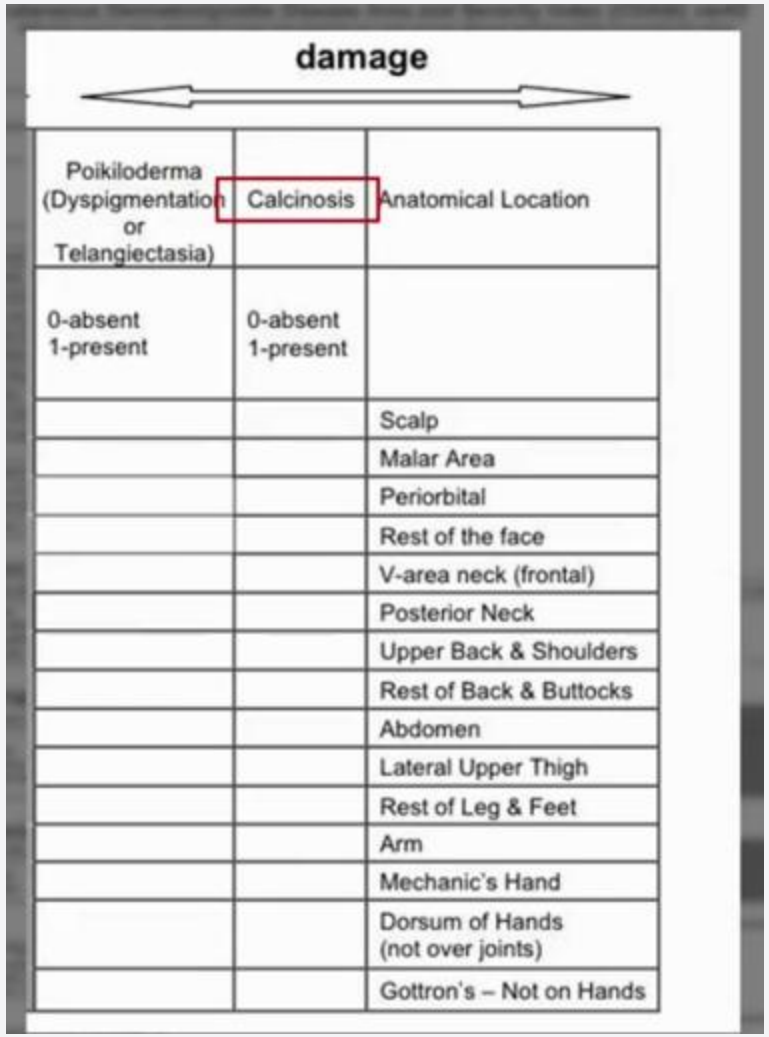
Recent Hair loss (within last 30 days as reported by patient)	
0-absent 1-present	

activity

Anatomical Location	Erythema	Scale	Erosion/ Ulceration
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present
Scalp			
Malar Area			
Periorbital			
Rest of the face			
V-area neck (frontal)			
Posterior Neck			
Upper Back & Shoulders			
Rest of Back & Buttocks			
Abdomen			
Lateral Upper Thigh			
Rest of Leg & Feet			
Arm			
Mechanic's Hand			
Dorsum of Hands (not over joints)			
Gottron's – Not on Hands			

Disease damage:

- **Poikiloderma** (dyspigmentation or teleangiectasias)
- **Calcinosis**



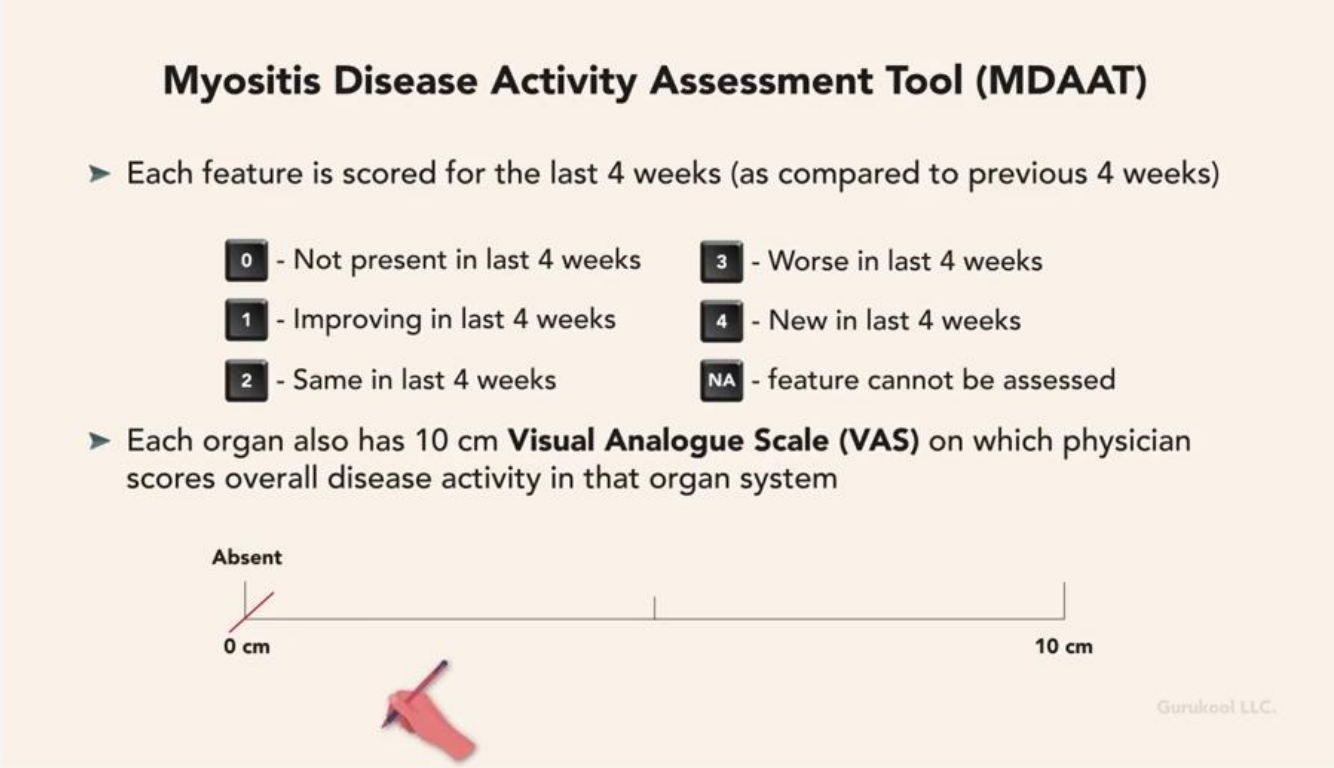
damage

Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
0-absent 1-present	0-absent 1-present	
		Scalp
		Malar Area
		Periorbital
		Rest of the face
		V-area neck (frontal)
		Posterior Neck
		Upper Back & Shoulders
		Rest of Back & Buttocks
		Abdomen
		Lateral Upper Thigh
		Rest of Leg & Feet
		Arm
		Mechanic's Hand
		Dorsum of Hands (not over joints)
		Gottron's – Not on Hands

Clinical evaluation: MDAAT (Myositis Disease Activity Assessment Tool)

Only active disease!

1) Constitutional
2) Cutaneous
3) Joints
4) Gastrointestinal
5) Pulmonary
6) Cardiovascular
7) Myositis
8) Global (overall)



Clinical evaluation: MMT-8 (manual muscle test-8)

Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**
Axial Muscles (0 – 10)			
Neck flexors	**X**	**X**	0-10
Proximal Muscles (0 – 100)			
Deltoid	0-10	0-10	**X**
Biceps	0-10	0-10	**X**
Gluteus maximus	0-10	0-10	**X**
Gluteus medius	0-10	0-10	**X**
Quadriceps	0-10	0-10	**X**
Distal Muscles (0 – 40)			
Wrist extensors	0-10	0-10	**X**
Ankle dorsiflexors	0-10	0-10	**X**
MMT- 8 score (0 – 150)	0-70	0-70	0-10
Muscle Groups	**Right (0 – 10)**	**Left (0 – 10)**	**Axial (0 – 10)**

MMT-8 grading using Kendall scale (0-10)

	Function of the muscle	Grade	
		Kendall	MRC
No Movement	No contractions felt in the muscle	0	0
	Tendon becomes prominent or feeble contractions felt but no visible movement	T=Trace (score as 0)	1
Test Movement	Gravity Eliminated (Movement in horizontal plane)		
	Moves through partial range of motion	1	2-
	Moves through complete range of motion	2	2
	Anti-Gravity Position		
	Moves through partial range of motion	3	2+
Test holding of Position	Gradual release from test position	4	3-
	Holds test position (no added pressure)	5	3
	Hold test position against slight pressure	6	3+
	Holds test position against slight to moderate pressure	7	4-
	Holds test position against moderate pressure	8	4
	Holds test position against moderate to strong pressure	9	4+
	Holds test position against strong pressure	10	5

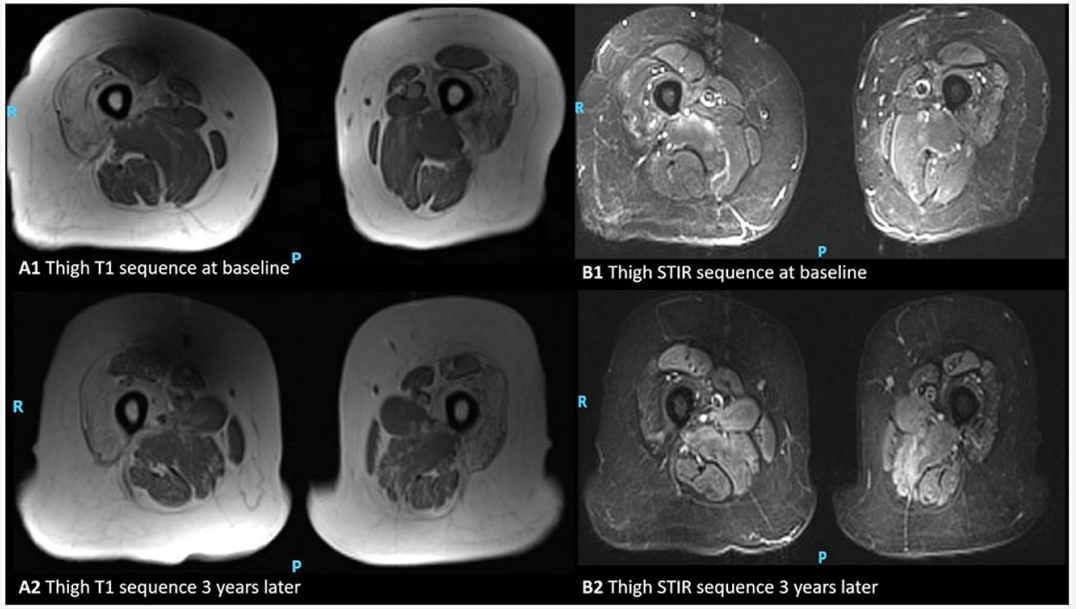
Investigators can use MRC scale (0-5) to evaluate patient and then convert it to Kendall (0-10) scale for scoring/recording.

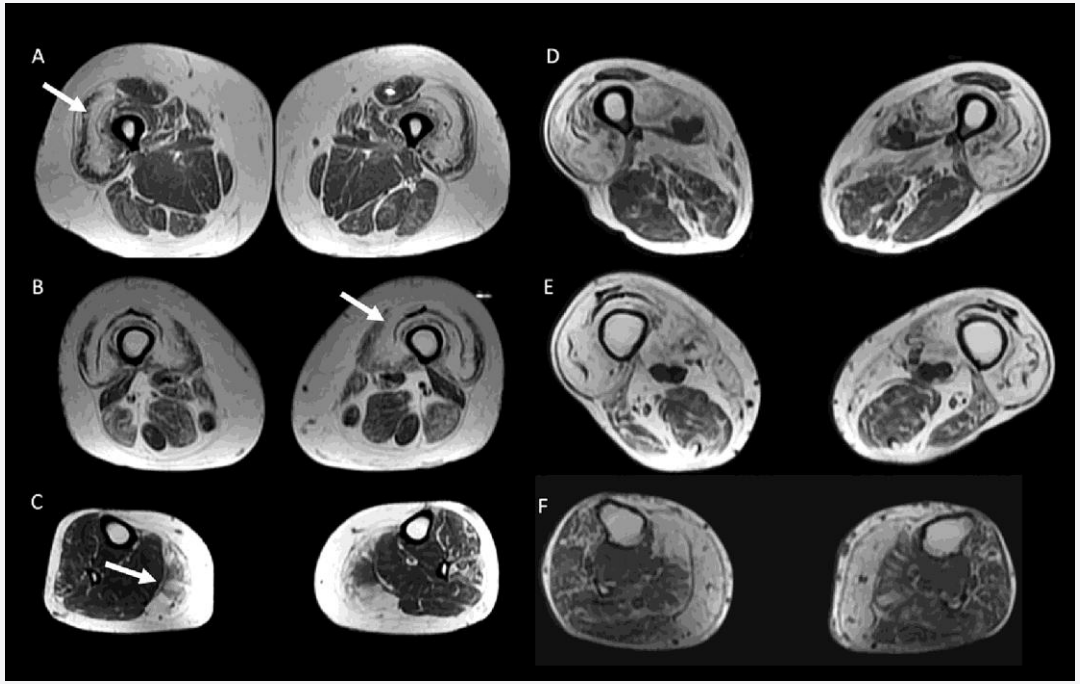
Florence P. Kendall et al. 1993

MRC, Aids to examination of peripheral nervous systems 1976

Magnetic resonance imaging

- Useful for distinguishing inflammatory from atrophic features.
- Single muscle (e.g. thighs as *pars pro toto*) vs whole body.
- Lack of validated scores and poor inter-rater agreement

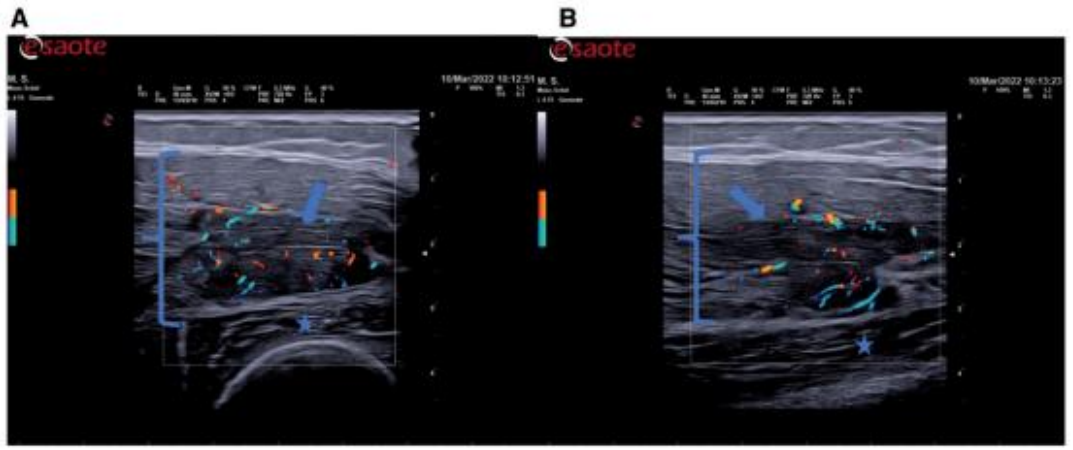


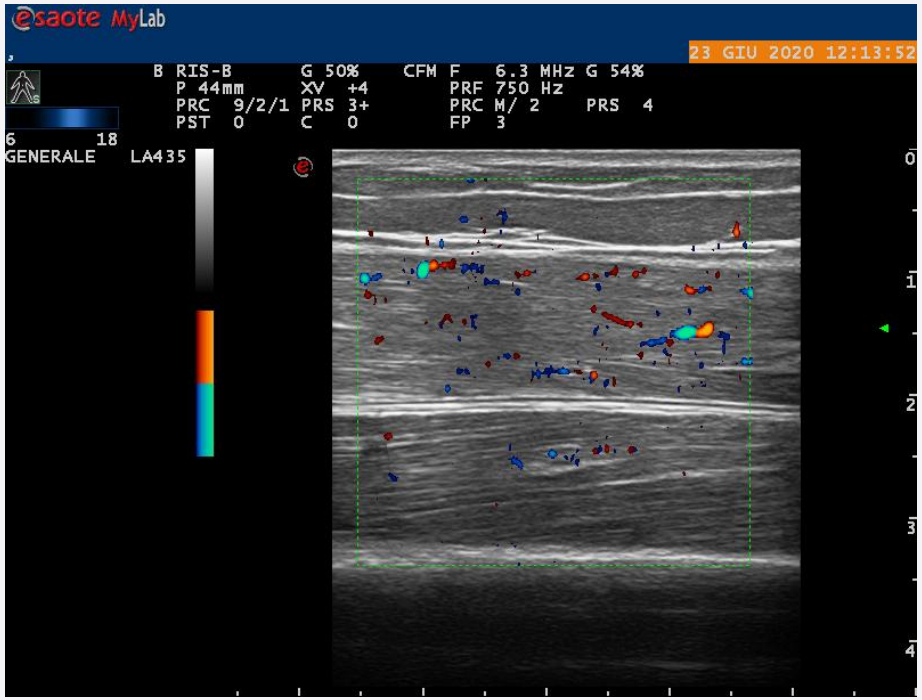


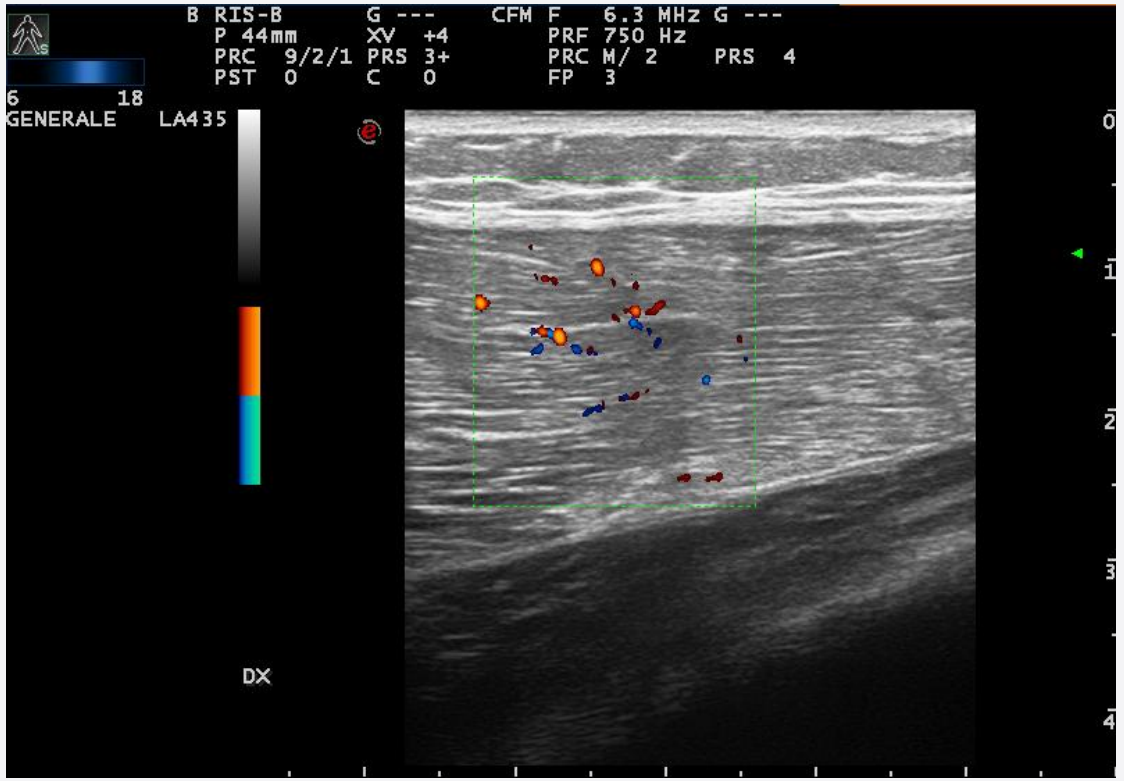
Essouma et al., *Rheumatol Int*, 2024; Shinjo S, Doria A et al., *under review;* Zubair et al., *Front Neurol,* 2023; Palmeira Cavalcante et al., *Front Neurol,* 2024

Ultrasonography

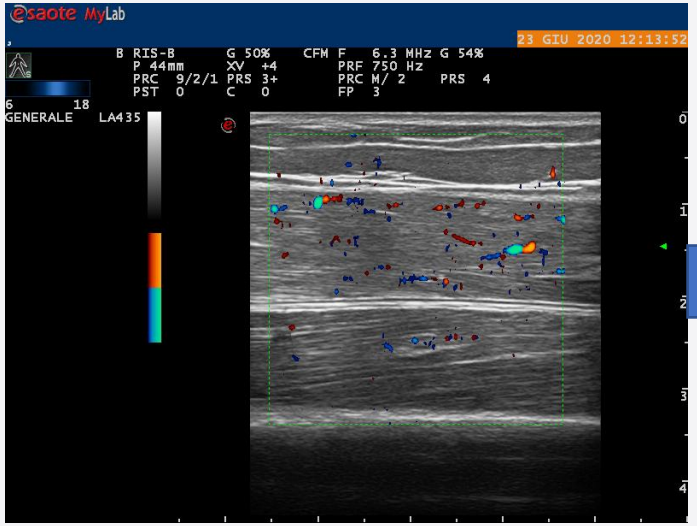
Fig. 1 Relapse of myositis in anti-synthetase syndrome

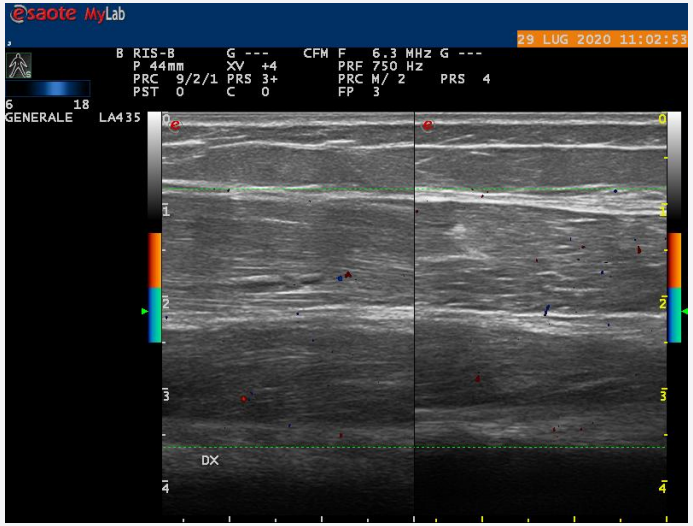






Conticini et al., *Rheumatology (Oxford)*, 2023





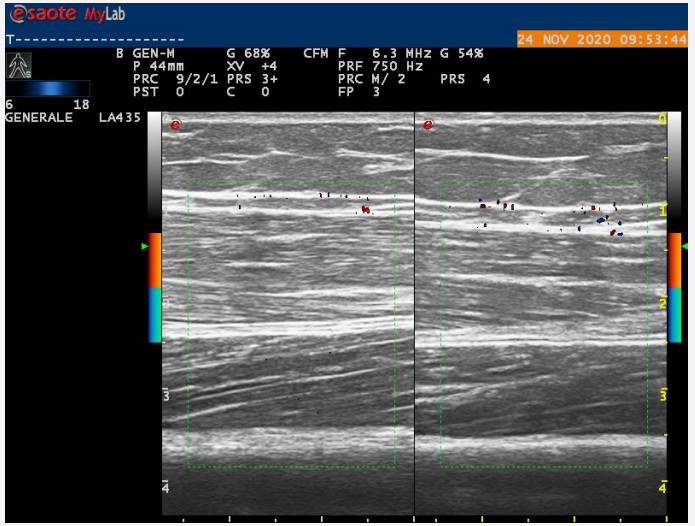
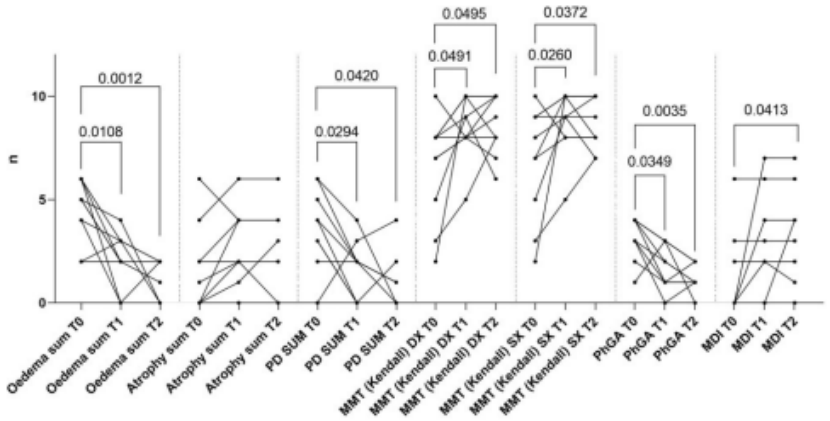
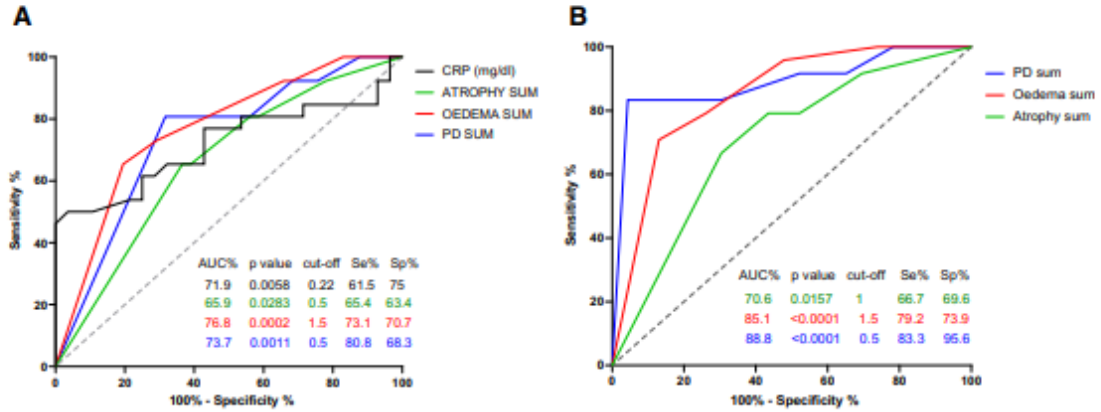


FIG. 5 Variation of PDUS and clinical findings during follow-up



Comparative analysis of clinical and immunological features in IIM patients during T0, T1 (2.2 [2.5] months) and T2 (7.8 [4.3] months). IIM: idiopathic inflammatory myopathies; MDI: myositis damage index; MMT: manual muscle testing; PD: power Doppler; PDUS: power Doppler ultrasonography; PhGA: physician global assessment. *P* values < 0.05 was stastistically significant.

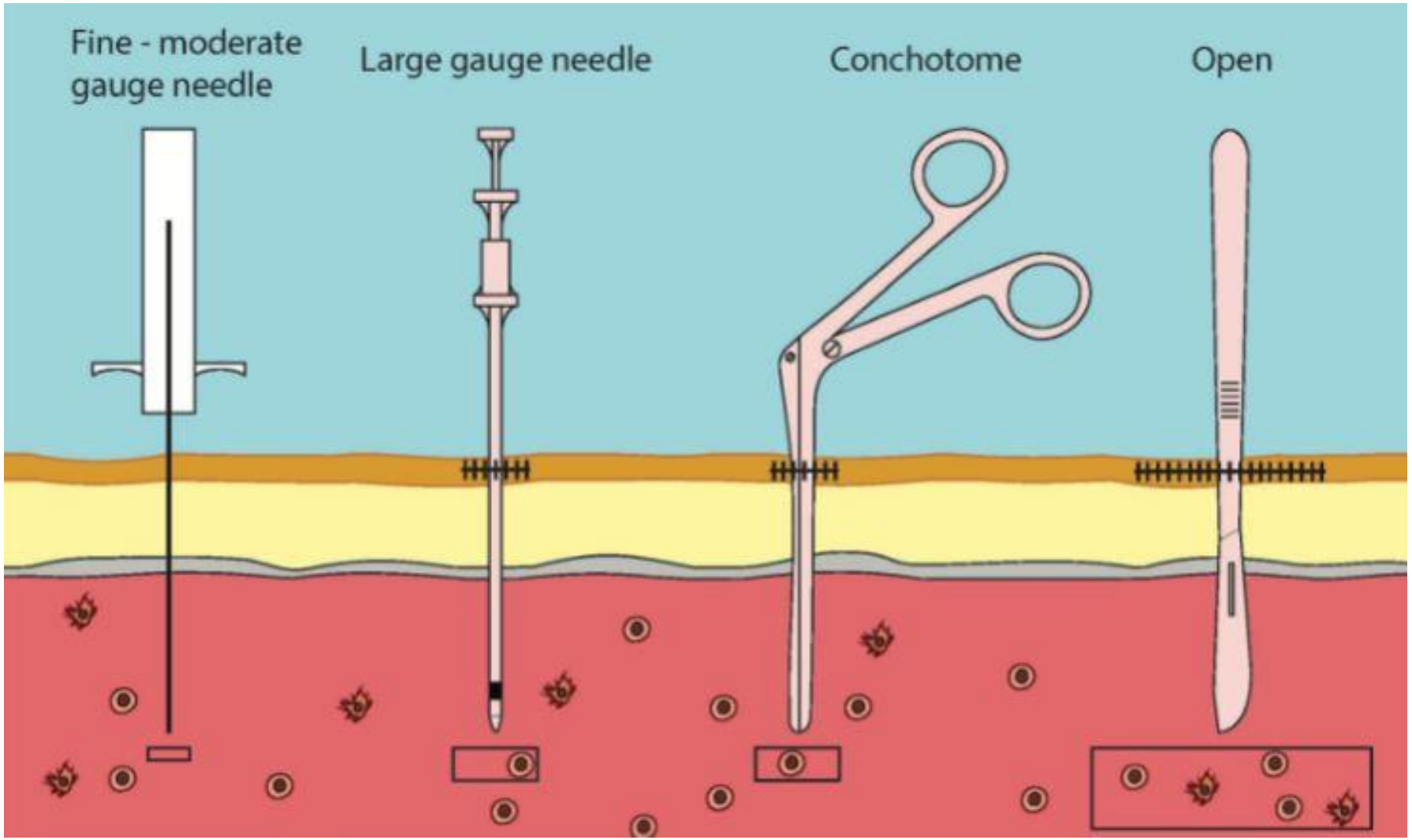
FIG. 4 Area under the receiver operating characteristic curve analysis of PDUS and CRP findings



(**A**) AUROC analysis of PDUS features and CRP values to distinguish IIM patients and controls. (**B**) AUROC analysis of PDUS features to distinguish active IIM patients and controls. AUROC: area under the receiver operating characteristic curve; IIM: idiopathic inflammatory myopathies; PDUS: power Doppler ultrasonography.

Conticini et al., *Rheumatology (Oxford)*, 2023

Muscle biopsy: how?



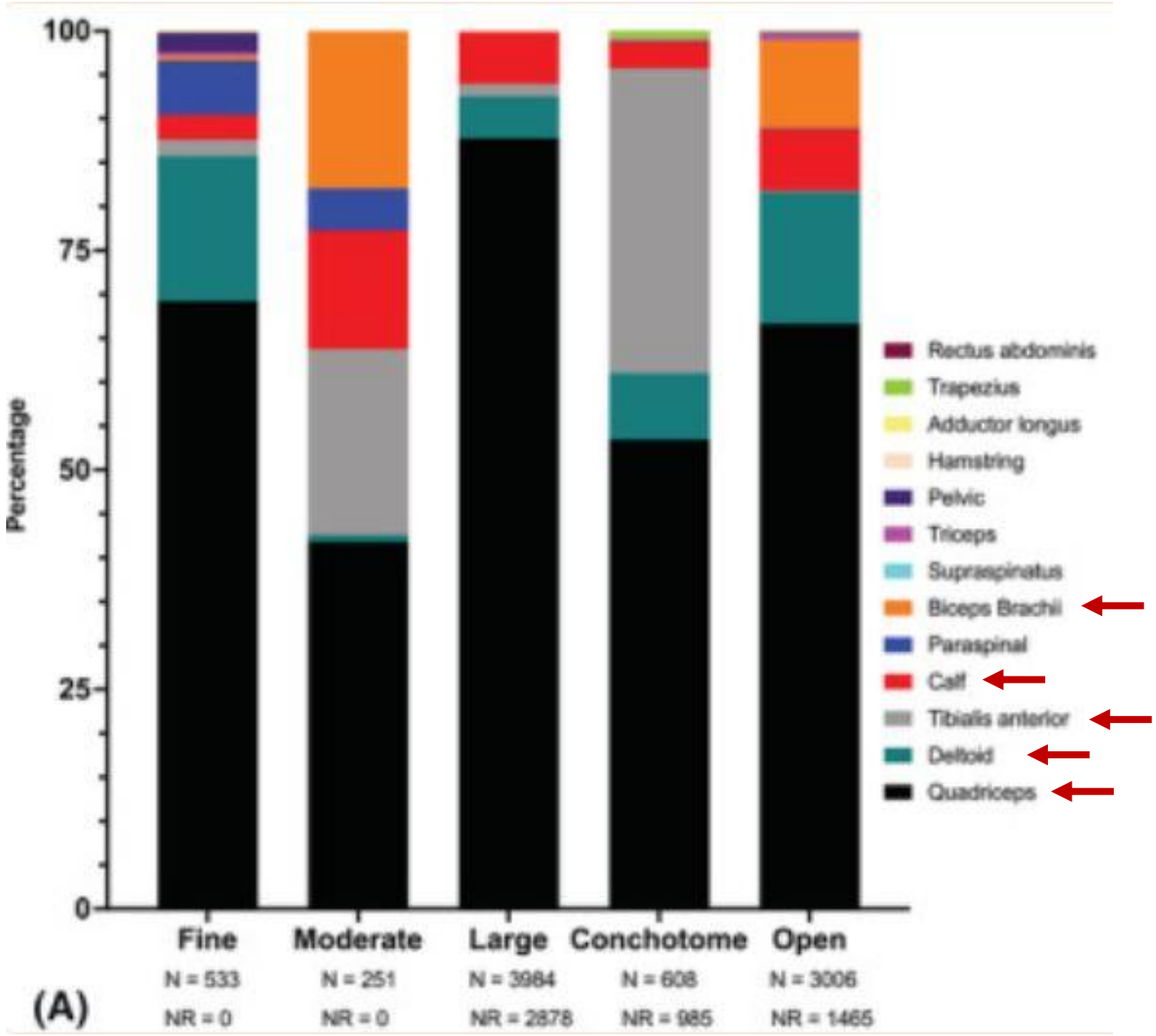
Ross et al., *Neuropathol Appl Neurobiol,* 2023.

Muscle biopsy: when?

- Clinical feature of IIM in the lack of MSA positivity
- MSA positivity in the lack of typical clinical
- Suspected inclusion body myositis (IBM)
- Previous diagnosis of IIM refractory to multiple lines of treatment

Muscle biopsy: where?

- Choose <u>moderately affected muscles.</u>
- Avoid muscles suffering from traumas or undergone further images (previous biopsies, EMG).
- Stay far from tendons, vessels and nerves.



Ross et al., *Neuropathol Appl Neurobiol,* 2023.

Inadequate sampling rate

- **Fine-gauge needle** 11,4%
- Moderate-gauge needle 3,3%
- Large-gauge needle w/o vacuum 0 % - 1,7%
- Conchotome 1,8%
- Open 0,3%

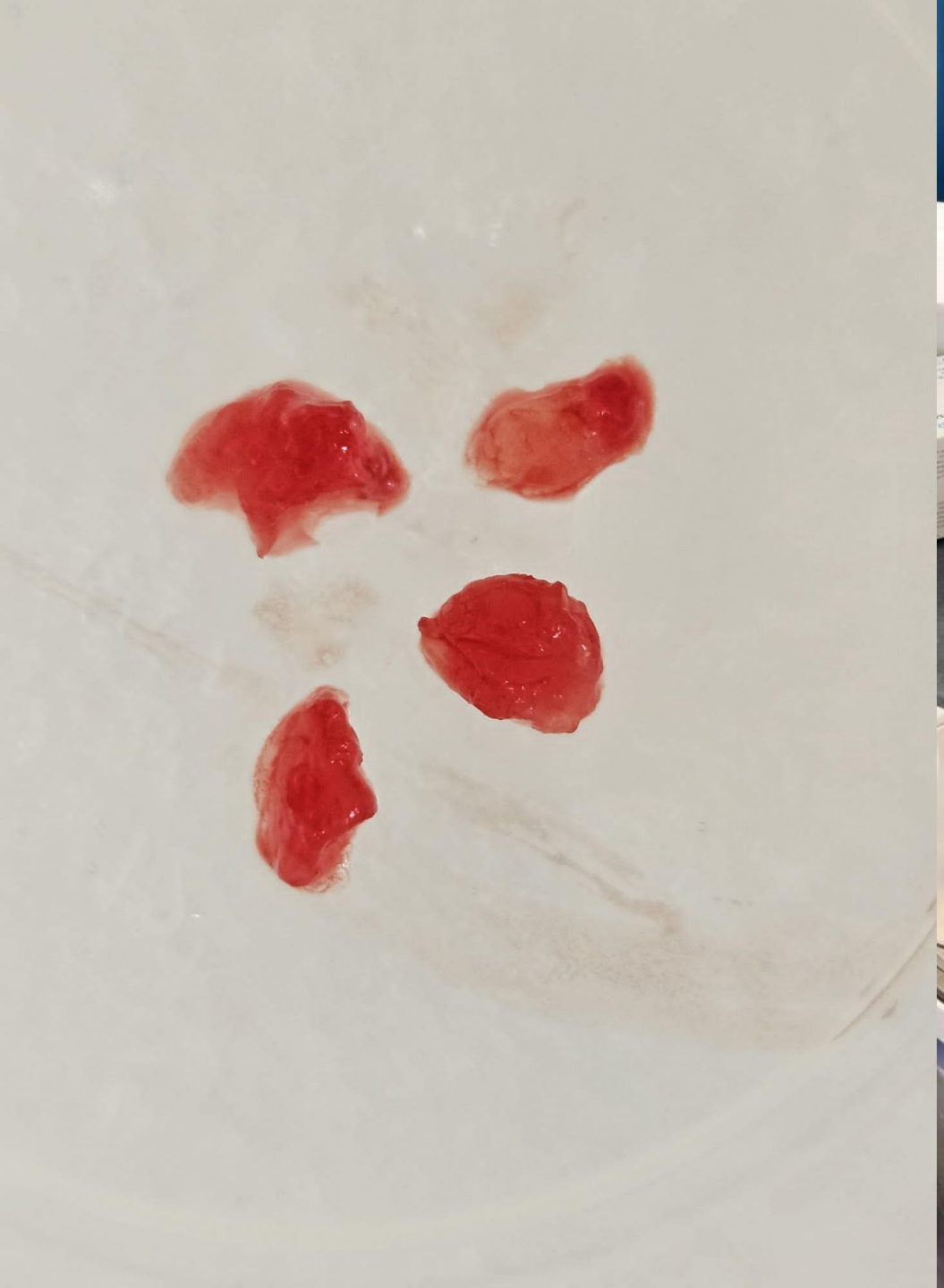
Complications

- **Peri-procedural pain**: **large-gauge needle** > open / fine-gauge needle / conchotome
- **Oematoma**: **moderate/large-gauge needle** > conchotome
- **Infections**: **open** (1 – 5%) > large-gauge needle (0,5%)
- **Cheloids**: **open** 3,1%
- **Sensitivity disorders**: **needle** 0,03 – 1,8%

No complications, regardless from techniques, in 33% of studies.

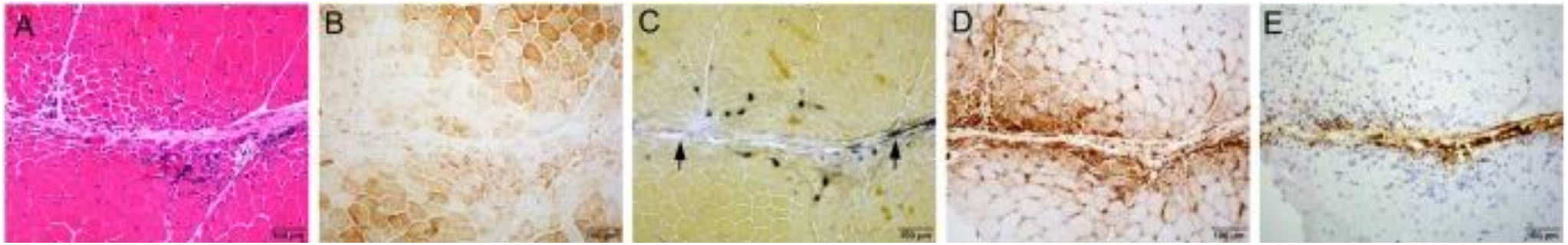
Ross et al., *Neuropathol Appl Neurobiol,* 2023.

LATEX FREE
Lidocaina Kabi 20 mg/ml
soluzione per infusione
4-0
(1.5 Ph. Eur.)
B-14 plus
22 mm 3/8c
75cm
ETHICON
Coated
VICRYL™
Polyglactin 910
violet braided absorbable suture
violet tressé suture résorbable
violett geflochten chirurg. Nahtmaterial resorbierbar
viola intrecciato sutura assorbibile
violeta trenzado sutura absorbible
violet gevlochten chirurgisch hechtmateriaal resorbeerbaar
REF JV294
2797
Johnson & Johnson International
2029-10



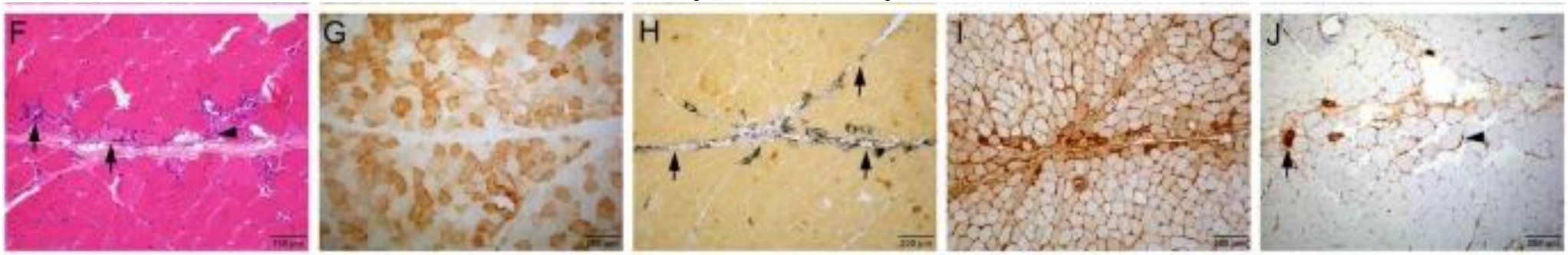
Bio - Optica

Dermatomyositis



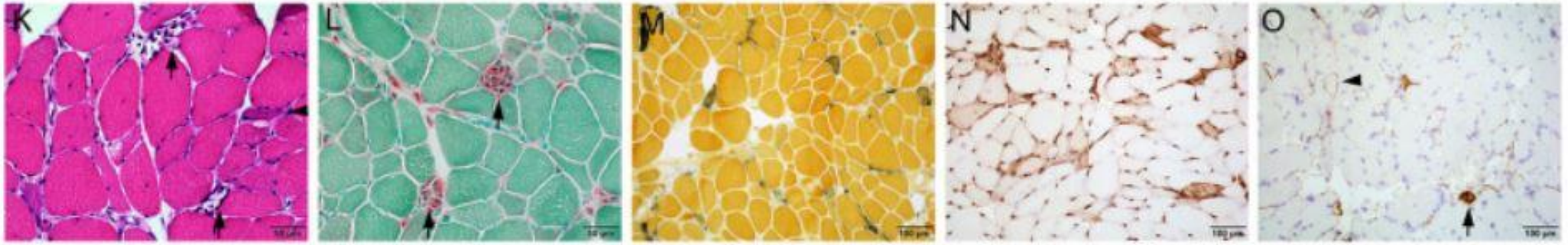
Perifascicular atrophy, COX- fibers, MHC- and C5b-9 capillaries, alkaline phosphatase

Anti-synthetase syndrome



Perifascicular necrosis and regeneration, diffuse COX- fibers, perimysium alkaline phosphatase +++, diffuse (+) and perifascicular (++) MCH-I, C5b-9 necrotic and vital perifascicular fibers

Immune mediated necrotizing myopathies

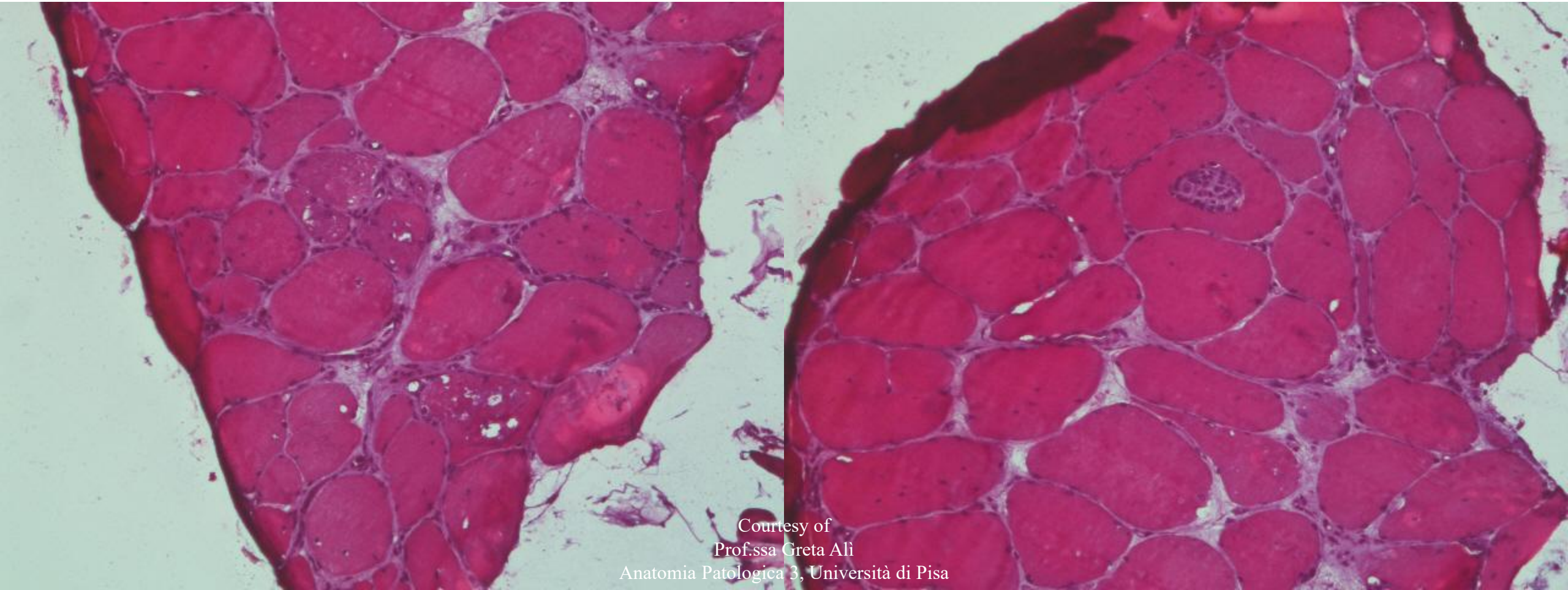


Diffuse necrosis and regeneration, myophagocitosis, alkaline phosphatase, MHC-I, C5b-9

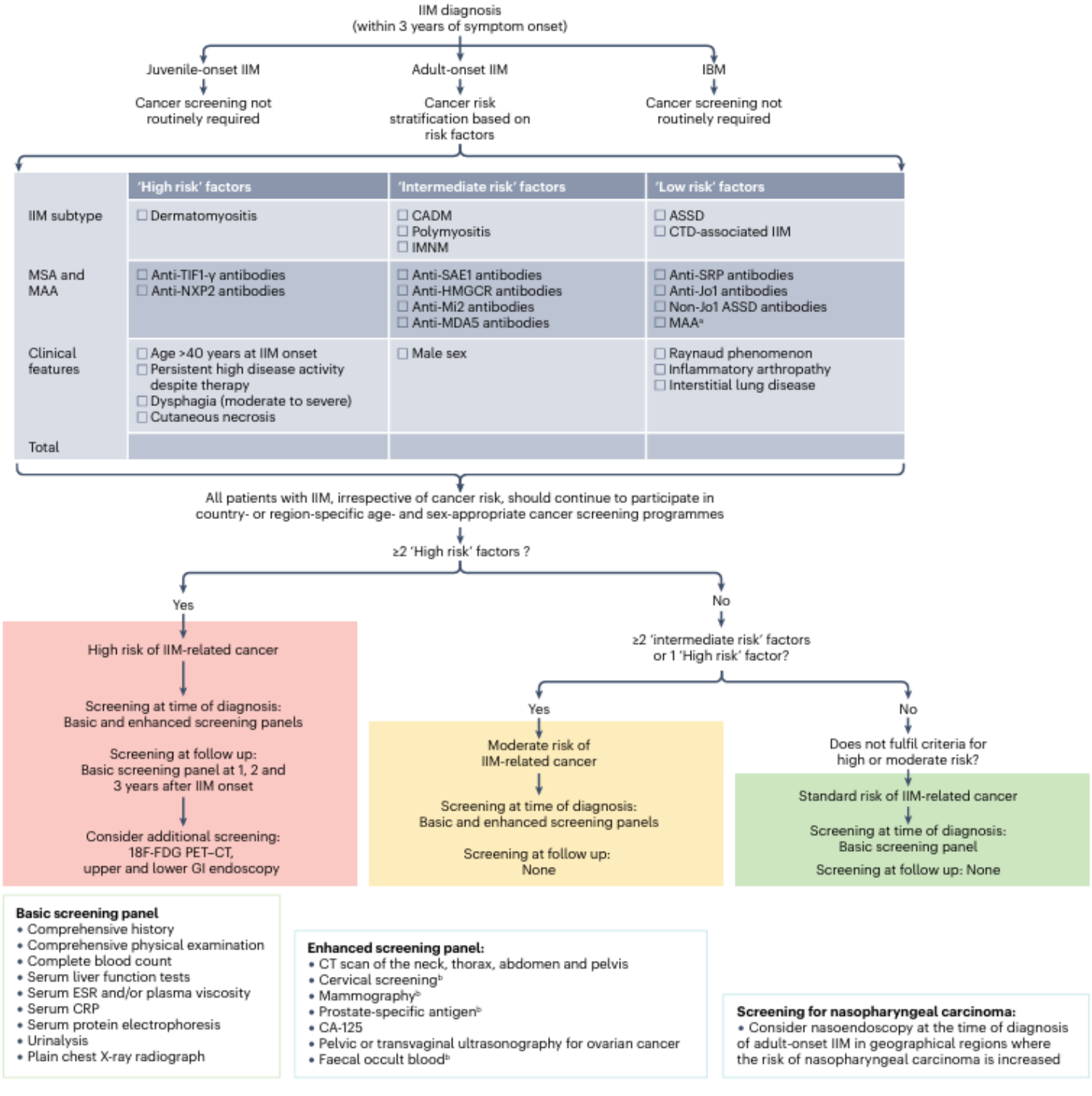
Cai et al., *Mod Pathol.* 2019

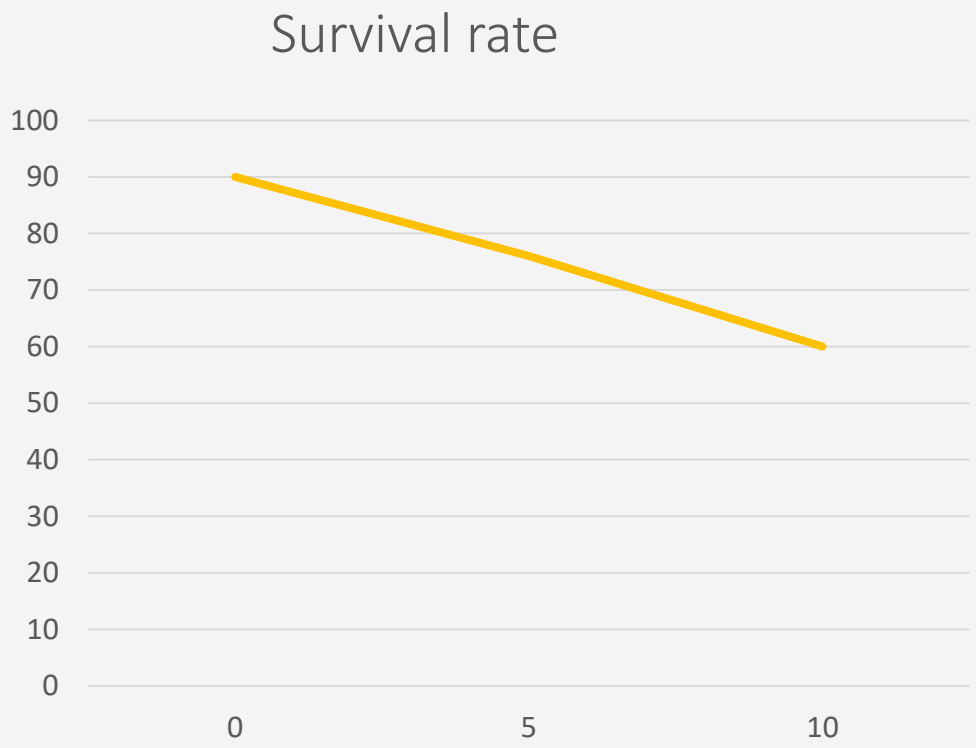
Inclusion body myositis

Endomisial infiltrates
Intracellular vacuoles
Diffuse COX– fibers
Diffuse/patchy MHC-I
C5b-9+ necrotic fibers



Courtesy of
Prof.ssa Greta Alì
Anatomia Patologica 3, Università di Pisa


IIM diagnosis
(within 3 years of symptom onset)
Juvenile-onset IIM
Cancer screening not routinely required
Adult-onset IIM
Cancer risk stratification based on risk factors
IBM
Cancer screening not routinely required
'High risk' factors
'Intermediate risk' factors
'Low risk' factors
IIM subtype
☐ Dermatomyositis
☐ CADM
☐ Polymyositis
☐ IMNM
☐ ASSD
☐ CTD-associated IIM
MSA and MAA
☐ Anti-TIF1-γ antibodies
☐ Anti-NXP2 antibodies
☐ Anti-SAE1 antibodies
☐ Anti-HMGCR antibodies
☐ Anti-Mi2 antibodies
☐ Anti-MDA5 antibodies
☐ Anti-SRP antibodies
☐ Anti-Jo1 antibodies
☐ Non-Jo1 ASSD antibodies
☐ MAA[a]
Clinical features
☐ Age >40 years at IIM onset
☐ Persistent high disease activity despite therapy
☐ Dysphagia (moderate to severe)
☐ Cutaneous necrosis
☐ Male sex
☐ Raynaud phenomenon
☐ Inflammatory arthropathy
☐ Interstitial lung disease
Total
All patients with IIM, irrespective of cancer risk, should continue to participate in country- or region-specific age- and sex-appropriate cancer screening programmes
≥2 'High risk' factors ?
Yes
High risk of IIM-related cancer
Screening at time of diagnosis:
Basic and enhanced screening panels
Screening at follow up:
Basic screening panel at 1, 2 and 3 years after IIM onset
Consider additional screening:
18F-FDG PET–CT,
upper and lower GI endoscopy
No
≥2 'intermediate risk' factors or 1 'High risk' factor?
Yes
Moderate risk of IIM-related cancer
Screening at time of diagnosis:
Basic and enhanced screening panels
Screening at follow up:
None
No
Does not fulfil criteria for high or moderate risk?
Standard risk of IIM-related cancer
Screening at time of diagnosis:
Basic screening panel
Screening at follow up: None
Basic screening panel
• Comprehensive history
• Comprehensive physical examination
• Complete blood count
• Serum liver function tests
• Serum ESR and/or plasma viscosity
• Serum CRP
• Serum protein electrophoresis
• Urinalysis
• Plain chest X-ray radiograph
Enhanced screening panel:
• CT scan of the neck, thorax, abdomen and pelvis
• Cervical screening[b]
• Mammography[b]
• Prostate-specific antigen[b]
• CA-125
• Pelvic or transvaginal ultrasonography for ovarian cancer
• Faecal occult blood[b]
Screening for nasopharyngeal carcinoma:
• Consider nasoendoscopy at the time of diagnosis of adult-onset IIM in geographical regions where the risk of nasopharyngeal carcinoma is increased



- Long-term disabilities in 80% of cases.
- Increased risk of death up to 5 times.
- The main cause of death is respiratory and cardiovascular diseases.
- Survival, unlike ANCA-associated vasculitis and lupus erythematosus, has not significantly increased over the last 20 years.

Adapted from Britta Maurer, EULAR 2024

HOW TO TREAT IIM: GENERAL CONCEPTS

TO PREVENT ORGAN DAMAGE, EXTRA MUSCULAR COMPLICATIONS AND RELAPSES

- Infections
- Iatrogenic complications
- CV complications
- Sun damage

PHYSICAL THERAPIES

TOPICAL THERAPIES

GLUCOCORTICOIDS

csDMARDs (MTX, AZA, MMF, CsA, CYC, TAC)

bDMARDs, tsDMARDs

IMMUNOGLOBULINS

Conventional immunosuppressants

Methotrexate

- First line treatment in most IIM
- Poorly effective (but not harmful) in ILD

Hydroxychloroquine

- Generally ineffective
- To be employed in selective cases of recalcitrant skin disease

Azathioprine

- Useful for maintenance, not for induction
- Ineffective for arthritis

Mycophenolate mofetil

- Second line treatment in many IIM
- Good efficacy also for ILD

Cyclophosphamide

- Rescue therapy (e.g. RP ILD in MDA5)
- Not to be employed for maintenance

Tacrolimus/Cyclosporine A

- Possible second line treatment in ILD
- Topical tacrolimus for recalcitrant skin disease

bDMARDs

RITUXIMAB

- RECITAL (phase II)
- EvER-ILD (phase III)

BELIMUMAB

- NCT02347891 (phase II)

ABATACEPT

- ARTEMIS (phase II)
- NCT02971683 (phase III)

ANIFROLUMAB (anti-IFN-I)

- JASMINE (phase III)

DAXDILIMAB (anti-ILT7)

ALEMTUZUMAB (anti-CD52)

DARATUMUMAB (anti-CD38)

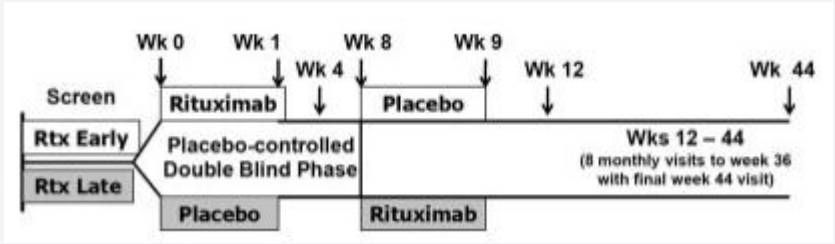
Rituximab

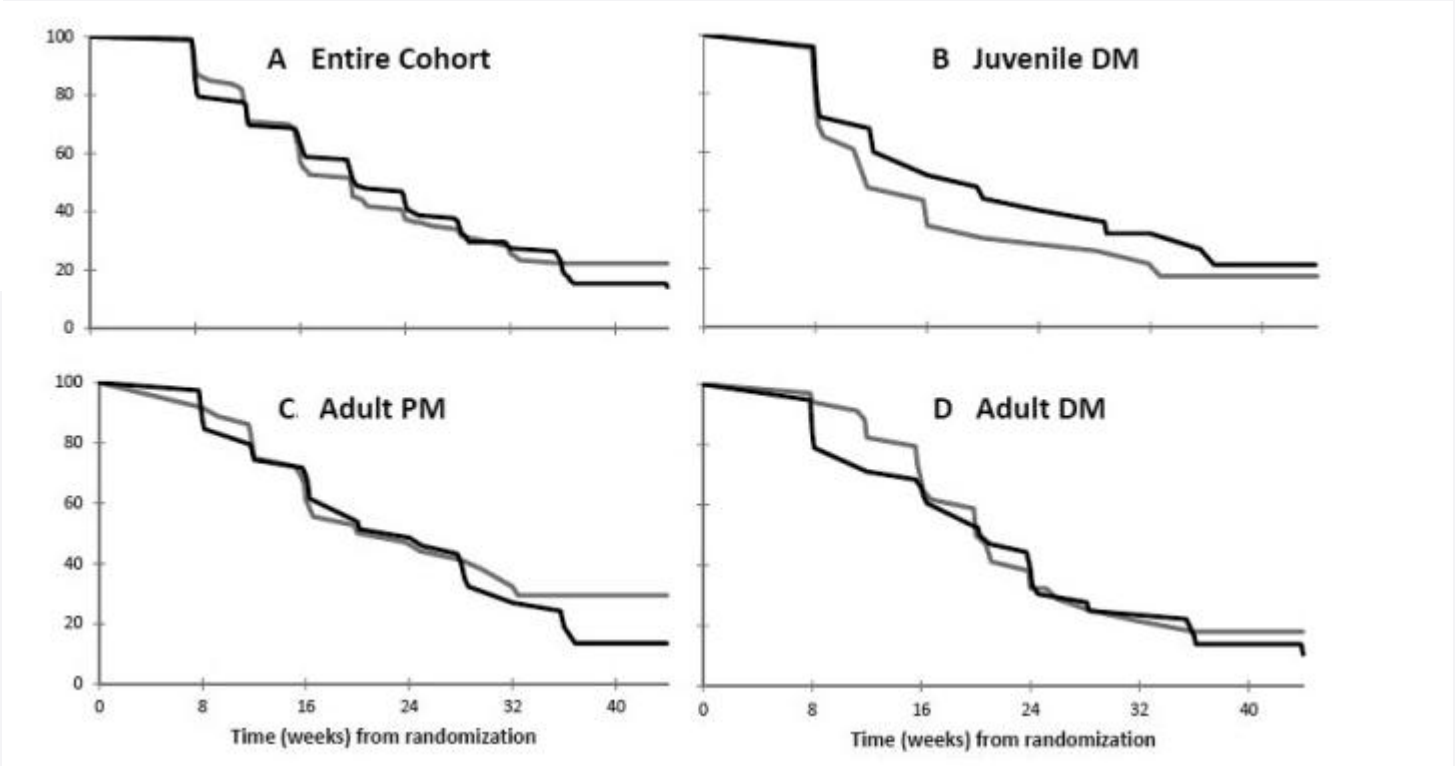
ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324
DOI 10.1002/art.37754
© 2013, American College of Rheumatology

Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

A Randomized, Placebo-Phase Trial

Chester V. Oddis,[1] Ann M. Reed,[2] Rohit Aggarwal,[1] Lisa G. Rider,[3] Dana P. Ascherman,[4] Marc C. Levesque,[1] Richard J. Barohn,[5] Brian M. Feldman,[6] Michael O. Harris-Love,[7] Diane C. Koontz,[1] Noreen Fertig,[1] Stephanie S. Kelley,[1] Sherrie L. Pryber,[8] Frederick W. Miller,[3] Howard E. Rockette,[1] and the RIM Study Group





Study [author, year]	ASyS patients (N, MSAs)	Muscle domain	Lung domain	Concomitant PDN / IS	Adverse events
Open label phase II trial [Allenbach, 2015]	10 patients Jo-1 = 9 PL7 = 1	Improvement of MMT-8 and decrease of CPK levels	Improvement (5) or stabilization (4) of FVC and DLCO (1)	Yes (decrease in dose) / Yes	Infections = 6
Retrospective study [Andersson, 2015]	34 patients Jo-1 = 19 PL7 = 3 PL12 = 2	Improvement of MMT-8 and decrease of CPK levels	Increase of FVC, FEV1 and DLCO (24/34) Improvement of CT findings	Yes / Yes	• Infections = 5 (3 urosepsis, 1 abscess, 1 P.jirovecii pneumonia) • Death due to infections = 7
Retrospective study [Bauhammer, 2016]	17 patients All Jo-1	Decrease of CPK levels	Improvement of VC, DLCO and DLCO/VA Improvement or stabilization of CT findings	Yes / Yes	• Several mild urinary tract and upper airways infections. • Death due to infections = 1
Retrospective case review [Doyle, 2018]	25 patients Jo-1 = 16 PL7 = 6 PL12 = 3	Not evaluated	Stability or improvement of FVC (79%) ,TLC and DLCO (at 3 years) Improvement or stabilization of CT findings (88%)	Yes (stable or decreased dose in 88%) / Yes	Several upper airways and urinary tract infections, cellulitis.
Retrospective study [Langlois, 2020]	28 patients Jo-1 = 82% PL7 = 14% PL12 = 4%	Improvement of MMT-8 and decrease of CPK levels	Improvement of DLCO and FVC Improvement (11) or stabilization (12) of CT findings	Yes / Yes	Death due to infections = 1

Grazzini et al., *Autoimmunity Reviews*, 2023

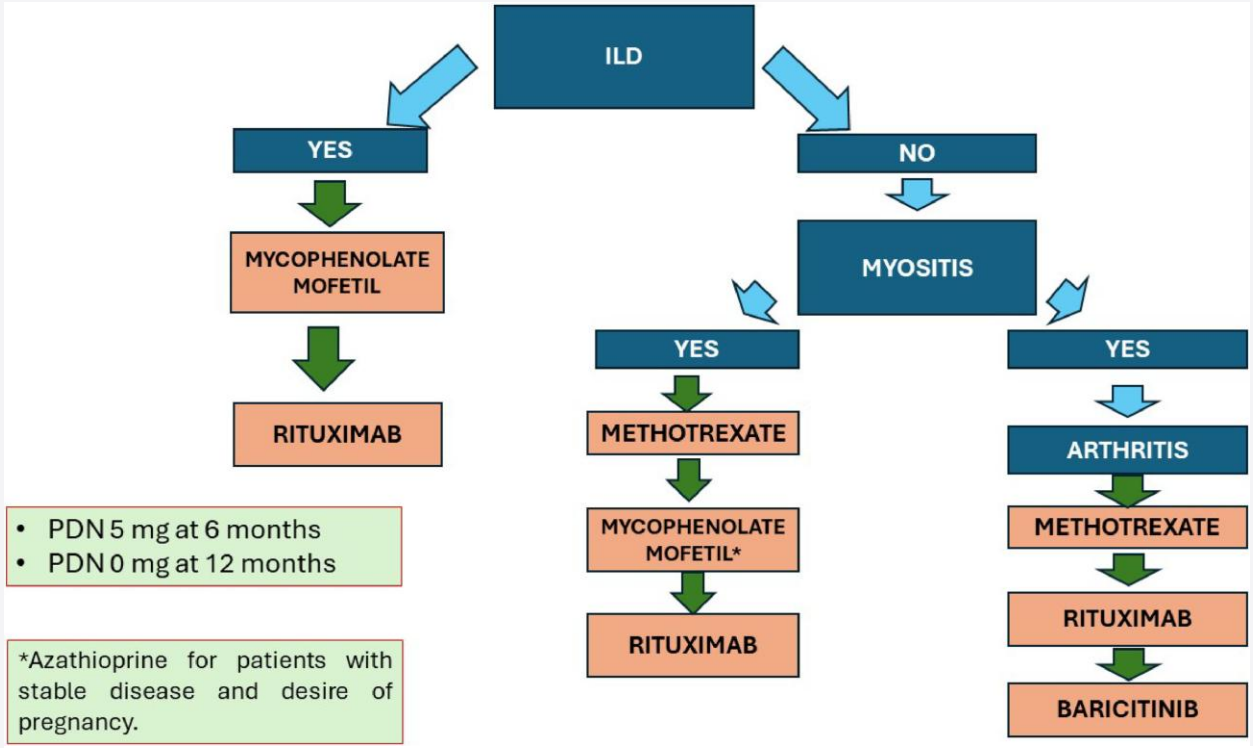


Table 2
Disease activity and damage indices at baseline and during follow-up.

		Baseline (mean value ± SD)	6 months (mean value ± SD)	12 months (mean value ± SD)	*p*
MDAAT					
	Constitutional	2,84 ± 2,57	1,39 ± 1,6	0,56 ± 0,9	<,001
	Cutaneous	1,76 ± 1,6	1 ± 1,4	0,31 ± 0,6	0,001
	Skeletal	3,36 ± 2,9	1,39 ± 2,2	0,75 ± 1,4	0,002
	Gastrointestinal	0,12 ± 0,6	0,11 ± 0,5	0,13 ± 0,5	0,333
	Pulmonary	3,2 ± 2,8	2,22 ± 2,1	1,06 ± 1,5	<,001
	Cardiovascular	0	0	0	
	Other	0	0	0	
	Extramuscular	4,4 ± 1,7	2,61 ± 1,7	1,31 ± 1,3	<,001
	Muscle	2,32 ± 2,1	1,22 ± 2,1	0,5 ± 1,1	<,001
	Global	4,56 ± 1,6	2,83 ± 1,7	1,38 ± 1,4	<,001
MDI		1,08 ± 1,6	1,56 ± 1,6	1,93 ± 1,6	0,028
MMT8		146,4 ± 5,1	148,1 ± 3,1	148,47 ± 3,6	0,019
CDASI activity		1,08 ± 1	0,61 ± 1,24	0,07 ± 0,26	<,001
CDASI damage		0	0	0	

Legend: CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; MDAAT: myositis disease activity assessment tool; MDI: muscle damage index; MMT-8: manual muscle test; SD standard deviation.

Conticini et al., *Semin Arthritis Rheum*, 2024

Cohort: 27 patients, age 54 ± 16 years, 21 ♀

MSA/MAAs: anti-Jo-1 = 15, anti-PL7 = 5, anti-PL12 = 2, anti-EJ = 2, anti-OJ = 1, anti-SSA/Ro52 = 18

Clinical response in patients treated with RTX

- Muscle (n = 18) → full remission in all patients
- Lungs (n = 18) → stabilization of PFTs and HRCT findings in all patients
- Joints (n = 8) → effective in 6 patients

Adverse events: mild infections (n = 6), infections requiring hospitalization (n = 1)

Table 3
Lung function tests at baseline and during follow-up.

	Baseline (mean value ± SD)	6 months (mean value ± SD)	12 months (mean value ± SD)	*p*
DLCO	75,47 ± 24,8	58,92 ± 12,4	63,23 ± 14,3	0,664
FEV1	96,69 ± 18,5	90,90 ± 20,6	89,64 ± 20,3	1
FVC	95,19 ± 20	92,2 ± 20	92,17 ± 23,7	0,498

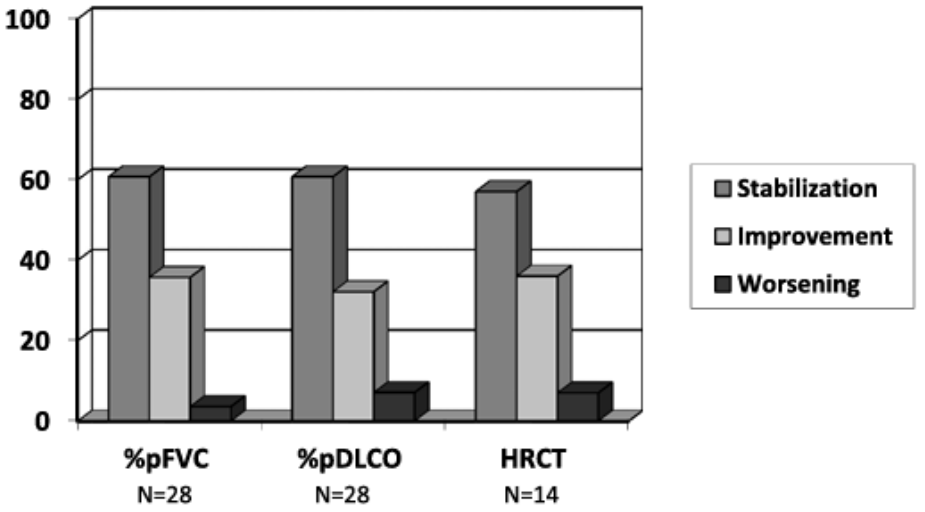
Legend: DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiration; FVC: forced vital capacity; SD standard deviation.

Table 1 Baseline characteristics of the 28 patients with progressive antisynthetase syndrome-related interstitial lung disease (ASS-ILD) treated with Rituximab

Number of patients	28
Age (mean ± SD), years	61 ± 15
Women/men (ratio)	20 (71.5%) / 8 (28.5%)
Median duration of ILD, months [IQR 25th–75th]	15 (12 – 21)
Frequency of clinical features	
Fever	9 (32%)
Raynaud's phenomenon	13 (46%)
Myositis	21 (75%)
Arthritis	15 (54%)
Mechanic's hands	18 (64%)
Hiker's foot	3 (11%)
Gottron's sign	5 (18%)
Periungual erythema	5 (18%)
Interstitial lung disease (ILD)	28 (100%)
Chest HRCT pattern of ILD	
Non-specific interstitial pneumonia (NSIP)	19 (68%)
Organizing pneumonia (OP) or NSIP superimposed with OP	6 (21%)
Usual interstitial pneumonia	3 (11%)
%FVC predicted at ILD diagnosis, mean ± SD (*IQR* 25%-75%)	76.3 ± 21.6 (57.9 – 87.8)
%DLCO predicted at ILD diagnosis, mean ± SD (*IQR* 25%-75%)	58,3 ± 16,9 (43 – 70)
Serological parameters	
Positive antinuclear antibodies (ANA)	22 (79%)
Myositis-specific antibody, n (%)	
Anti-Jo-1	17 (61%)
Anti-PL-7	4 (14%)
Anti-PL-12	4 (14%)
Anti-EJ	3 (11%)
Myositis-associated antibody, n (%)	
Anti-Ro52	18 (64%)

HRCT thoracic high-resolution computed tomography, *%pFVC* predicted forced vital capacity, *%pDLCO* predicted diffusing capacity for carbon monoxide, corrected for hemoglobin

Table 4 Lung function tests results (according to the definitions of the ATS) and response of the ILD radiologic features after Rituximab therapy

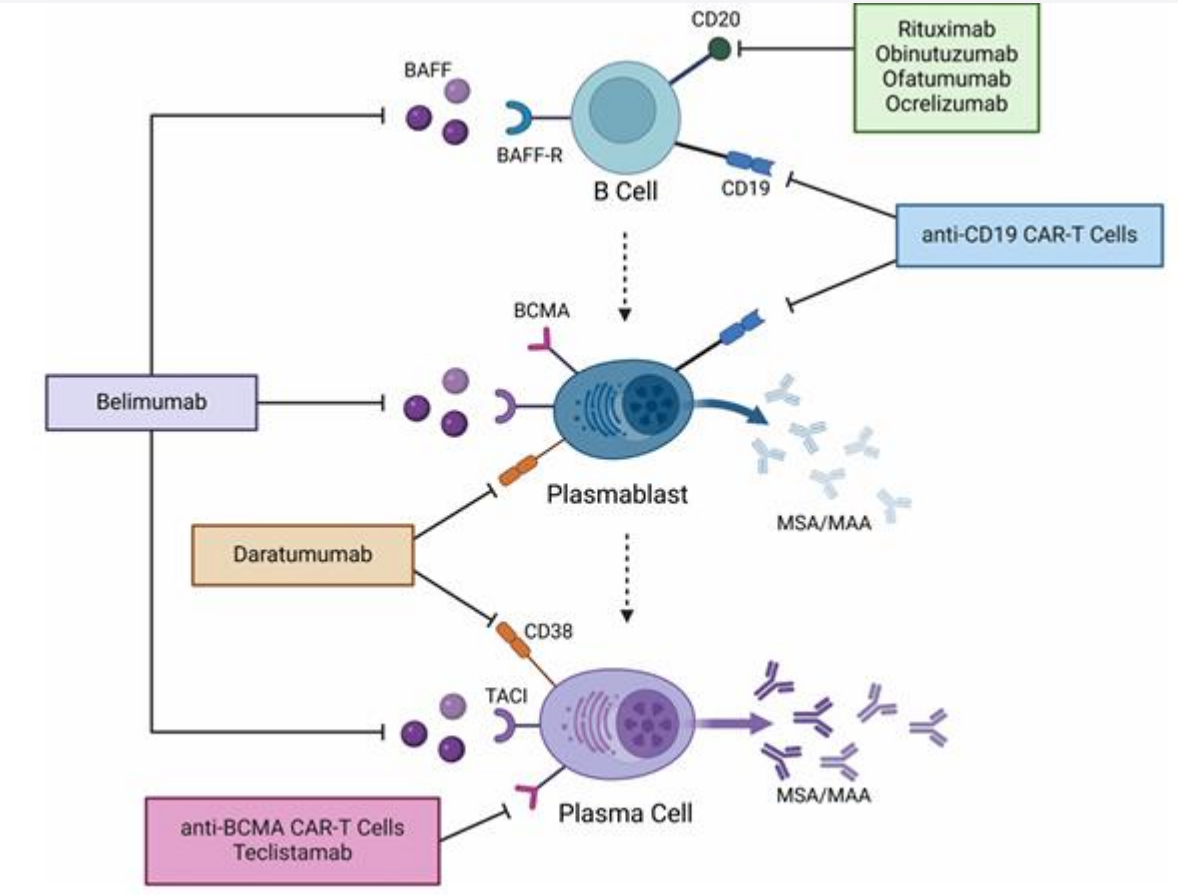


	%pFVC			%pDLCO		
	Improvement	**Stabilization**	**Worsening**	**Improvement**	**Stabilization**	**Worsening**
6 months post-RTX N=28	35,7% (10)	60,7% (17)	3,6 % (1)	32,1% (9)	60,7% (17)	7,1% (2)
After 1 year of treatment N=24	50% (12)	50% (12)	0%	54,2% (13)	37,5% (9)	8,3% (2)
After 2 years of treatment N=22	54,6% (12)	40,9% (9)	1 (4,5%)	63,6% (14)	27,4% (6)	9% (2)

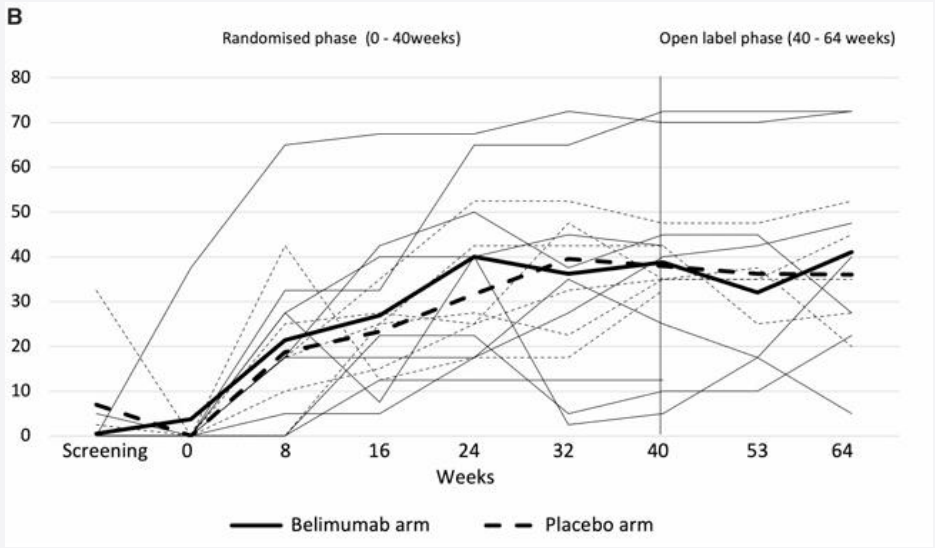
%pFVC predicted forced vital capacity, *%pDLCO* predicted diffusing capacity for carbon monoxide, corrected for hemoglobin, *RTX* Rituximab

Narvaez et al., *Arthritis Research & Therapy*, 2024

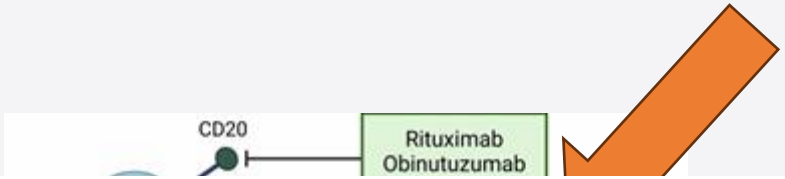
Targeting B cells: not only RTX



- Most molecules have not been extensively investigated, yet.
- Currently available data come from case reports or small case series encompassing different disease subtypes.
- **Belimumab**, investigated in BIM phase II trial, was **not superior to PBO**.



Groener & Paik, *Front Immunol,* 2025; Marder et al., *Rheumatology (Oxford)*, 2024

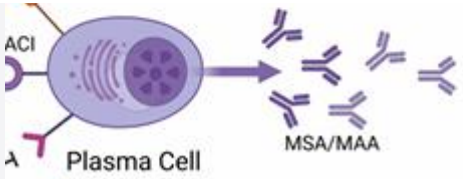


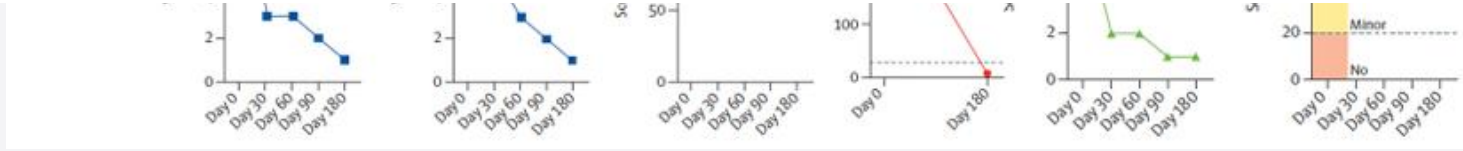
Phase 2 Study of Rapcabtagene Autoleucel in Myositis

Last Update: Jul 29, 2025

A Phase 2, Randomized, Open-label, Controlled Study to Evaluate the Efficacy and Safety of Rapcabtagene Autoleucel Versus Comparator in Participants With Severe Refractory Idiopathic Inflammatory Myopathies (IIM)

ClinicalTrials.gov Identifier:NCT06665256 Novartis Reference Number:CYTB323L12201





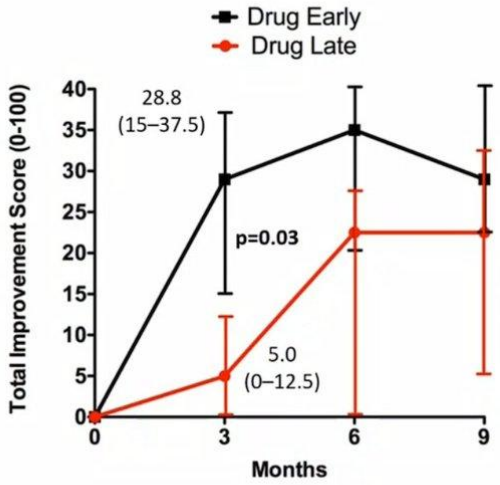
	Autoantibody	Baseline	Follow-up
Patient 3 (idiopathic inflammatory myositis)	ANA — U/ml (normal <25)	1:100	1:100
	MDA5 — RU (normal <15)	38	18

Groener & Paik, *Front Immunol,* 2025; Müller et al., *Lancet*, 2024; Hagen et al., *N Eng J Med*, 2024

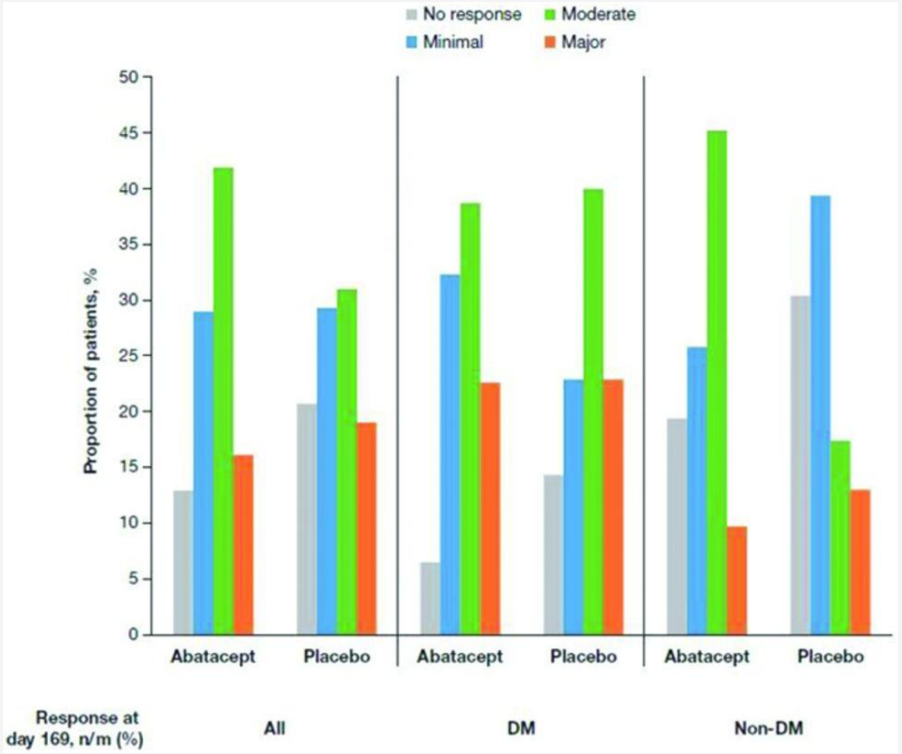
ARTEMIS TRIAL (PHASE II)

ARTEMIS

- DOI in 8/19 (42%) after 6 months of treatment
- Significant improvement after 6 months in:
  - MMT-8, from (median) 70 to 74 (p = 0.0471)
  - Muscle disease activity from 18 to 10 (p = 0.0435)
  - FI-2 signif. improved for shoulder flexion and heel lift
  - SF-36 increased from a median (IQR) of 31 (24–35) to 37 (24–45) (p=0.0054)
- At 3 months
  - 5/10 (50%) responders in arm A
  - 1/9 (11%) responder in arm B
  - p = 0.1409



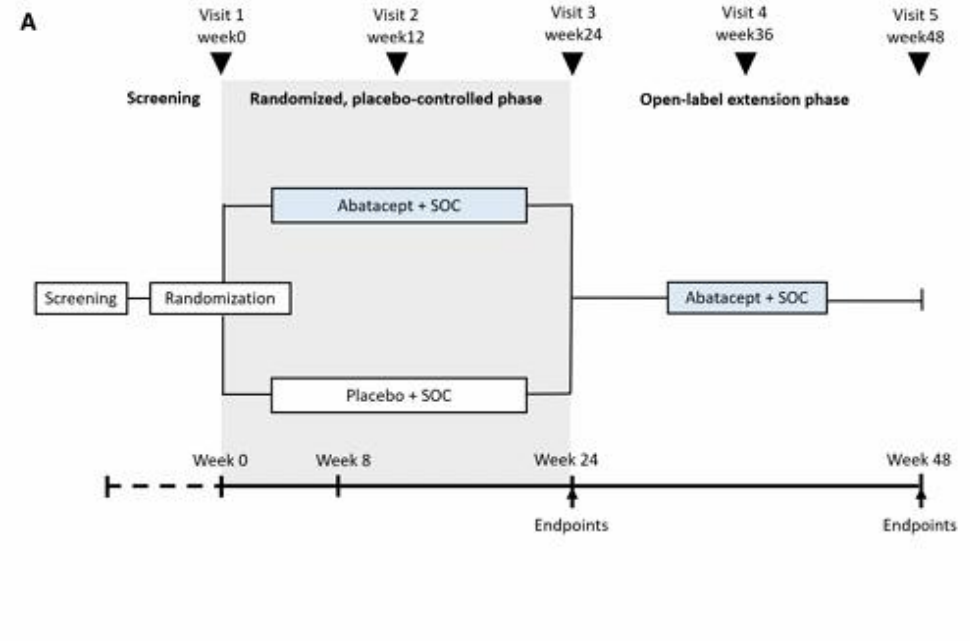
NCT02971683 TRIAL (PHASE III)

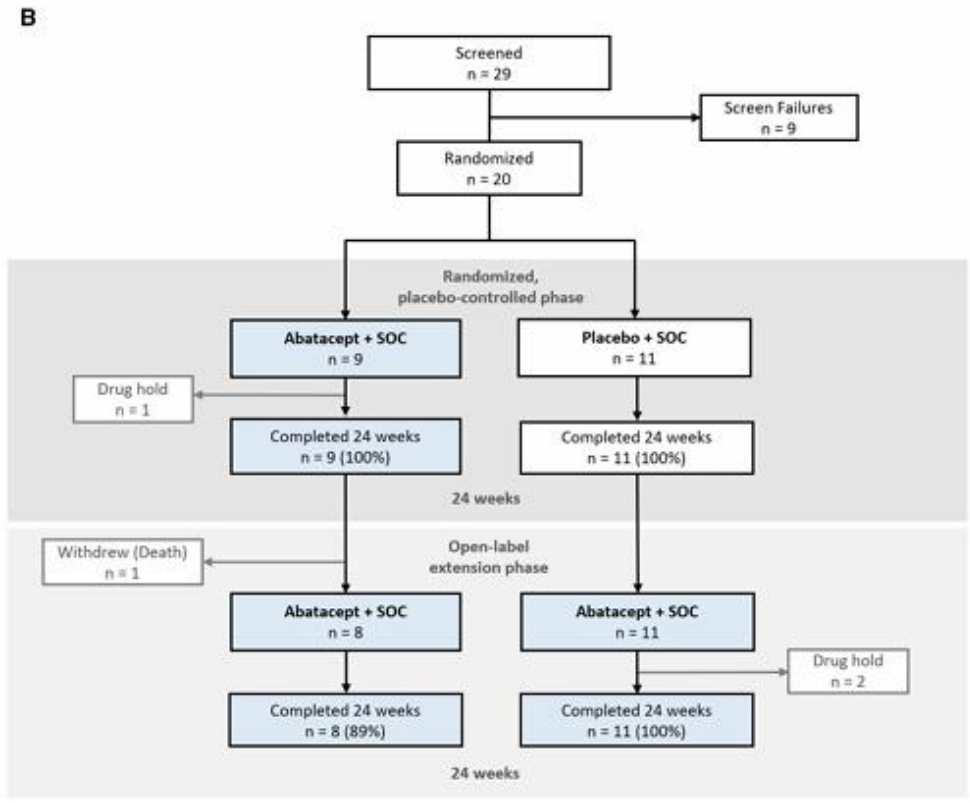


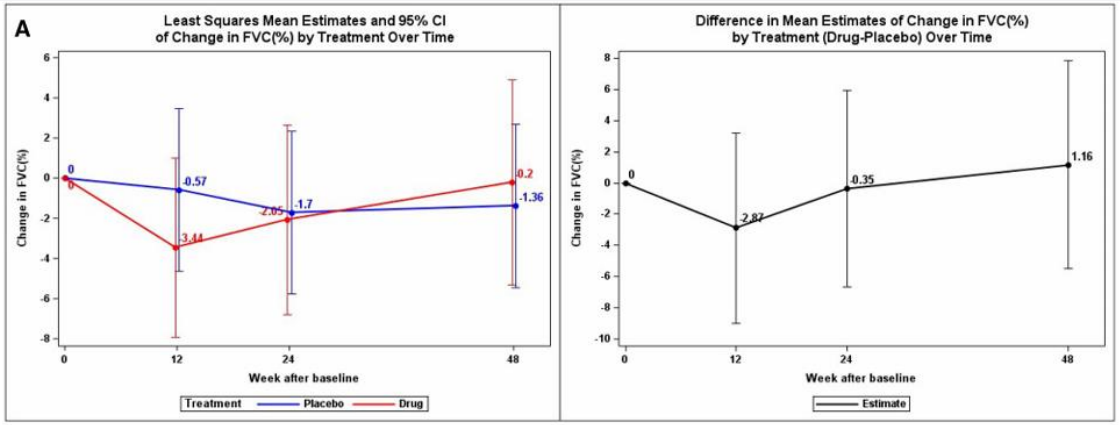
- Week 24 IMACS DOI rates were 56% for ABA group and 42,5% for PBO group (OR 1,8, p=0,083)
- Pre-specified IMACS DOI analysis showed no differences for DM, but notable benefit for non-DM subtypes.

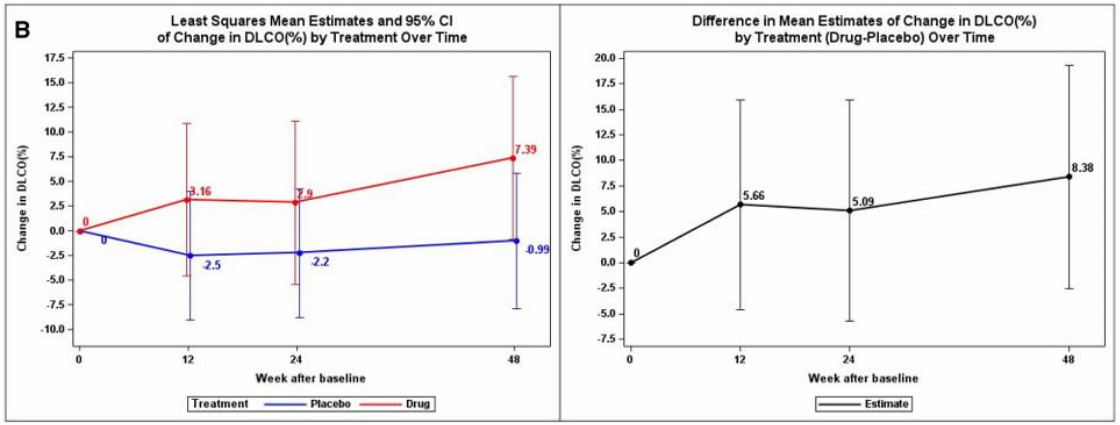
Tjärnlund et al., *Ann Rheum Dis,* 2018

AttackMy-ILD trial



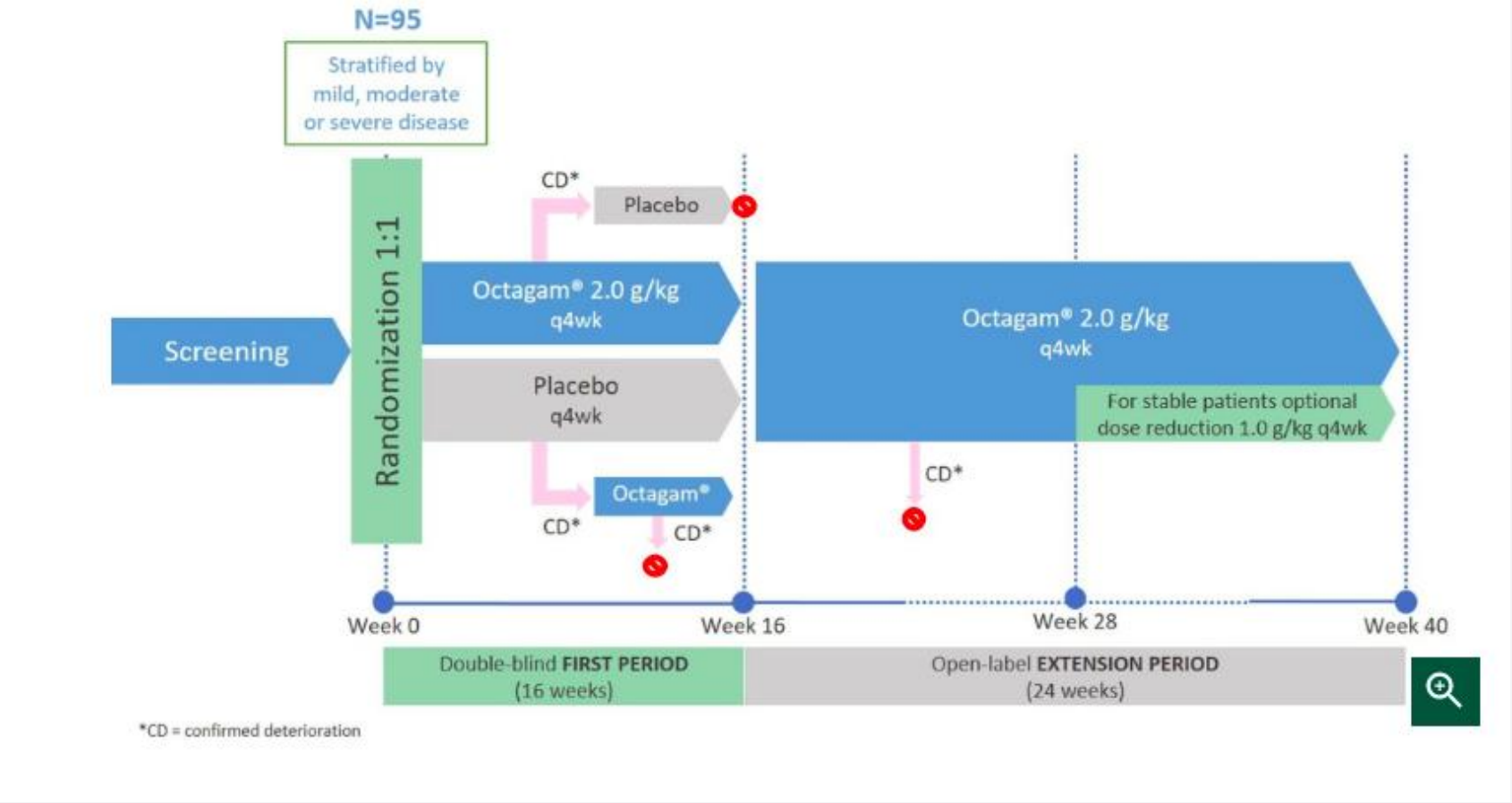






Aggarwal et al., *Rheumatology (Oxford),* 2025

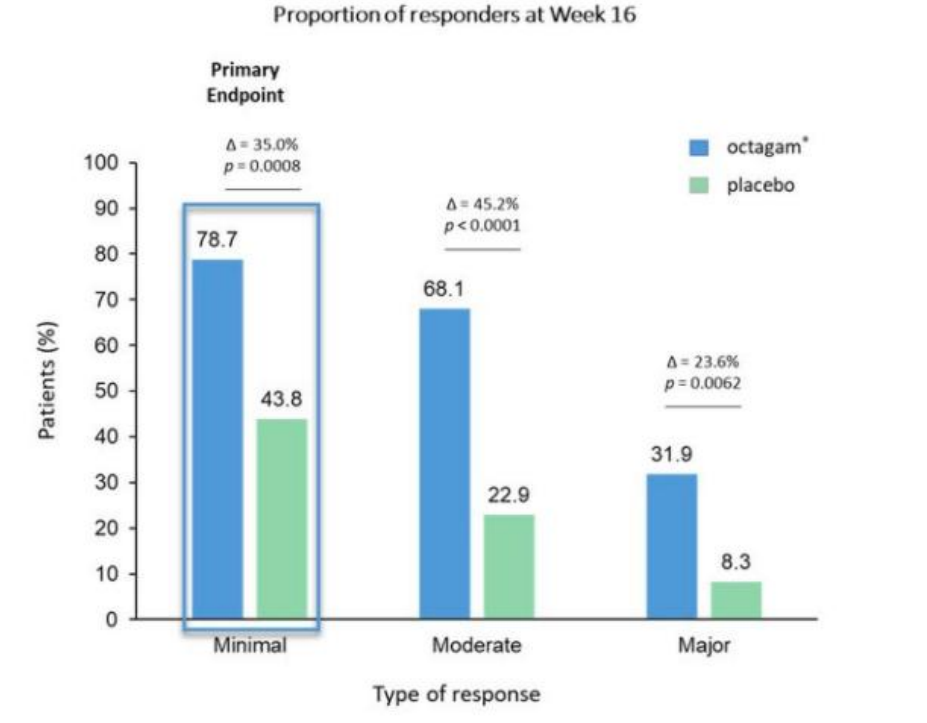
Immunoglobulins



<u>Trial ProDERM</u>:

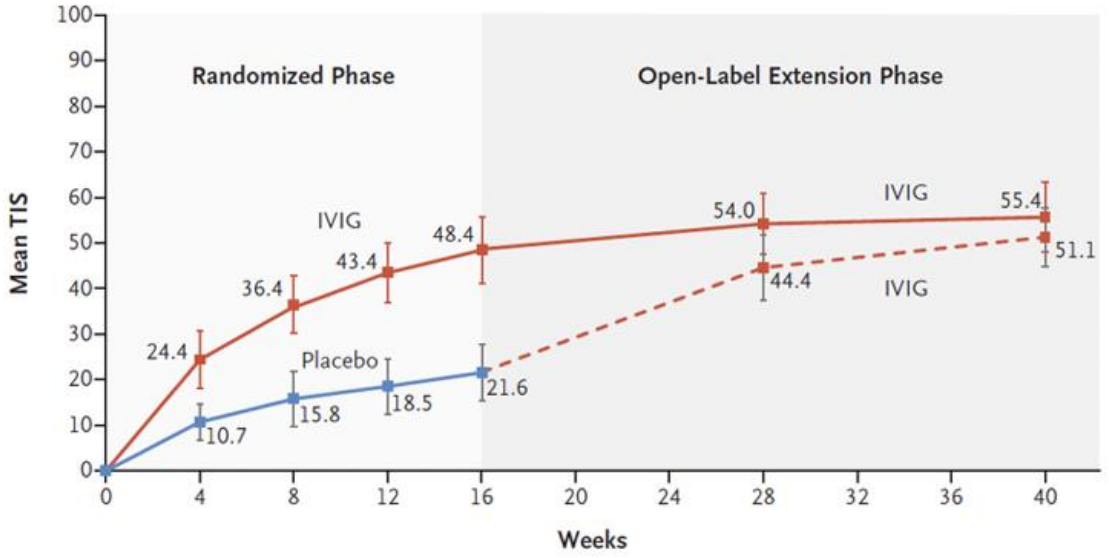
IvIG 10% 2 g/kg every 4 weeks vs placebo for 16 weeks plus open-label 24 weeks extension period

Aggarwal et al., *N Eng J Med,* 2022



Parameter	Least square (LS) mean change from baseline to Week 16		
	octagam®	Placebo	Difference in LS mean change (p value)
Extramuscular disease activity (MDAAT)	-2.1	-0.9	-1.2 (0.0010)
Physician Global Disease Activity (MDAAT)	-2.5	-1.1	-1.4 (< 0.0001)
Patient Global Disease Activity	-2.3	-1.3	-1.0 (0.0211)
MMT-8	15.1	6.5	8.6 (0.0001)
CDASI total activity score	-10.3	-2.3	-8.0 (< 0.0001)
CDASI total damage score	-0.7	-0.1	-0.6 (0.0304)
HAQ total score	-0.5	-0.1	-0.4 (0.0002)

Total Improvement Score (TIS) at Week 16 and Week 40



No. at Risk

IVIG→IVIG	47	45	45	45	45	37	34
Placebo→IVIG	48	48	47	46	43	40	35

Aggarwal et al., *N Eng J Med,* 2022

Open access Protocol

BMJ Open

Treatment with add-on IVIg in Myositis Early In the diSease course May be sUperior to Steroids alone for reaching CLinical improvEment (TIME IS MUSCLE): study protocol of a phase-2 double-blind placebo-controlled randomised trial

Renske G Kamperman ,[1] Johannes A Bogaards,[2] Sanne W Evers,[1] Hannah A W Walter ,[1] Marianne de Visser,[3] Corianne de Borgie,[4] Jantine C A Colen - de Koning,[5] Camiel Verhamme,[1] Mario Maas,[6] Filip Eftimov,[1] Ivo N van Schaik,[1,7] Anneke J van der Kooi,[1] Joost Raaphorst[1]

Table 1: Overview of study procedures.

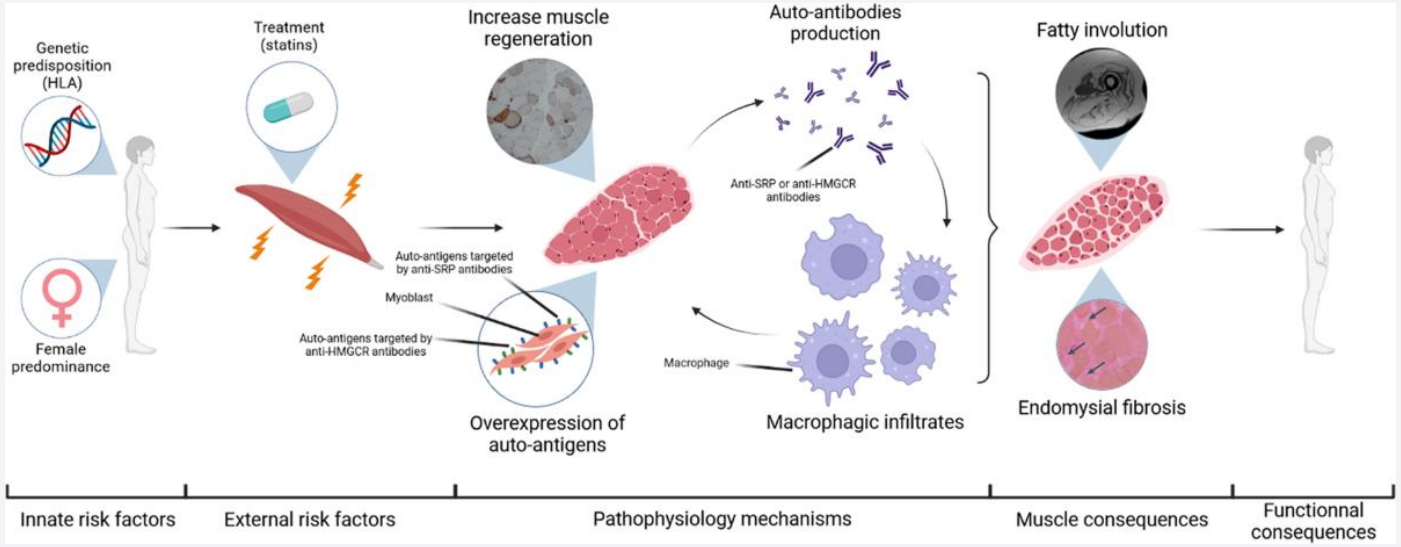
		Treatment period 12 weeks									Primary outcome	Follow-up assessment	Follow-up assessment
Actions	**Screening**	**Week 0**		**Week 2**	**Week 4**		**Week 6**	**Week 8**		**Week 10**	**Week 12**	**Week 26**	**Week 52**
		Day 1	Day 2-4*	Day 1	Day 1	Day 2-4*	Day 1	Day 1	Day 2-4*	Day 1			
Informed consent	X												
Medical history	X												
Blood sampling standard of care	X										X	X	X
Blood sampling study related	X			X	X		X	X		X			
Myositis response criteria/ IMACS TIS score	X				X			X			X	X	X
Administer IVIG/placebo		→			→			→					
PROMs		X			X			X			X	X	X
EQ-5D-5L		X			X			X			X	X	X
Accelerometer		→			→			→				→	
CIS - fatigue		X			X			X			X	X	X
Mean daily prednisone dosage					X			X			X	X	X
Whole body MRI		X									X	X	X
Questionnaire iMCQ + iPCQ		X									X		X

Clinical Scenario	Recommended Use of IVIG
Refractory IIM (muscle weakness not responding to steroids or immunosuppressants)	Used as **second-line or adjunctive therapy** to control disease activity.
Severe IIM at onset (life-threatening, rapid progression)	Can be used as **first-line therapy**, particularly when rapid immunosuppression is needed or when steroids are contraindicated.
Dysphagia	Strong indication for IVIG; shown to significantly improve swallowing function, often within weeks.
Dermatomyositis (DM)	Supported by high-quality evidence (e.g. **ProDERM trial**) — IVIG is **effective for both muscle and skin involvement**. Less data for other subtypes of IIM
Pregnancy	Preferred over traditional immunosuppressants due to better safety profile for fetus.
Interstitial Lung Disease (ILD)	Limited evidence of benefit; IVIG may **stabilize** lung disease in some cases, but often not the first choice.
Calcinosis	Generally **ineffective**.
Steroid-sparing	Useful for **reducing corticosteroid dose** or avoiding long-term immunosuppressive therapy.
Patients with contraindications to immunosuppressants	Preferred option due to **non-cytotoxic nature and immune-modulating effects**.

Adapted by Gandiga et al., *Curr Rheum Rep,* 2023

Feature	IVIG	SCIG
Administration	Intravenous infusion in hospital/clinic	Subcutaneous injection (home-based)
Infusion time	Long (4–6 hours per session)	Shorter, more frequent (1–2 hrs/week)
Dose interval	Monthly	Weekly or biweekly
Onset of action	Rapid (especially useful in severe IIM)	Slower, may take longer to see benefit
Tolerability	Systemic side effects more common	Fewer systemic reactions; local irritation may occur
Efficacy	Strong evidence in DM, dysphagia	Comparable efficacy in maintenance; less data in acute settings
Patient preference	Better for acute control	Preferred for **long-term use**, maintenance, and home therapy
Cost-effectiveness	Higher cost due to hospital-based care	More cost-effective in long term

Adapted from Gandiga et al., *Curr Rheum Rep,* 2023



Dallevet et al., *Curr Opin Rheumatol*, 2023; Allenbach et al., *Neuromuscular Disorders*, 2018

A — Anti-SRP-Myopathy

	Non-severe	Severe*
Initial treatment	• ± **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d	• **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d

At the same time or within 1 month, start 2nd or 3rd agent
- **Oral/sc Methotrexate°** (0.3 mg/kg/w, max 15 & 25 mg/w in child & adult, respectively)
- **Rituximab**[£,§] 750 mg/m² (max 1g) D1 + D7-D15

eventually
- **IVIG** 2 g/kg/m, 3-6 times

If no adequate response within 6m: reconsider **Rituximab** (*if not started*) and keep giving other treatments.

B — Anti-HMGCR-Myopathy

	Non-severe	Severe*
Initial treatment	• ± **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d	• **IV steroids** 0.5-1 g/d, 3-5 d • **oral steroids** 1 mg/kg/d

At the same time or within 1 month, start 2nd or 3rd agent
- **Oral/sc Methotrexate°** (0.3 mg/kg/w, max 15 & 25 mg/w in child & adult, respectively)
- **IVIG** 2 g/kg/m, 3-6 times *(possibly alone in case of steroids contraindication or intolerance)*

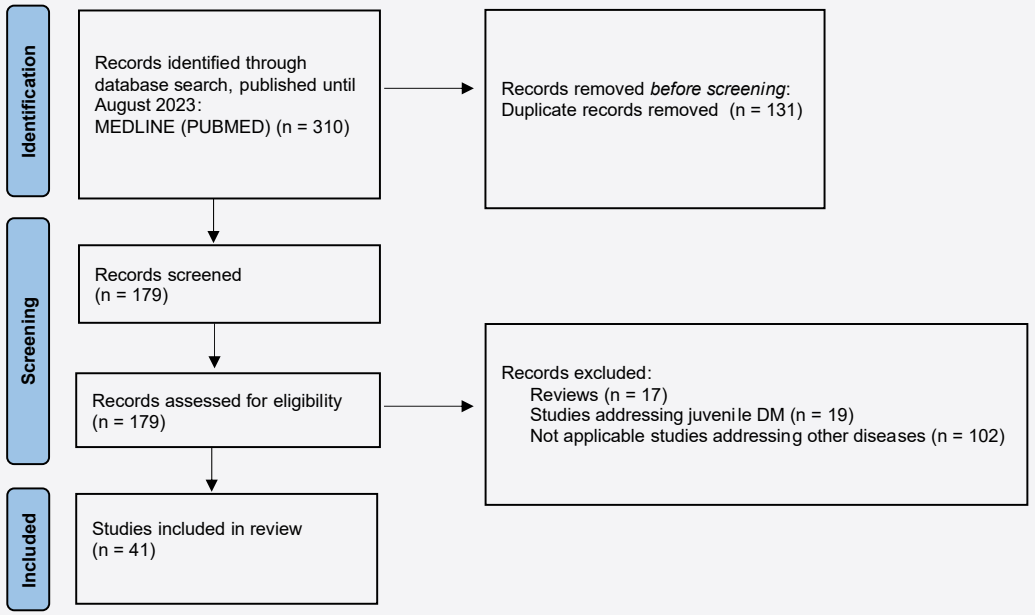
eventually
- **Rituximab**[£] 750 mg/m² (max 1g) D1 + D7-D15

If no adequate response within 6m: reconsider **Rituximab** (*if not started*) and keep giving other treatments.

Anti-SRP & anti-HMGCR-Myopathy

Maintenance treatment
- Taper **oral steroids** to the lowest dose as tolareted or as soon as possible (regarding the maximum benefit)
- Continue **Methotrexate** at least 2 years of well-controlled disease (slowly tapered later: 2.5 mg/w each month)
- Continue **Rituximab** every 6 months, at least 2 years of well-controlled disease
- If started **IVIG** are stopped or tapered, as tolerated.Nota bene: many HMGCR+patients may required IVIG

JAK inhibitors



Baricitinib	Targeting Janus kinase pathway, blocking IFN signalling	Oral	DM, PM	Phase 2 study
Ruxolitinib	Targeting Janus kinase pathway, blocking IFN signalling	Oral	IBM	Phase 2/3 study

- **Strong rationale** (up-regulation of IFN in both adult DM and JDM).
- Substantial lack of placebo-controlled trials.
- Most data about **Tofacitinib**, particularly in in Asian cohorts.
- Small case series about **Upadacitinib** and **Baricitinib**.
- Overall efficacy rate ranging from 83 to 100% according to different domains.
- Excellent response for refractory skin disease, encouraging findings also for severe ILD in anti-MDA5 DM.

Rizzo et al., *Reumatismo,* 2024; Paik et al., *Clin Exp Rheum*, 2023; Ma et al., *Front Imm*, 2023

Real-world study
Effectiveness and safety of tofacitinib *versus* calcineurin inhibitor in ILD secondary to anti-MDA5-positive dermatomyositis: a multicentre cohort study

Population

515 adults from five tertiary referral centres in China

- Diagnosed with anti-MDA5-positive dermatomyositis (MDA5⁺DM)
- ILD confirmed by HRCT within 3 months before admission
- Patients with concurrent use of TOF and CNI were excluded
- Combined use of other biologics or immunosuppressants were allowed

Exposure

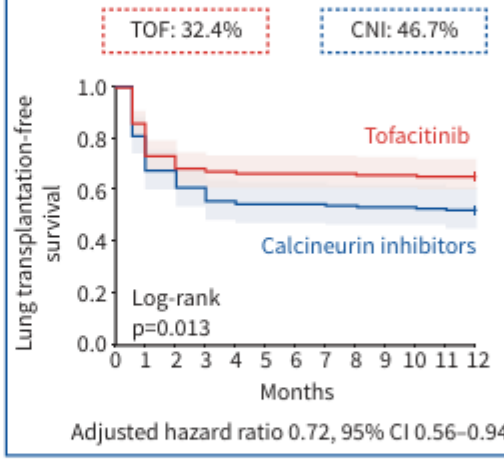
Initial immunosuppressive regimens

Tofacitinib (TOF) used in **290** patients

Calcineurin inhibitors (CNI) used in **225** patients

Findings

Death or lung transplantation within 1 year



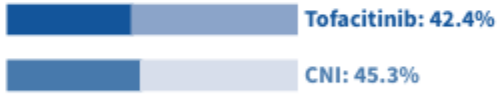
Adjusted hazard ratio 0.72, 95% CI 0.56–0.94

Subgroup analysis

Who might benefit more from tofacitinib:

Severe adverse event within 1 year

Overall infection rate:



Primary end-point

- Composite end-point of all-cause death and lung transplantation within 1 year from admission
- Primary analysis was based on IPTW

Research in context

Before this study

Tofacitinib showed promising efficacy for MDA5⁺DM-ILD in small-sized proof-of-concept studies and case series

Added value

In this large multicentre cohort study, tofacitinib significantly reduced the 1-year mortality of newly diagnosed MDA5⁺DM-ILD compared to CNI

Implications

This real-world study provides new evidence for tofacitinib in MDA5⁺DM-ILD and further studies are warranted

Wu et al., *Eur Resp J,* 2025

Brepocitinib (JAK1-TYK2 inhibitor)

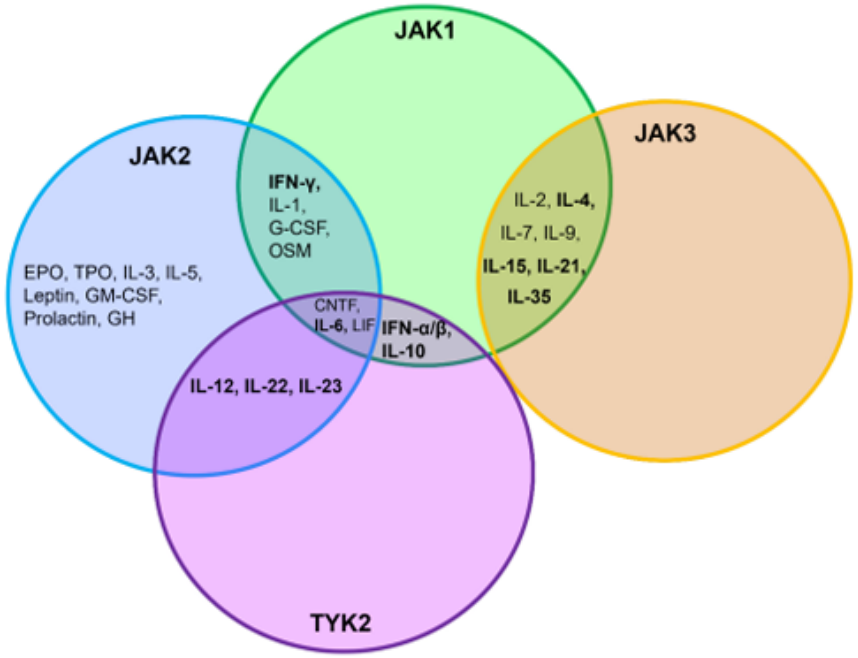


Fig. 1. JAK combinations required for various cytokines. Cytokines that appear in one circle only require a homodimer of the JAK. Cytokines that appear in between two circles require a heterodimer of the respective JAKs. Cytokines that appear in between three circles may signal with heterodimers of any two or three JAKs represented. Cytokines in bolded text are involved in DM pathogenesis. All DM-related cytokines require JAK1 and/or TYK2 to signal.

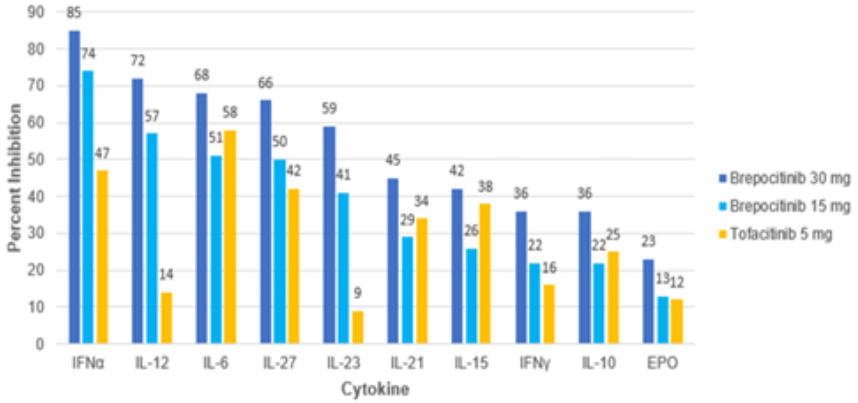
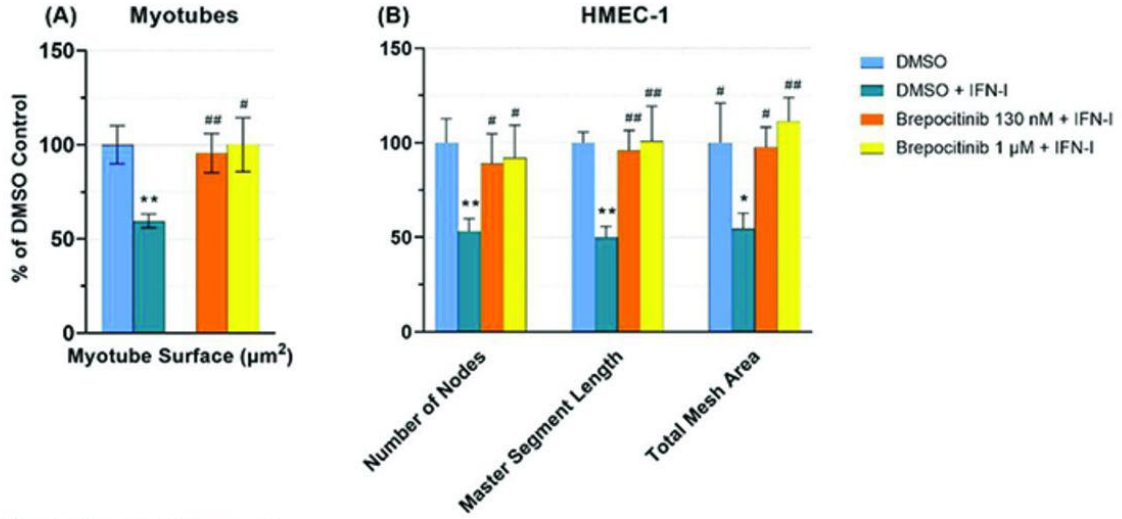


Fig. 2. Brepocitinib is a potent inhibitor of type I interferons and other DM-relevant cytokines. The percent inhibition values are from separate studies, not direct head-to-head comparisons. The percent inhibition was calculated from unbound IC_{50} and unbound C_{avg} values for each compound using the following formula: $(C_{avg} * 100) / (C_{avg} + IC_{50})$. The tofacitinib C_{avg} value was obtained from its FDA-approved label and the IC_{50} values for each cytokine as well as the tofacitinib unbound fraction were obtained from Dowty *et al*. (64).

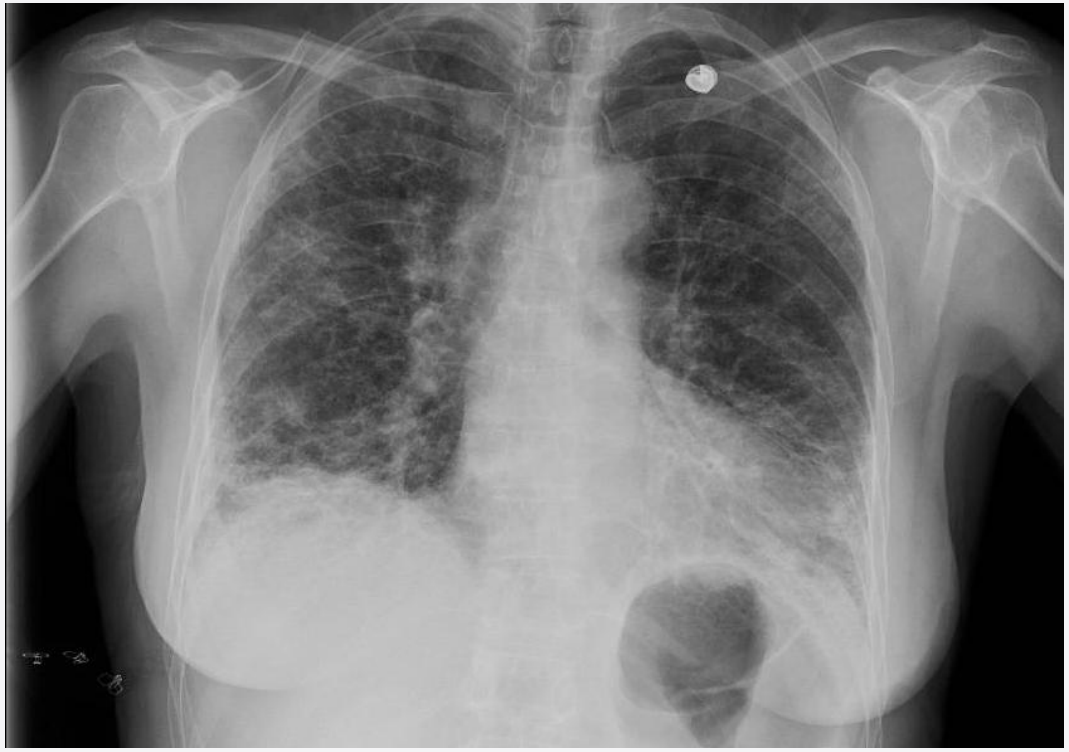
Figure 1.
(A) Brepocitinib Effects on IFN-I Induced Myotube Damage and (B) Brepocitinib Effects on IFN-I Induced Endothelial Cell Damage

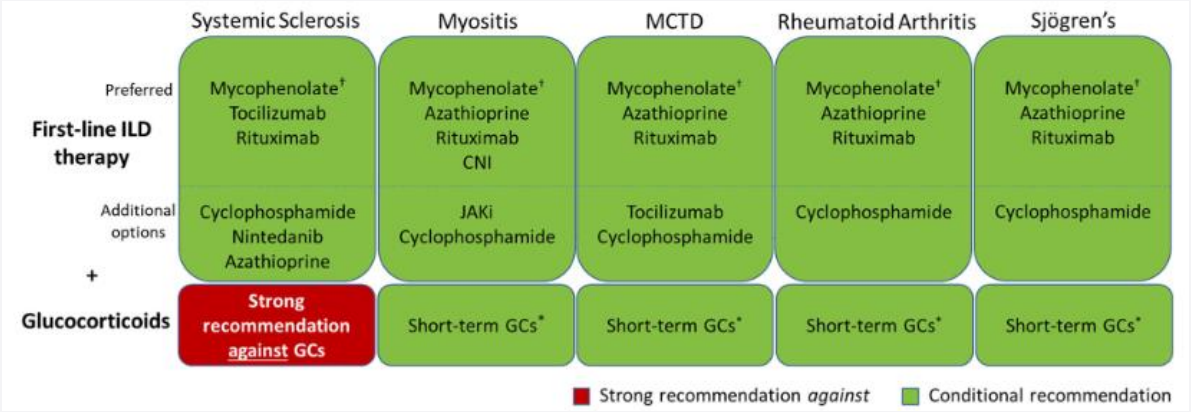


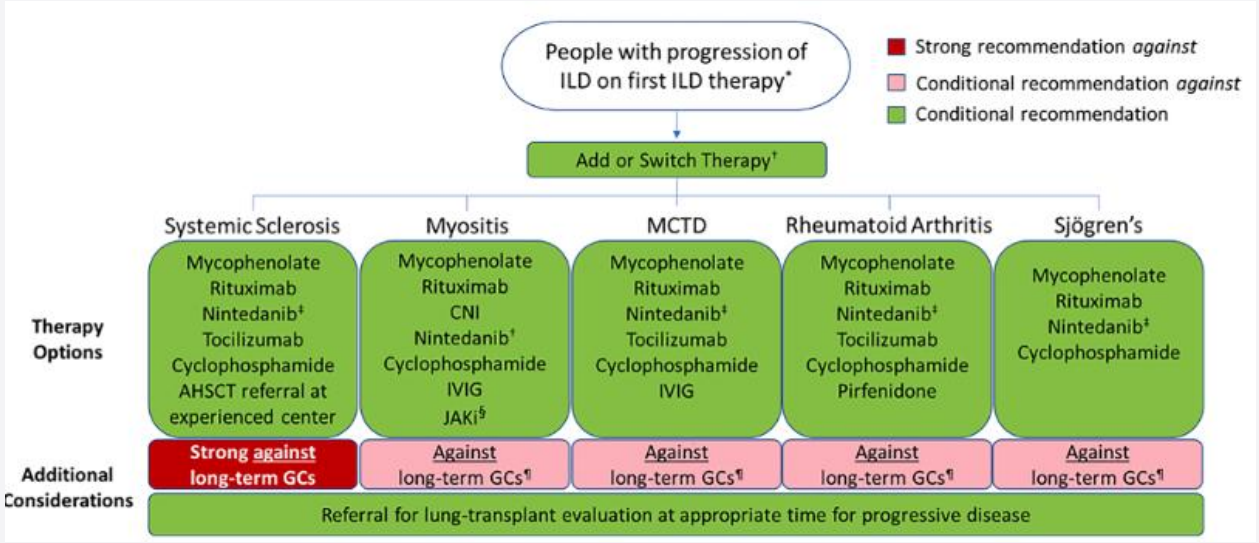
** p<0.0001; *p<0.001 relative to DMSO Control
p<0.0001; # p<0.001 relative to DMSO+IFN-1

Paik et al., *Clin Exp Rheum,* 2025; Vencovsky et al., EULAR congress, 2023

Nintedanib







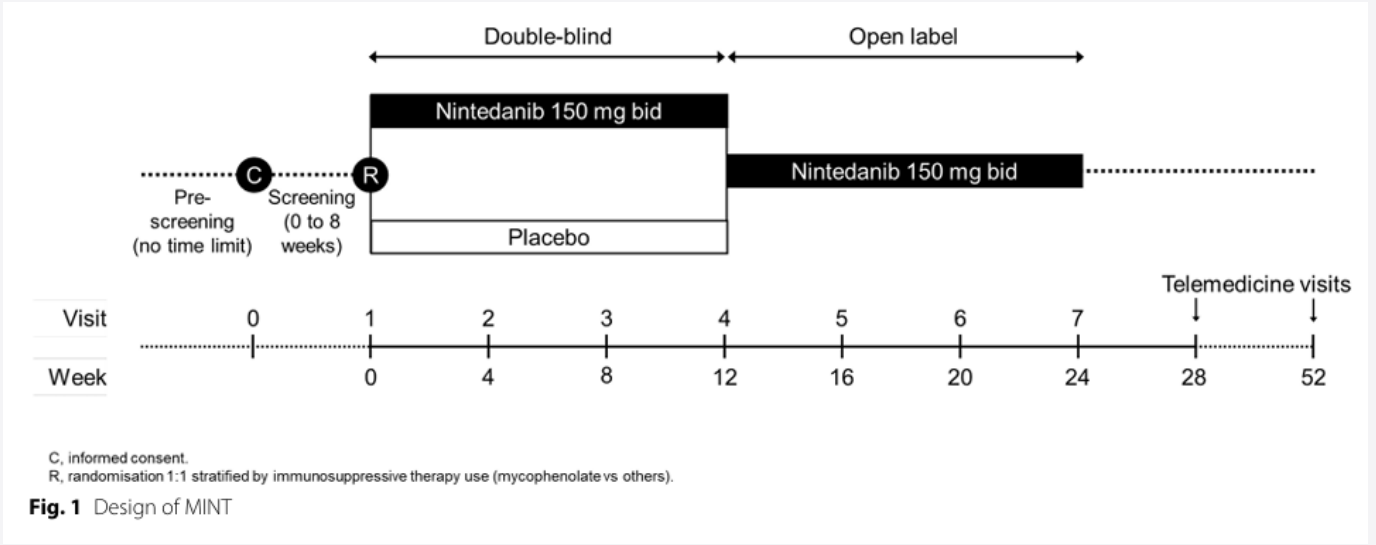


Fig. 1 Design of MINT

Johnson et al., *Arthritis Care & Research,* 2024;
Aggarwal et al., *BMC Pulmonary Medicine*, 2023

IFN inhibitors

Drug name	Mechanism of action	Route	Disease subtype	Phase
Anifrolumab	IFNAR1	SC	DM, PM	III
Daxdilimab	IFNAR1	SC	DM, ASyS	II
Dazukibart	IFNβ	IV	DM, PM	III

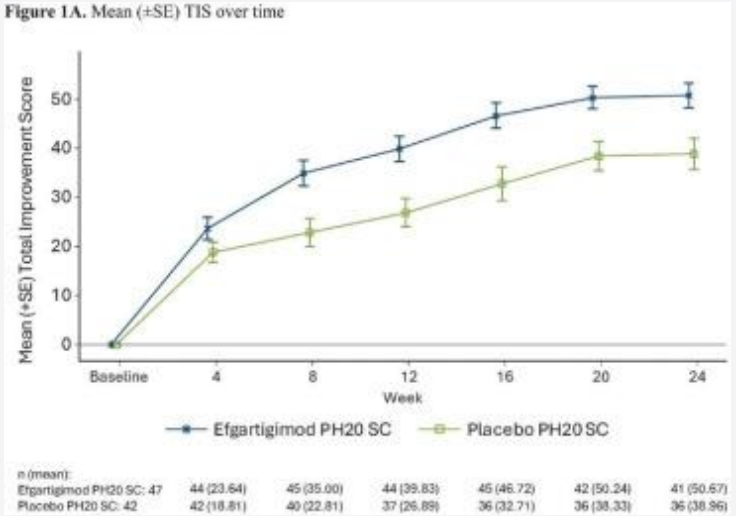
Table 1. Demographics, disease characteristics, clinical features and treatment response of four adult patients treated with anifrolumab for recalcitrant dermatomyositis

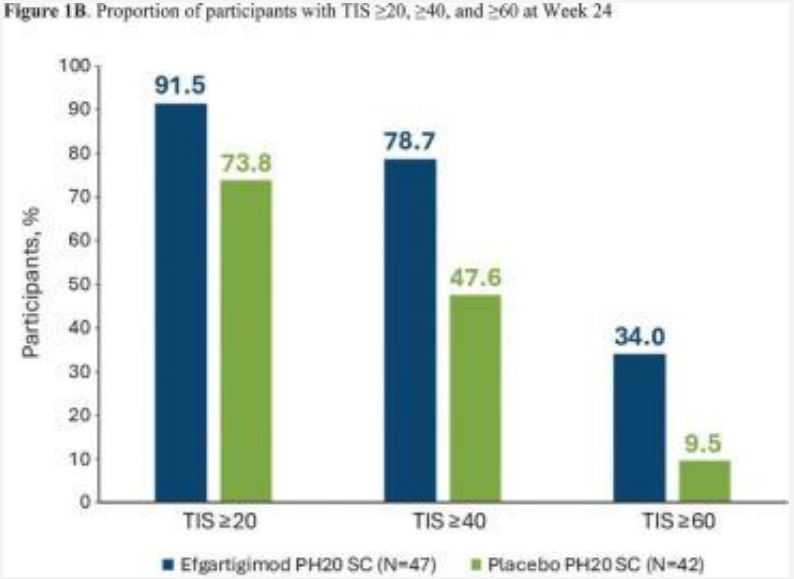
Subject	1	2	3	4
Age/sex, race or ethnicity	40s/F, Hispanic	50s/M, Caucasian	40 s/F, Caucasian	40 s/F, Hispanic
DM subtype, MSA	Classic, TIF1γ	Classic, MDA5	Classic, TIF1γ	Amyopathic, TIF1γ
# Failed systemics	8	5	7	4
Previous failed systemic therapies	HCQ, MTX, MMF, RTX, IVIg, APR, AZA	MTX, MMF, TOF, IVIg	MTX, MMF, AZA, BEL, IVIg, HCQ, PRED	HCQ, MMF, IVIg
Baseline therapy	IVIg q4 weeks, MMF 1500 mg BID, APR 30 mg BID, AZA 50 mg BID, PRED 12.5 mg daily	IVIg q4 weeks, MTX 12.5 mg weekly, PRED 5 mg daily	IVIg q4 weeks, HCQ 200 mg BID	IVIg q4 weeks, MMF 1.5 g BID, BEL 200 mg weekly, HCQ 200 mg BID
Indication for anifrolumab	Rash, dysphagia, synovitis	Rash, muscle weakness, dysphagia, synovitis	Rash, arthritis	Rash
Follow-up period	12 weeks, 4 days (3 infusions)	15 weeks (2 infusions)	14 weeks (3 infusions)	10 weeks, 5 days (2 infusions)
CDASI-A (% decrease)	26 → 9 (65.4%)	26 → 19 (26.9%)	15 → 10 (33.3%)	27 → 6 (77.8%)
TJC and SJC	TJC: 17 → 12 SJC: 2 → 0	2 → 0 2→ 0	5 → 0 N/A	N/A
CK (24-170 U/L)	36 → 31	350 → [a]974 → 473 → 292	70 → 49	28 → 38
MMT-8[b]	150 → 150	135 → 138 → 140 → 144	150 → 150	150 → 150
DLQI (follow-up period)[c]	12 → 4 (6 months)	N/A → 6 (8 months)	12 → 8 (8 months)	N/A → 6 (4 months)
Clinical response	Improvement in rash, dysphagia, synovitis (resolved)	Improvement in rash, muscle strength, dysphagia, synovitis (resolved)	Improvement in rash, arthritis	Improvement in rash
Current therapy	ANI 300 mg q4 weeks, IVIg q4 weeks, MMF 1500 mg BID, PRED 3 mg daily	ANI 300 mg q4 weeks, IVIg q4 weeks, PRED 5 mg daily	ANI 300 mg q4 weeks, IVIg q4 weeks, HCQ 200 mg BID	ANI 300 mg q4 weeks, MMF 1.5 g BID, HCQ 200 mg BID

Raaphors et al., *Lancet Neurol,* 2025; Patel et al., *Rheumatology (Oxford)*, 2025

FcRN inhibitors

Drug name	Mechanism of action	Route	Disease subtype	Phase
Efgartigimod	Targeting FcRN, prevention recycling IgG	SC	DM, PM, IMNM	II/III
Nipocalimab		IV		II





Raaphorst et al., *Lancet Neurol,* 2025, Chinoy et al., EULAR Congress, 2025

Lung transplantation

- Lack of good-quality data.
- Most study **do not stratify patients** according to disease activity.
- Lung transplant recipients with CTD-ILD and IPF seem to have similar rates of co morbidities and all-cause mortality while **those with IIM-ILD, particularly those with active myositis, appear to have poorer outcomes** due to complications not directly related to allograft dysfunction..

Table 3 Incidence and Incidence Rate Ratios for the Primary Outcome and Secondary Outcomes at 3 Years, Adjusted for Pulmonary Vascular Resistance

Outcome	CTD-ILD N (IR, 95% CI) (n = 24)[a]	IPF N (IR, 95% CI) (n = 24)[a]	All CTD Combined IRR (95% CI) (n = 24)[a]	Myositis-ILD IRR (95% CI) (n = 6)[a]	Other CTD-ILD IRR (95% CI) (n = 18)[a]
3-year allograft failure	6 (0.25, 0.08-0.42)	5 (0.21, 0.05-0.37)	1.13 (0.30-4.23)	2.28 (0.42-12.31)	0.84 (0.19-3.77)
Death due to respiratory failure	2 (0.08, 0.00-0.19)	1 (0.04, 0.00-0.12)	0.98 (0.07-14.06)	0.99 (0.02-50.89)	0.97 (0.06-15.86)
CLAD	4 (0.17, 0.02-0.32)	4 (0.17, 0.02-0.32)	1.11 (0.23-5.34)	2.57 (0.37-17.85)	0.78 (0.13-4.72)
3-year all-cause mortality	7 (0.29, 0.11-0.47)	3 (0.13, 0.00-0.26)	2.03 (0.51-8.01)	5.02 (1.02-24.81)	1.24 (0.25-6.15)

Abbreviations: CI, confidence intervals; CLAD, chronic lung allograft dysfunction; CTD, connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IR, incidence rate; IRR, incidence rate ratio.

[a]The cohort for analysis of posthospitalization events was restricted to those patients who had a full 3 years of follow-up (i.e., received their lung transplantation 3 or more years prior to the study end date).

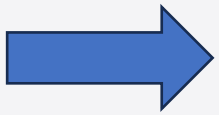
Table 2. Short- and long-term post-transplant outcomes

Variables	IIM (n=18)	SSc (n=23)	IPF (n=64)	P value
Dominant explant pathology				
UIP, n (%)	3 (17)	1 (4)	62 (97)	IIM-IPF: **< 0.001** SSc-IPF: **< 0.001** IIM-SSc: 0.91
NSIP, n (%)	6 (33)	14 (61)	0 (0)	IIM-IPF: **< 0.001** SSc-IPF: **< 0.001** IIM-SSc: 0.35
OP, n (%)	3 (17)	0 (0)	0 (0)	IIM-IPF: **0.028** SSc-IPF: 1.0 IIM-SSc: 0.23
Mixed NSIP/UIP, n (%)	2 (11)	3 (13)	0 (0)	IIM-IPF: 0.14 SSc-IPF: **0.050** IIM-SSc: 1.0
Mixed NSIP/OP, n (%)	1 (6)	0 (0)	0 (0)	Insufficient Data
Unclassifiable, n (%)	3 (17)	5 (22)	2 (3)	IIM-IPF: 0.20 SSc-IPF: **0.038** IIM-SSc: 1.0
1 Year outcomes				
Alive, n (%)	16 (89)	19 (83)	59 (92)	0.44
Post-transplant ICU days, median [IQR]	33 [21 - 50]	7 [3 – 15.5]	4 [3 – 9]	**< 0.001** IIM-IPF: **< 0.001** SSc-IPF: 0.28 IIM-SSc: **0.004**
Post-transplant hospitalization days, median [IQR]	65 [34 - 112]	30 [20 – 41]	22 [17 – 31]	**< 0.001** IIM-IPF: **< 0.001** SSc-IPF: 0.18 IIM-SSc: **0.005**
FVC (% of predicted), median [IQR]	64 [52 - 86]	64 [55 – 72]	84 [67 – 99]	**0.002** IIM-IPF: **0.014** SSc-IPF: **0.002** IIM-SSc: 0.76
DLCO (%of predicted), median [IQR]	56 [41 - 62]	57 [48 – 64]	61 [45 – 75]	0.28
Acute Rejection, n (%)	6 (33)	11 (48)	31 (48)	0.51
Pneumonia requiring hospitalization, n (%)	5 (28)	11 (48)	20 (31)	0.35
Non-pulmonary infection requiring hospitalization, n (%)	6 (33)	12 (52)	14 (22)	**0.025** IIM-IPF: 1.0 SSc-IPF: **0.045** IIM-SSc: 1.0
Fungal infection requiring therapy, n (%)	2 (11)	9 (39)	22 (34)	0.11
CMV viremia requiring therapy, n (%)	6 (33)	6 (26)	15 (23)	0.70
Long-term outcomes				
Follow-up duration (years), median [IQR]	2.8 [1.8 - 5.8]	2.1 [1.1 – 5.1]	3.6 [2.1 – 6.2]	0.18
Alive at last follow-up, n (%)	13 (72)	18 (78)	42 (66)	0.95
CLAD, n (%)	2 (11)	2 (9)	18 (28)	0.63
Post-transplant malignancy (excluding non-melanoma skin cancer), n (%)	1 (6)	1 (4)	12 (19)	0.36

Khan et al., *JHLT Open,* 2025; Rivière et al., *Am J Transplant*, 2022; Saleh et al., EULAR congress, 2025

Conclusions and shortcomings

- Rapidly growing number of trials (but reaching adequate numerosity is difficult for such rare diseases).
- Trials are often inhomogeneous, including patients affected by different disease subtypes and carrying different MSA.
- Lung involvement is still the ugly duckling (which criteria for stable disease, progression etc.?).
- Do we need specific criteria for ASyS?
- What's the optimal duration of a clinical trial? (24 vs 52 weeks vs more).
- Do clinical trials really mirror real-life? Which are the main differences?

MCTC Ongoing 2025 Scientific Projects

#	Full Title
1	Developing and Validating “Remission” and “Low Disease Activity” Criteria for Idiopathic Inflammatory Myopathies
2	Standardizing the Definition of Progression in IIM-related ILD
3	Evaluation and Revision of the “Clinical Worsening” Definition in IIM Clinical Trials
4	Appropriateness and Feasibility of Outcome Measures in IIM
5	Global Patterns and Challenges in Patient Recruitment for Idiopathic Inflammatory Myopathy Clinical Trials: Results from the 2024 MCTC Investigators’ Survey
6	Gaps in Training and Expertise in Myositis Outcome Measures: Insights from the 2024 MCTC Investigators' Survey
7	Characteristics of IIM Patients Enrolled in Clinical Trials Compared to "Non-Study" IIM Populations
8	Assessment of the Potential for Shorter Duration of IIM Clinical Trials (52 vs. 24 weeks)
9	Scoping of Perceived Reasonable Fair Market Values in Myositis Clinical Trials
10	Pharmacokinetics and Optimal Dosing of IVIG in Dermatomyositis