TREATMENT PARADIGM IN IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM)

4ο Διαπανεπιστημιακό Πρόγραμμα Εκπαίδευσης στη Ρευματολογία - 8ος Κύκλος Μαθημάτων - Σάββατο 11.2.2023

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Disclosures

- Advisory board meeting fees from Horizon Therapeutics

Outline

- Overview of the Different Classification Schemes of IIM
- Treatment Algorithm of IIM
- Approach of recalcitrant IIM
- Specific Considerations

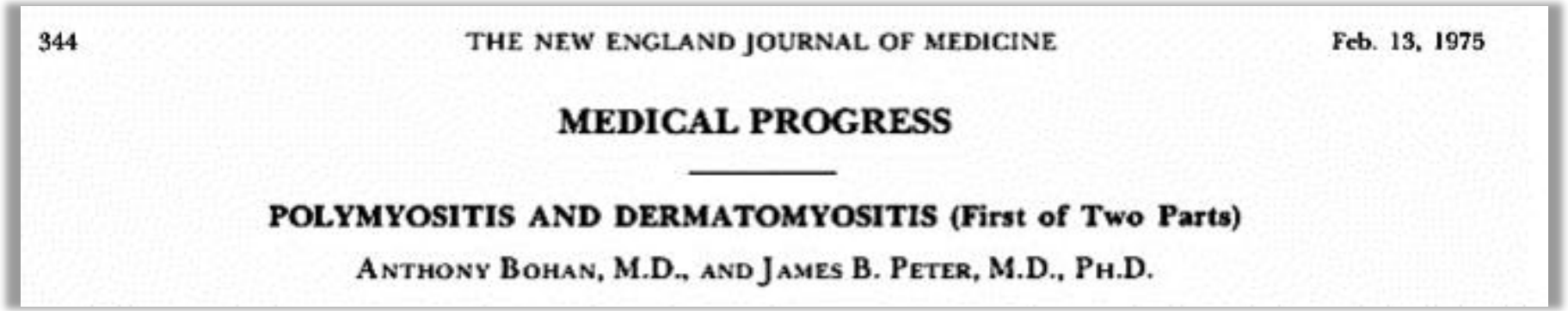
Idiopathic Inflammatory Myopathies (IIM)

Heterogeneous group of autoimmune syndromes characterized by:

(i) proximal muscle weakness

(ii) skeletal muscle inflammation

(iii)+/- skin



344 THE NEW ENGLAND JOURNAL OF MEDICINE Feb. 13, 1975

MEDICAL PROGRESS

POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)

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

MUSCLE

- Symmetric proximal muscle weakness
- Elevated muscle enzymes (CK, Aldolase, AST/ALT, LDH)
- Myopathic EMG abnormalities
- Typical changes on muscle biopsy (regeneration; degeneration; primary inflammation)

SKIN

- Typical rash of dermatomyositis

*Definite: 4/4, Probable ¾, possible 2/4

Bohan A, Peter JB. NEJM 1975

Idiopathic Inflammatory Myopathies (IIM)

Heterogeneous group of autoimmune syndromes characterized by:

(i) proximal muscle weakness

(ii) skeletal muscle inflammation of diverse patterns

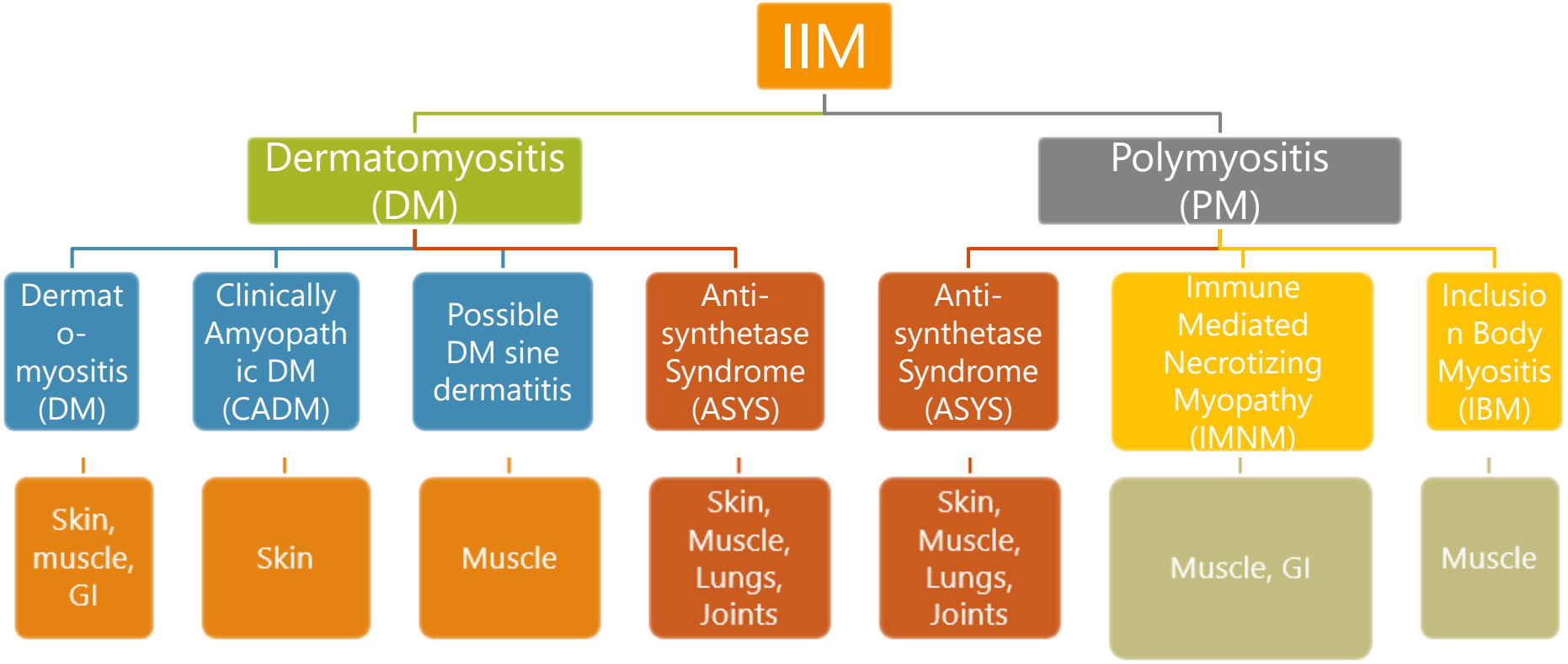
(iii) +/- skin

(iv) +/- lungs and joints

(v) autoantibodies

- Heterogeneous phenotypes and multiple subtypes
- Atypical presentations
- Non-pathognomonic findings
- Pathognomonic findings not always present

Defining subgroups in IIM



Does the patient have autoimmune myositis?

1. **Skin rash?** (typical skin rash, biopsy)
2. **Extra-muscular manifestations?** (Raynaud's, ILD, arthritis)
3. **Muscle involvement?**
4. **Myositis-specific antibodies?** (present in ~70%)
5. **EMG? Muscle MRI? Muscle biopsy?**
6. **Response to immunosuppression?**

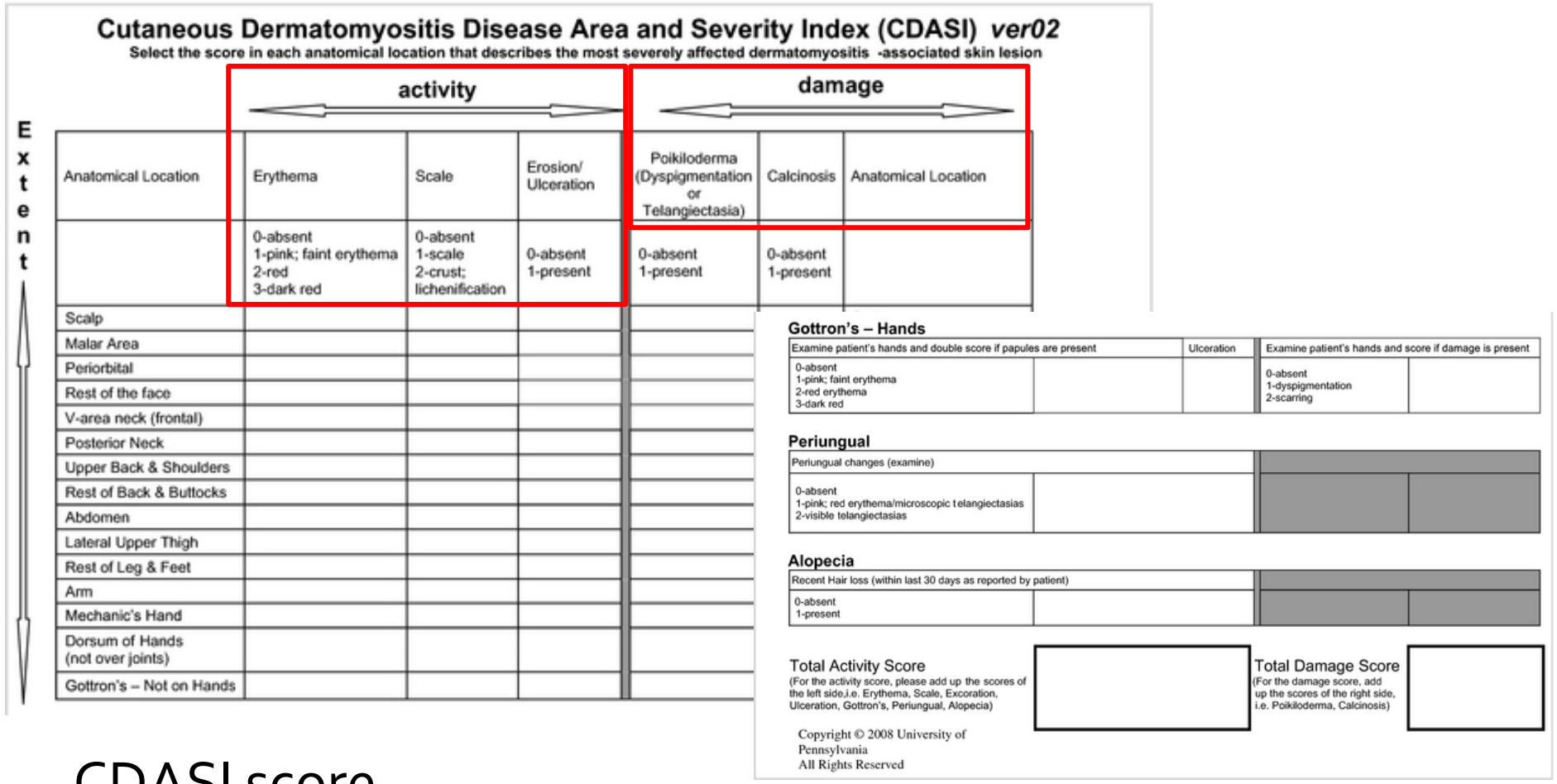
Framework for assessment

1) Does the patient have myositis?
2) If they have myositis, what organs are involved?
3) Activity versus damage?
4) Known antibody?
5) What treatments have been tried/can be used?

MRI imaging for muscle weakness

- MRI
  - T2-weighted, STIR with fat suppression; hyperintensity=edema
  - T1-weighted; fat replacement
- When to order muscle MRI?
  - Supportive of diagnosis;
  - ⇧diagnostic yield of muscle biopsy;
  - assess response to treatment-differentiate between activity and damage

Hoogendijk JE, et al. Neuromuscul Disord 2014
Van De Vlekkert J, et al. Muscle Nerve 2015
Lotz BP, et al. Brain 1989



Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) *ver02*

Select the score in each anatomical location that describes the most severely affected dermatomyositis -associated skin lesion

Extent

	activity			damage		
Anatomical Location	Erythema	Scale	Erosion/ Ulceration	Poikiloderma (Dyspigmentation or Telangiectasia)	Calcinosis	Anatomical Location
	0-absent 1-pink; faint erythema 2-red 3-dark red	0-absent 1-scale 2-crust; lichenification	0-absent 1-present	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						

Gottron's – Hands

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

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			

Total Activity Score
(For the activity score, please add up the scores of the left side,i.e. Erythema, Scale, Excoration, Ulceration, Gottron's, Periungual, Alopecia)

Total Damage Score
(For the damage score, add up the scores of the right side, i.e. Poikiloderma, Calcinosis)

CDASI score

Tiao J, et al. Br J Dermatol. 2017

Skin Examination

Activity

- Erythema
  - Pink/faint erythema
  - Red
  - Dark red/purple
- Scale
  - Scale
  - Crust/lichenification
- Erosion/Ulceration

Damage

- Poikiloderma
  - Dyspigmentation
  - Telangiectasia
- Calcinosis

Assessment for other organ involvement

- Arthritis
  - Symmetric arthritis of small joints
  - Non-erosive
- Interstitial Lung Disease
  - Symptoms: Chronic cough, exertional dyspnea
  - Signs: crackles, decreased lung volumes
- Cardiac Involvement
  - Symptoms: Chronic cough, exertional dyspnea, arrhythmias
  - Signs: rate, rhythm, bruits

- PFTs, 6 min walk test, chest CT, echocardiogram, pro-BNP, cardiac MRI

Guidelines of IIM treatment

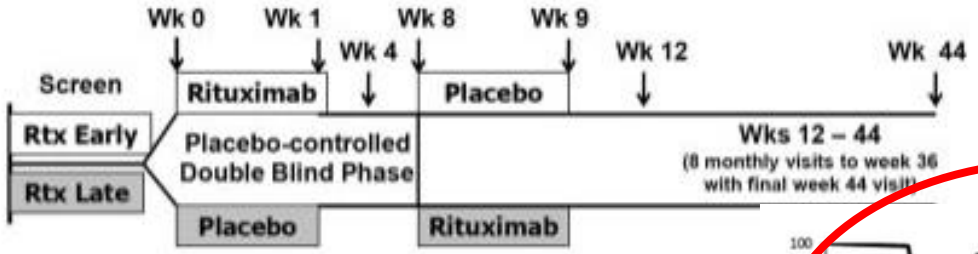
The majority of clinical trials have failed meeting primary end-points:

- Inadequate assessment tools
  - Lack of tools to assess Activity versus Damage
- Significant placebo effect
- Heterogeneous groups

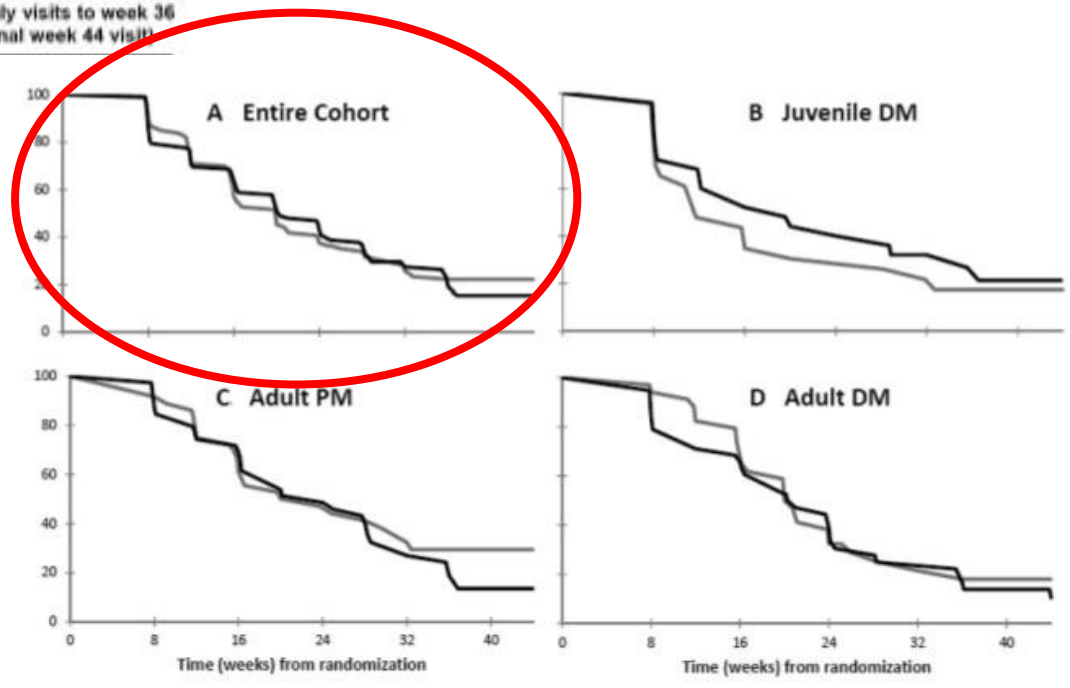
Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

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

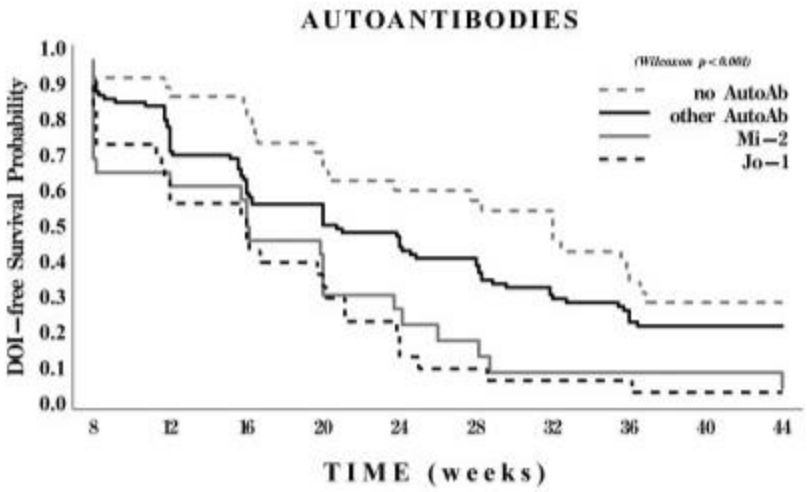


Patient population:
PM (n=76)
DM (n=76)
JDM (n=48)



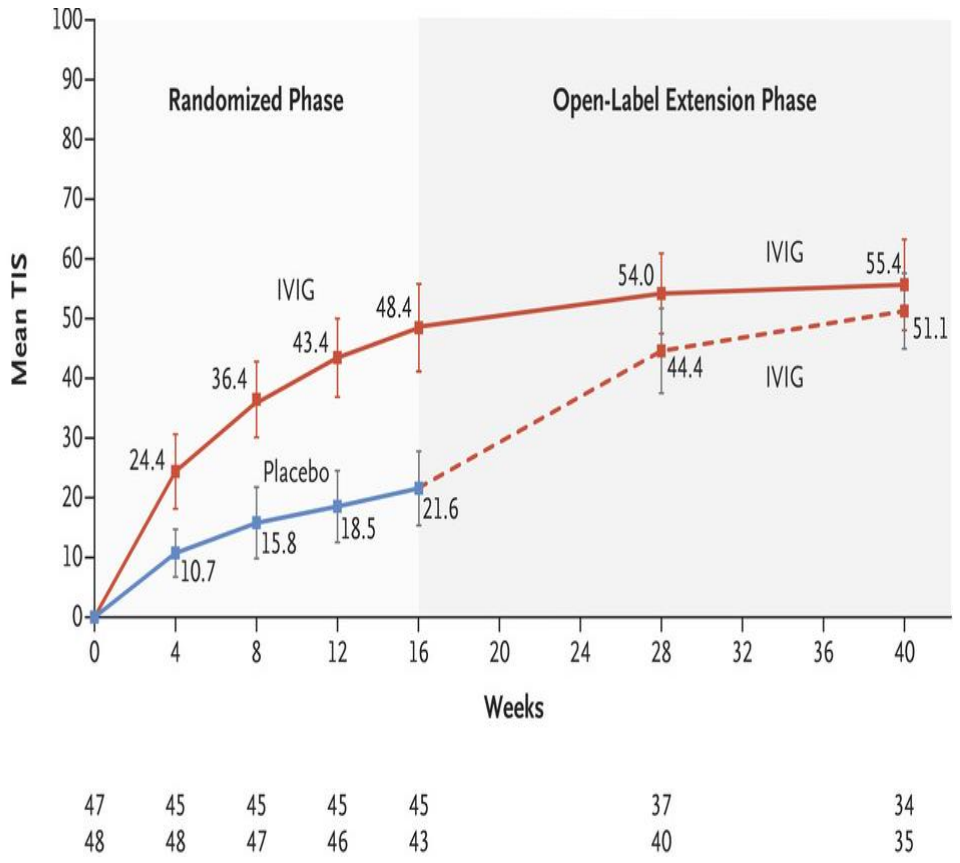
Predictors of Clinical Improvement in Rituximab-Treated Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

Rohit Aggarwal,[1] Andriy Bandos,[1] Ann M. Reed,[2] Dana P. Ascherman,[3] Richard J. Barohn,[4] Brian M. Feldman,[5] Frederick W. Miller,[6] Lisa G. Rider,[6] Michael O. Harris-Love,[7] Marc C. Levesque,[1] the RIM Study Group, and Chester V. Oddis[1]



ProDERM Study Design: IVIg Therapy for Adults With DM

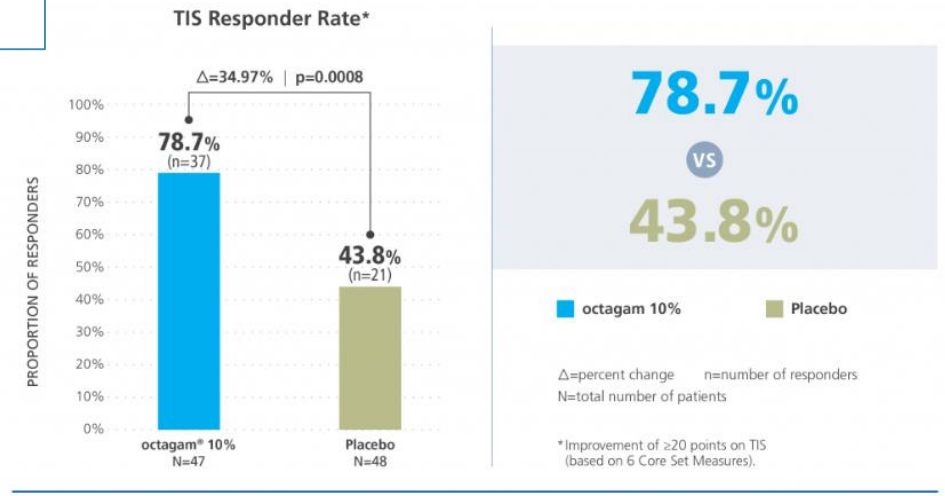
- Phase 3, double-blind, parallel-group, randomized placebo-controlled trial
- DM, but required at least mild muscle weakness (4/5 on MRC scale or <142 on MMT-8)
- Concomitant therapy allowed, up to 2 immunosuppressive agents and glucocorticoids

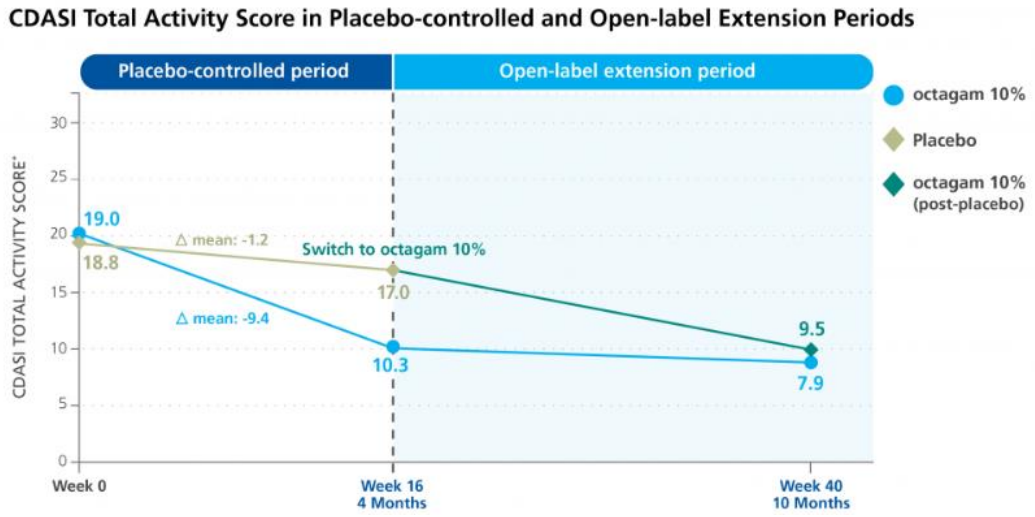


Aggarwal et al. N Engl J Med 2022;387:1264-1278

ProDERM Study Design: IVIg Therapy for Adults With DM

- Response at 16 weeks:
  - 79% versus 44%
  - 68% versus 23% for moderate improvement
  - 32% versus 8% for major improvement
- Skin score at 16 weeks:
  - -9.4 versus -1.2





The first FDA approved medication for DM

Aggarwal et al. N Engl J Med 2022;387:1264-1278

ProDERM Study Design: IVIg Therapy for Adults With DM

- Inclusion criteria were based on Bohan and Peter criteria (definite or probable)
- Allowed decrease of dose from 2 gr/kg to 1 gr/kg at 28 weeks
- Decreased risk for VTE when rate 0.04 mL/kg/min compared to 0.12 mL/Kg/min
- ESR can be elevated after IVIG!

Guidelines of IIM treatment

FDA approved medications for IIM:

- Acthar
- IVIG

There are no specific guidelines for management of IIM due to limited data

Our practice is determined by:

- Cost
- Insurance coverage
- Side effects
- Provider's experience and comfort level

Basic rules for IIM treatment

- Optimize dosage of chosen agent
- Allow enough time before assessing for effectiveness (usually 3 months)
- Target is to document a positive trajectory and not full improvement
- Ability to taper off steroids

Medication/Treatment	Dose	How it works	Comments
Steroids	Weight based	Interferes with processing of antigens; triggering of T- and B cells; proliferation of T- and B-cells	Side effects
Azathioprine	2.5 mg/kg daily	Proliferation of T- and B-cells	Blood counts; ⇧risk of cancer
Methotrexate	20-25 mg weekly	Proliferation of T- and B-cells	Liver damage; avoid alcohol
Mycophenolate mofetil	1000-1500 mg twice daily	Proliferation of T- and B-cells	GI side effects; ⇧risk of cancer
Tacrolimus	Titrate to target blood levels 5	Keeps T cells from stimulating production of T- and B-cells (upstream of AZA/MTX)	Hypertension, kidney failure, high blood sugar, elevated K; avoid NSAIDs
Hydroxychloroquine	5 mg/kg or based on blood levels	Unknown	DM rash
IVIG	2 gr/kg every 4 weeks	Unknown	Kidney failure, hyperviscosity
Plasmapheresis		Removes antibodies and proteins	Rarely used
Rituximab	1000 mg day 0 and day 14	Attacks B-cells	PML
Tofacitinib	11 mg XR once daily	JAK inhibitor	CV risk, malignancy

Treatment Paradigm of IIM

Methotrexate (MTX)	Skin/Muscle/**Joints**	
Azathioprine (AZA)	**Lung**/Muscle/Skin	+ Glucocorticoids
Mycophenolate mofetil (MMF)	**Lung/Skin**/Muscle	

Can be avoided depending on patient's symptoms and tolerance

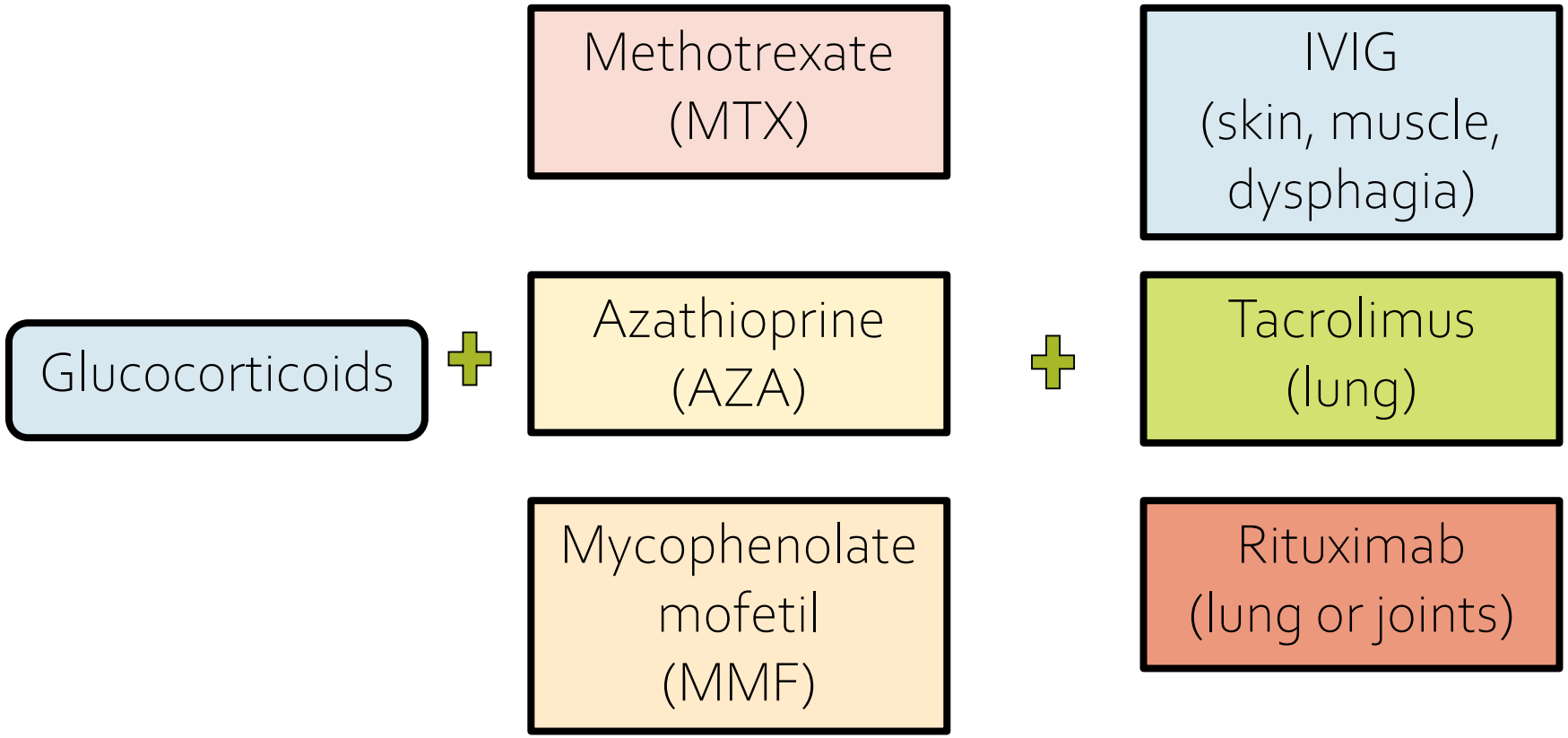
Joffee M et.al Am J Med 1994, 379-387
Majithia V et. al Rheumatology 44, 386-9, 2005

Treatment Paradigm of IIM

Combination therapy is commonly used

Villalba L et.al Arthritis Rheum 41, 392-99 (1998)

Treatment Paradigm of IIM



Joffee M et.al Am J Med 1994, 379-387
Majithia V et. al Rheumatology 44, 386-9, 2005
Villalba L et.al Arthritis Rheum 41, 392-99 (1998)

JAK inhibitors in Dermatomyositis

Remission of Recalcitrant Dermatomyositis Treated with Ruxolitinib

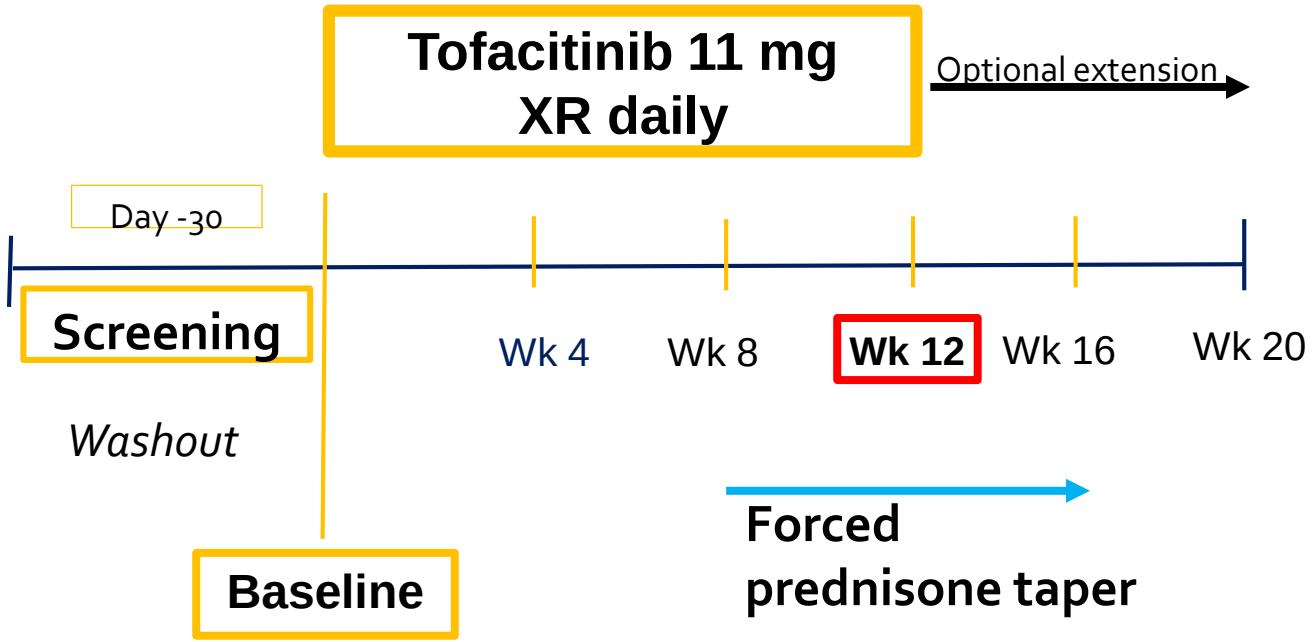
TO THE EDITOR: We report a case of recalcitrant dermatomyositis in a 72-year-old woman with skin lesions typical for the disease (heliotropic patient presented with fever and marked splenomegaly. Testing for the Janus kinase 2 mutation *JAK2 V617F* was positive, and the patient received

- Regulates activation of dendritic cells and T lymphocytes
- Blocks IFN-β induced signal transducers + activators of transcription 1 (STAT1) in vitro

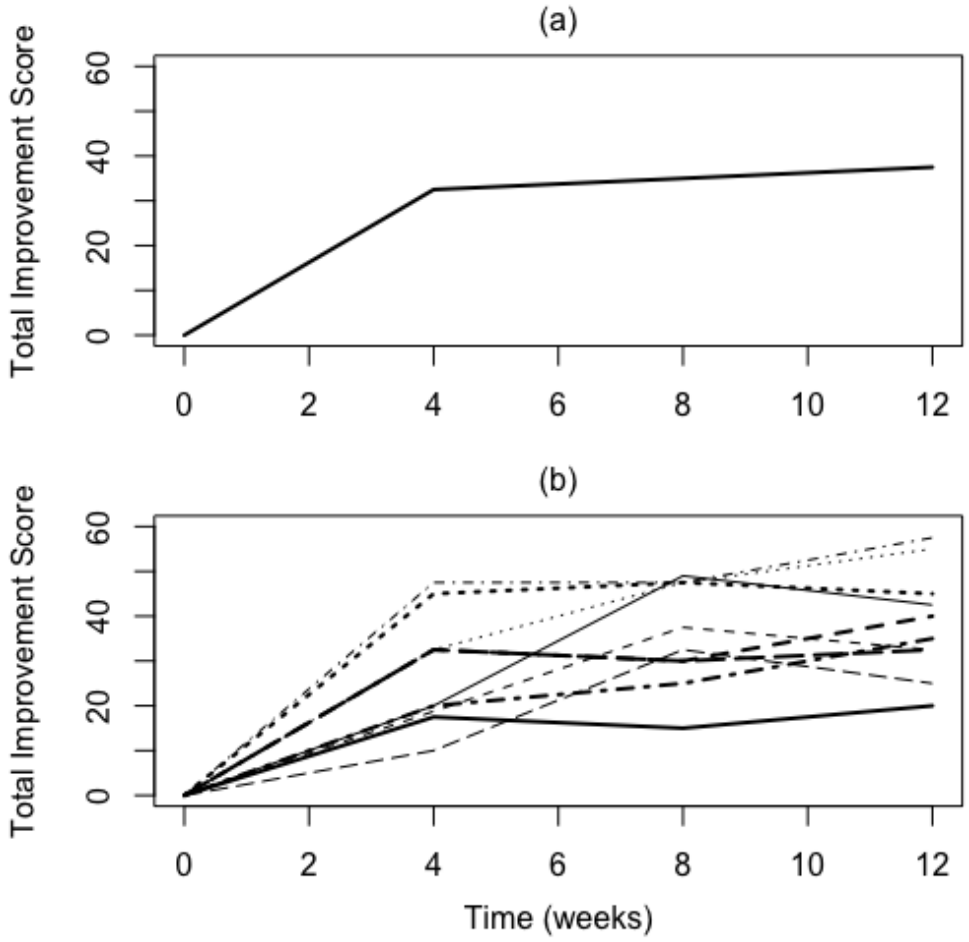
Hormung T et. al N Engl J Med 2014 Dec 25; 371 (26):2537-8

Study of Tofacitinib in Refractory Dermatomyositis: An Open-Label Pilot Study of Ten Patients

Julie J. Paik,[1] Livia Casciola-Rosen,[1] Joseph Yusup Shin,[1] Jemima Albayda,[1] Eleni Tiniakou,[1] Doris G. Leung,[1] Laura Gutierrez-Alamillo,[1] Jamie Perin,[1] Liliana Florea,[1] Corina Antonescu,[1] Sherry G. Leung,[1] Grazyna Purwin,[1] Andrew Koenig,[2] and Lisa Christopher-Stine[1]



Primary Outcome Measure



The composite **median TIS** was 40 [IQR 32.5, 47.5] indicative of at least **moderate improvement** in all 10 subjects.

Tofacitinib more effective for skin involvement

Paik JJ, Casciola-Rosen L, Shin JY et.al Arthritis and Rheumatology 2021 March 24

Recalcitrant Disease

Unable to taper off steroids
Lack of improvement on combination therapy

1) Evaluate disease activity versus chronic damage

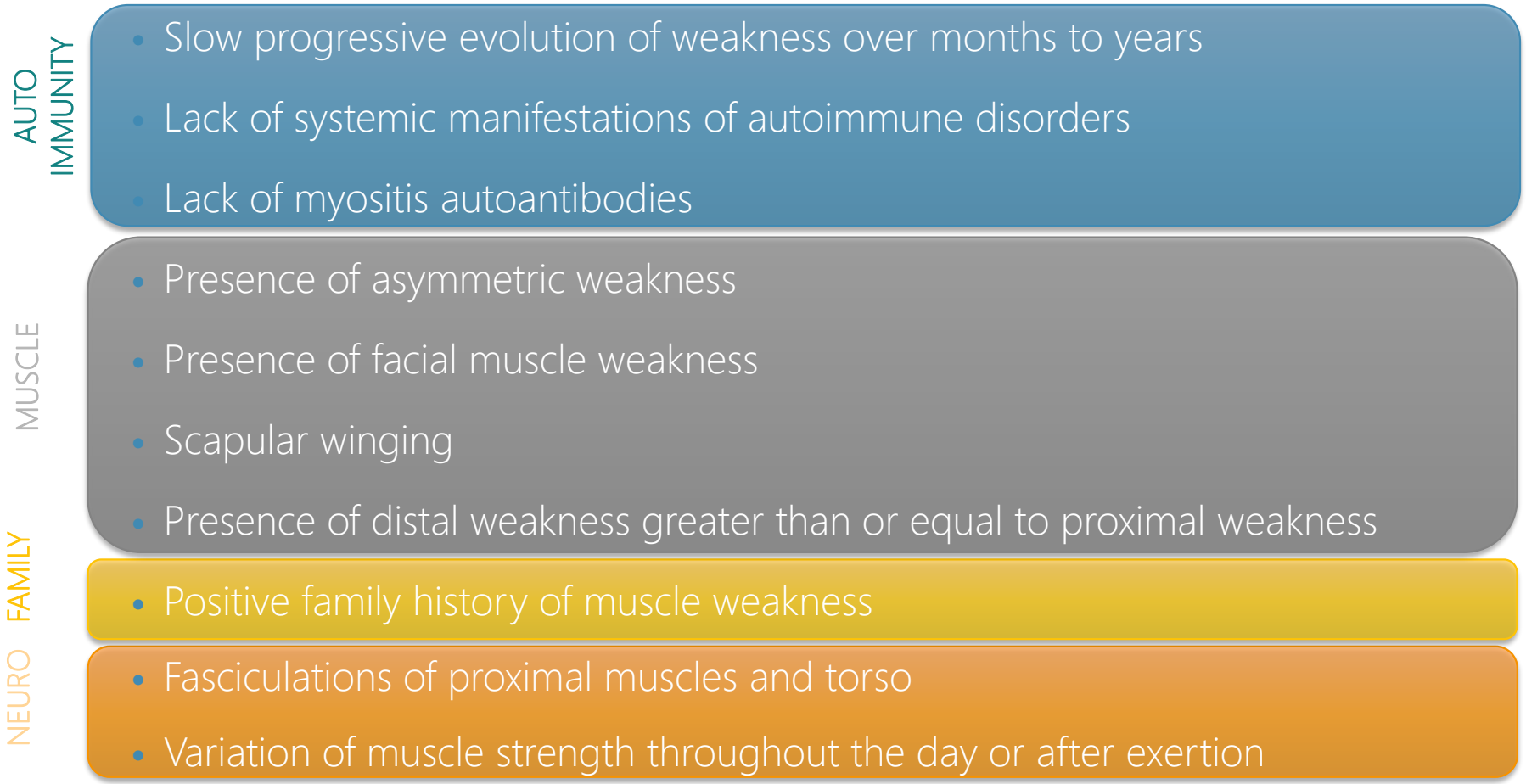
2) Evaluate for other comorbidities that could drive disease activity (malignancy?)
    1) Chest/abdomen/pelvis CT or PET CT
    2) Mammogram
    3) Pap smear
    4) Transvaginal US
    5) PSA
    6) Colonoscopy

3) Re-evaluate diagnosis

Myopathy: Differential Diagnoses

- Electrolyte disturbances
- Drugs and toxins (alcohol, statins)
- Infection
- Active endocrinopathy
  - hyper- or hypothyroid, hyperparathyroid, Cushing's
- Deconditioning
- Inflammatory/autoimmune
- Neuromuscular disorders
  - e.g. spinal muscular atrophy, myasthenia gravis
- Inherited or acquired diseases
  - e.g. muscular dystrophies, metabolic myopathies

Features suggestive of non-autoimmune myopathy

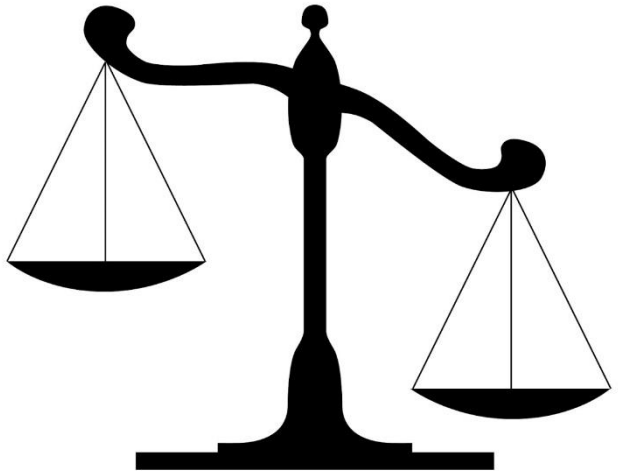


SPECIFIC TREATMENT CONSIDERATIONS

Amyopathic Dermatomyositis

- Unclear the benefit of treating mild skin rash

- Risks of medications versus Benefit from skin rash improvement:
  - Hydroxychloroquine



EVIDENCE-BASED DERMATOLOGY: ORIGINAL CONTRIBUTION

Adverse Cutaneous Reactions to Hydroxychloroquine Are More Common in Patients With Dermatomyositis Than in Patients With Cutaneous Lupus Erythematosus

Michelle T. Pelle, MD; Jeffrey P. Callen, MD

- Cutaneous reactions may occur in approximately 1/3 of patients with dermatomyositis

JAMA Dermatology | Brief Report

Association Between Autoantibody Phenotype and Cutaneous Adverse Reactions to Hydroxychloroquine in Dermatomyositis

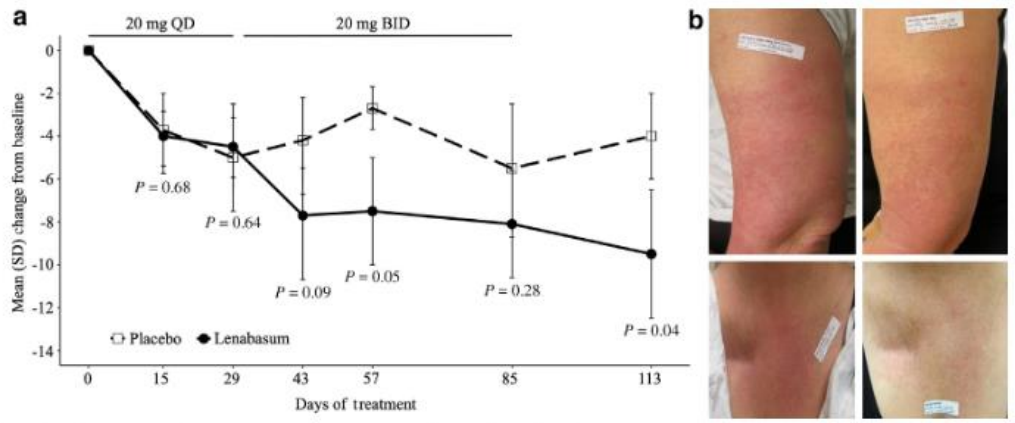
Paige W. Wolstencroft, BA; Livia Casciola-Rosen, PhD; David F. Fiorentino, MD, PhD

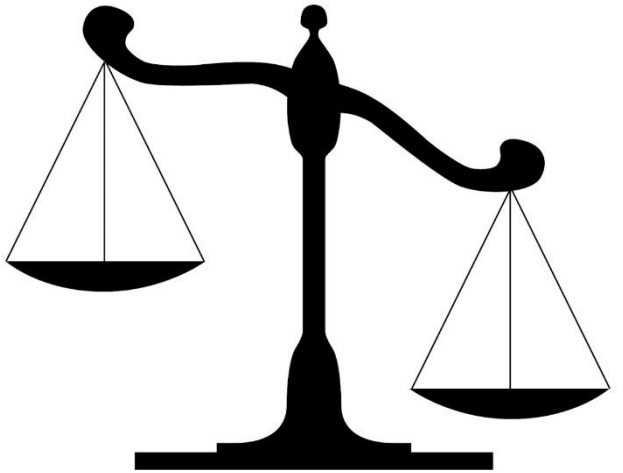
- Adverse skin reactions to hydroxychloroquine are relatively common in a US cohort of patients with dermatomyositis (~20%)
  - +association with anti-SAE
  - -association with anti-MDA5

Amyopathic Dermatomyositis

- Unclear the benefit of treating mild skin rash

- Risks of medications versus Benefit from skin rash improvement:
  - Hydroxychloroquine
  - Lenabasum
    - Agonist to cannabinoid receptor type 2





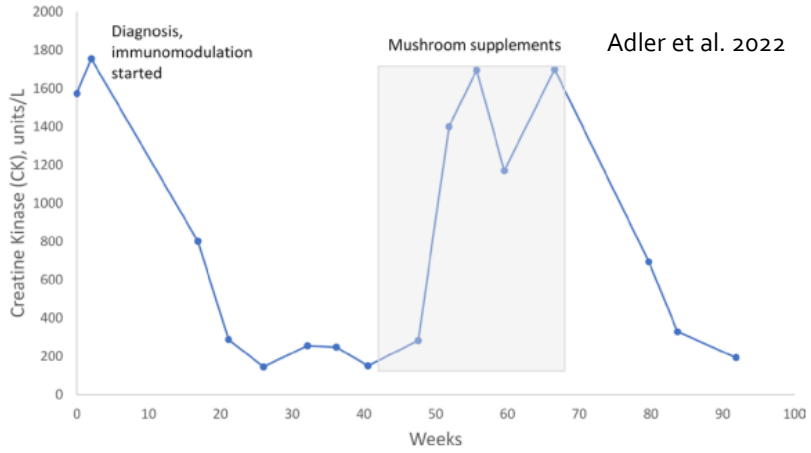
Werth VP, et al. J Invest Dermatol. 2022

Specific Treatment Considerations in IMNM

- The younger the patient, the worse the prognosis
- Atrophy establishes quite early in the disease
- **Combination treatment with various immunosuppressive agents**

- Anti-SRP+ IMNM
  - Rituximab

- Anti-HMGCR+ IMNM
  - IVIG monotherapy
  - PCSK9 inhibitors
  - Avoid statins and other natural sources of statins (e.g. oyster mushrooms)

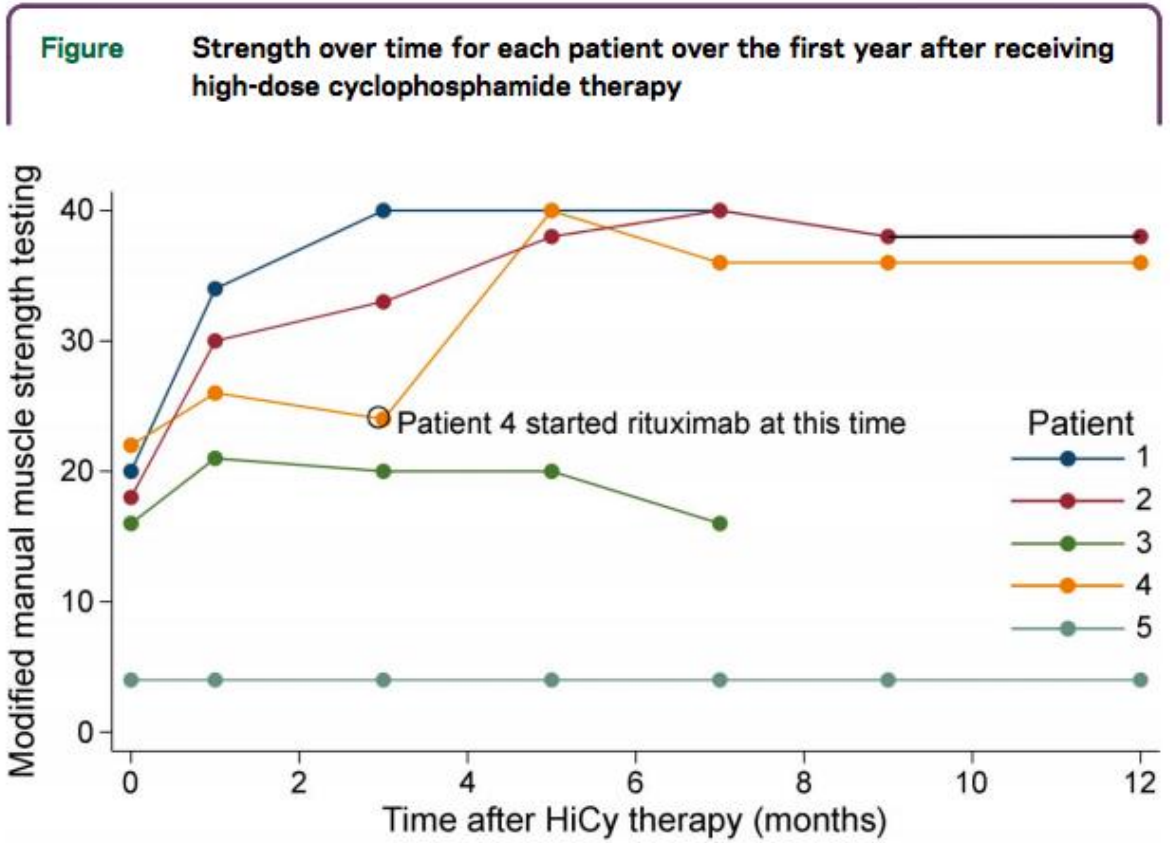


Adler et al. 2022

Miller T, et al. J Neurol Neurosurgery Psychiatry 2002
Kao AH, et al. Arthritis Rheum 2004
Hengstman GJ, et al. Ann Rheum Dis 2006
Maeshima K, et al. Rheumatol. 2014
Tiniakou E, et al Rheumatology 2017
Allenbach Y, et al Medicine 2014
Watanabe Y, et al Medicine 2015
Mammen AL, et al NEJM 2015
Tiniakou E, et al. Arthritis Rheum 2019

High-dose CYC in IMNM

Patient	Age at diagnosis	Myositis Specific Ab
1	53	Anti-SRP
2	33	Anti-SRP
3	36	Anti-SRP/anti-Ro
4	38	Anti-HMGCR
5	22	Anti-HMGCR



Adapted from Mecoli CA, et al.Neurol Neuroimmunol Neuroinflamm 2017

Treatment of Antisynthetase Syndrome

- No randomized clinical trial for treatment
- Treatment is driven by the organ manifestation
- Large case series reported MMF and AZA to be beneficial in pts with ILD
- Tacrolimus- option in refractory disease
- Rituximab showed improvement in subanalysis of the RIM trial
- IVIG
  - Important adjuvant therapy
  - Open label IVIG trial in refractory ILD associated PM/DM
  - 5 patients who failed high dose steroids and cyclosporine or cyclophosphamide
  - Case reports of rapidly progressive ILD remission within 3 mos of treatment

Anti-MDA-5-Treatment

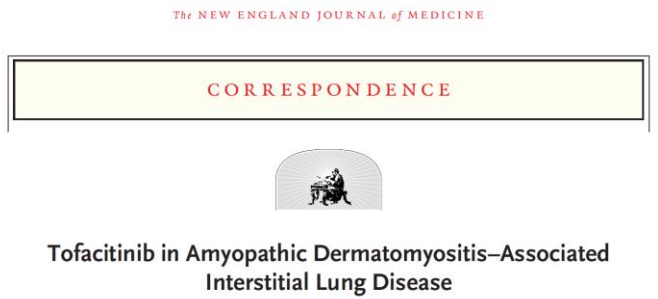
- Aggressive Rx

High dose steroids+

Cyclosporine/tacrolimus+

Cyclophosphamide and/or IVIG

+Tofacitinib (Jak inhibitor)
3/5 patients survived


The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Tofacitinib in Amyopathic Dermatomyositis–Associated Interstitial Lung Disease

Kurasawa K. et al. Rheumatology 2018
Hamada-Ode K, et al. EJR 2015
Koguchi-Yoshioka H, et al. Br J Dermatol 2017
Chen Z. et al. NEJM 2019

Fujita Y, et al. Intern Med 2018
Tokunaga K. et al. Intern Med 2017
Silveira MG, et al. QJM 2016

Tx of Myositis associated-ILD

Steroids
+
Mycophenolate mofetil
or
Azathioprine

+/-

IVIG
(Adjunctive/
refractory cases)

Rituximab
(Best outcomes:
Disease duration <12 months and/or
acute exacerbation

Tacrolimus

Andersson H et al. Rheumatology 54, 1420-1428
Huapaya JA et al Respir Med 2019
Huapaya JA Chest 2019 Nov;156(5): 896-906
Keir G et al Respirology 19, 353-359

Inclusion Body Myositis management

- Immunosuppression can lead to earlier difficulty in ambulation
- Physical and occupational therapy
  - Blood flow restriction
- Speech therapy
  - Esophageal dilatation
- Orthotics

Peter Frampton Found New Purpose After Inclusion Body Myositis Diagnosis

The rocker says he has a renewed sense of purpose and was inspired to start a research foundation.

Jensen KY, et al. BMJ Open. 2021
Jørgensen AN, et al. Scand J Rheumatol. 2018
Benveniste O, et al. Brain 2011
Jensen KY, et al. Neuromuscul Disord. 2022

Open label trial of ABCoo8 in IBM

- Phase 1 clinical trial in IBM
- ABCoo8 is a first-in-class humanized monoclonal antibody that binds to KLRG1 to selectively deplete highly differentiated T cells

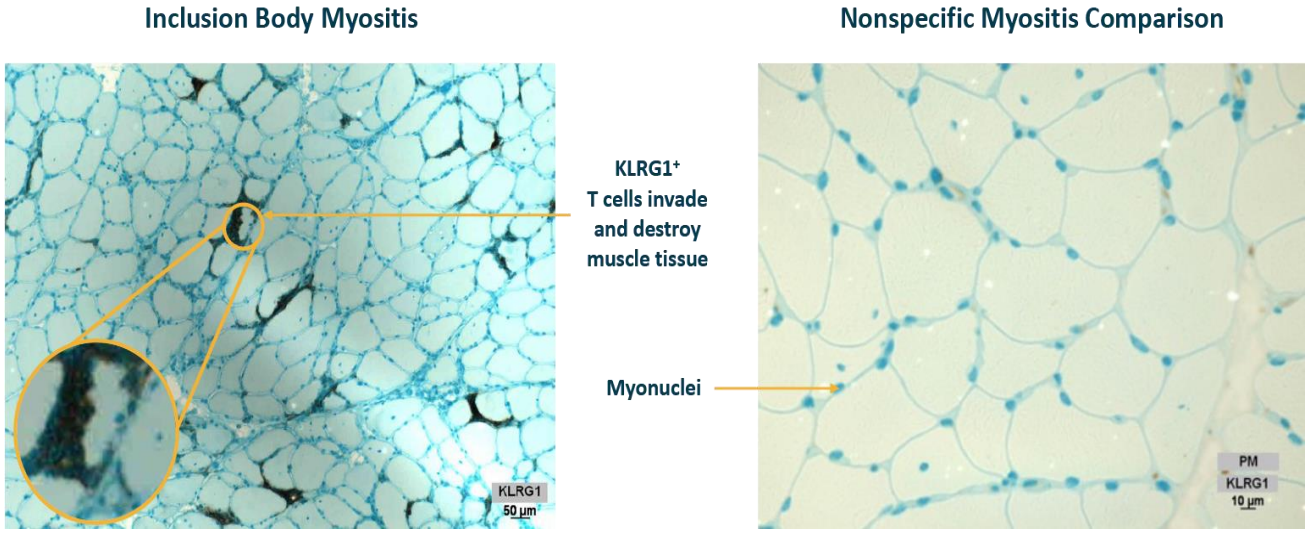


Image from abcuro.com

Treatment highlights

- Optimize drug dose and allow adequate time to reach effectiveness
- Steroids not always necessary
- Steroids and IVIG are the fastest acting agents
- Hydroxychloroquine can cause skin rash worsening!

Pelle MT, Callen JP. Arch Dermatol.
Wolstencroft PW, et al. JAMA Dermatol.

Thank you!
Any questions, email
etiniak1@jhmi.edu

Post-doc position open at our lab!
Please contact me if you are interested

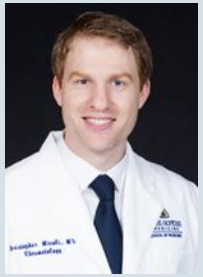
The Johns Hopkins Myositis Center Team

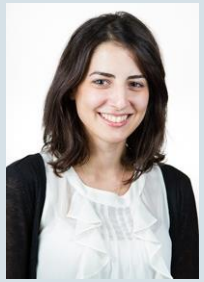
Rheumatology


Jemima Albayda


Lisa Christopher-Stine


Livia Casciola-Rosen

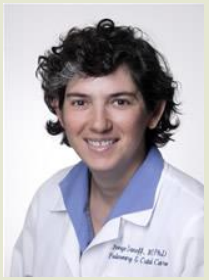

Christopher Mecoli


Eleni Tiniakou


Britany Adler


Julie Paik

Pulmonary


Sonye Danoff


Kathrik Suresh

Neurology


Tom Lloyd


Ricardo Roda


Andrew Mammen

PM&R / Neuro-muscular


Tae Chung

JOHNS HOPKINS MEDICINE