

University of Pittsburgh

Anti-Synthetase Syndrome: Update

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A Case

- 60 y/o Caucasian Female presents to the hospital with worsening dyspnea on exertion over 2 months.
- New O2 requirement
- She was diagnosed as "pneumonia" twice at local hospital 1 and 2 month ago (with low grade fever)
- Raynaud's phenomenon since last winter
- SH: Non smoker, no alcohol, works as a clerk
- FH: No h/o lung disease or autoimmune syndrome

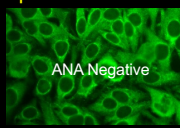
No rash, No arthritis, No muscle weakness
No sclerodactyly, dysphagia, GERD, SICCA

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Work up



ANA Negative



Abnormal nailfold capillaroscopy

CK: 368 (<200);
Aldolase: 6
CBC, LFT : Normal
Creatinine: Normal
ESR: 55 (elevated)
CRP: 3.4 (elevated)

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Diagnosis: Anti-synthetase syndrome (anti-PL7 antibody +ve)

- Anti-synthetase syndrome:
 - ILD (Acute/Subacute)
 - Raynaud's
 - Nail fold capillary abnormality
 - Elevated muscle enzymes
- No Myositis
- No Rash
- No Arthritis
- No Fevers
- No Mechanics hand

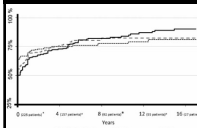
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Clinical Features Of Anti-synthetase Syndrome



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Classic Triad of Anti-Synthetase Syndrome



ILD
Myositis
Polyarthritits
Any 1: 50%; 2: 30%; 3: 20%

Fever: 25-35%
Mechanics hand: 20-30%
Raynaud's: 24-37%

Cavagna et al. Medicine 2015

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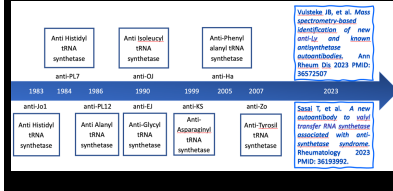
Anti-synthetase Autoantibodies - 40% of Myositis

Antibody	Antigen (tRNA synthetase)	Prevalence in IIM (%)
Jo-1	histidyl	20-30
PL-7	threonyl	5
PL-12	alanyl	5
OJ	isoleucyl	<5
EJ	glycyl	<5
KS	asparaginyl	<1
YRS/Tyr	tyrosyl	<<1
Zo	phenylalanyl	<<1

Non-Jo-1 Ab

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The evolution of antisynthetase antibodies



Adapted from Galindo-Feria AS, et al. Front Immunol. 2023 PMID: 35634293

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Anti-synthetase Cohort

Autoantibody	Number (% synthetases)
Jo-1	140 (60%)
PL-12	36 (16%)
PL-7	27 (12%)
EJ	11 (5)
OJ	6 (3)
KS	9 (4)
Total Synthetase cases	229

Aggarwal, Ann Rheum Dis, 2013

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Target different Aminoacyl-tRNA synthetase enzymes

- Anti-Jo-1 autoantibody
- Directed against histidyl-tRNA synthetase

histidine
his tRNA syn.
Agg
tRNA for histidine

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A Negative ANA Does Not Imply Antibody Negativity in Myositis

Homogeneous, diffuse cytoplasmic staining
ANA Homogenous Nucleolar
Anti-Synthetase Syndrome patient
Scleroderma patient

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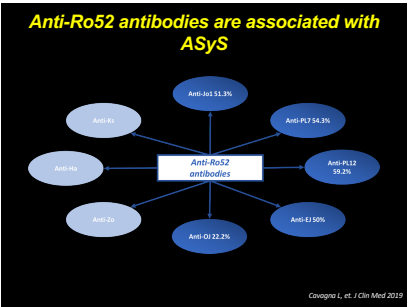
Frequency of ANA and Cytoplasmic Staining in Anti-Synthetase Patients

Anti-Synthetase	ANA +	Anti-CytAb +	p value
All Jo-1	50%	72%	p < 0.001
All non-Jo-1	48%	81%	p = 0.026
			p < 0.001

Screening for Anti-Synthetase syndrome	
Anti-Cytoplasmic (Anti-CytAb+)	Sensitivity 72% Specificity 91%
ANA	50% 0.6%
Anti-CytAb or Jo-1	92% 90%

ICAP nomenclature AC-35 to AC-23
Aggarwal et al. J Rheum 2016

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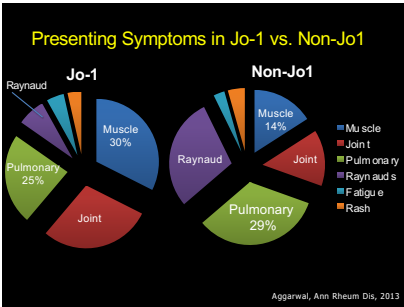
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High False Negative Rate for non-Jo-1 ASyS

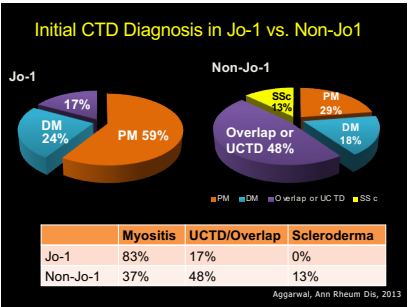
	False Positive Rate (%)	False Negative Rate (%)
anti-ARS (all methods)	9.9	4.1
Jo-1	0.2	3.1
All Non-Jo-1	7.9	15.2
PL7	2.8	28.6
PL12	2.7	15.2
EJ	1.5	16.7
OJ	0.6	-
KS	0.8	100
ES	-	-

Loganathan A, Zanfranco G et al. Clin Exp Rheumatol. 2024

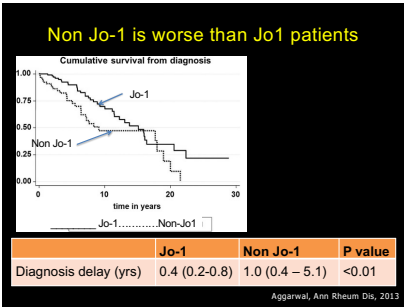
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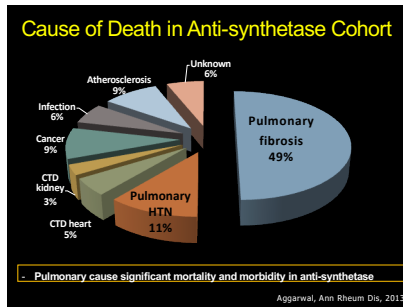
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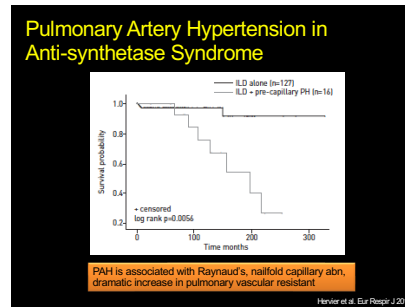
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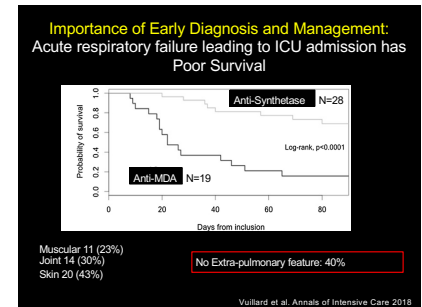
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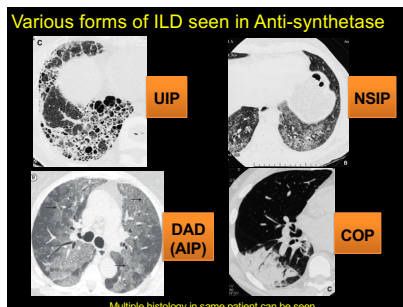
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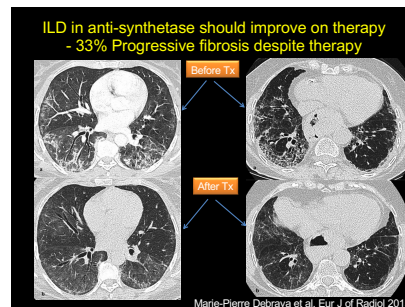
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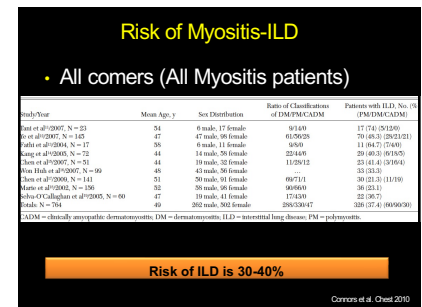
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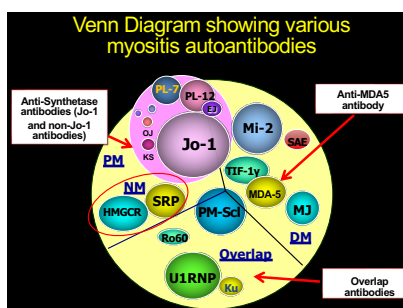
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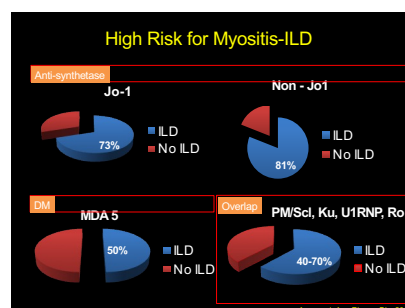
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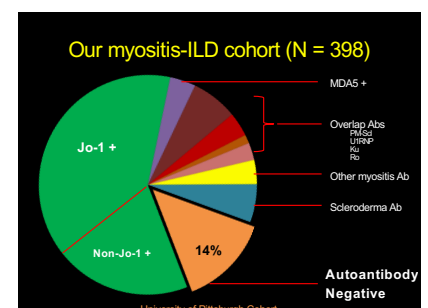
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Treatment of Anti-Synthetase Syndrome

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No effective FDA Approved Therapies (until recently)

- Until recently, there were no FDA approved therapies for myositis beyond steroid and ACTH since in 1950s.



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Efficacy and Safety of IVIG in patients with active dermatomyositis.

A Randomized, Double-Blind, Placebo-Controlled Phase III Trial

Progress in Dermatomyositis (ProDERM) Study

THE NEW ENGLAND JOURNAL OF MEDICINE

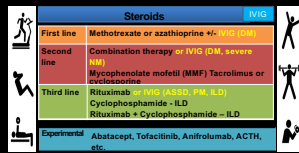
ORIGINAL ARTICLE

Trial of Intravenous Immune Globulin in Dermatomyositis

R. Aggarwal, C. Charles-Schoeman, J. Schessl, Z. Bata-Csörgő, M.M. Dimachkie, Z. Gringer, S. Moiseev, C. Oddis, E. Schiopu, J. Vincovsky, I. Beckmann, E. Clodi, O. Bugnion, N. Dankó, F. Ernste, N.A. Goyal, M. Heuer, M. Hudson, Y.M. Hussain, C. Karam, N. Magnolo, R. Nelson, N. Pozur, L. Prystopa, M. Sárdy, G. Valenzuela, A.J. van der Kooi, T. Yu, M. Worm, and T. Levine, for the ProDERM Trial Group†

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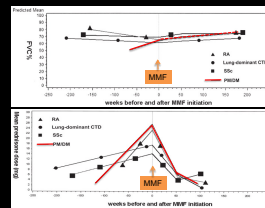
Pharmacologic Therapy of IIM



Oddis & Aggarwal et al. Nature Reviews: Treatment in Myositis 2018

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Mycophenolate: 1st line for ILD (ASyS)



Retrospective study (N = 32)

Fischer et al. 2013

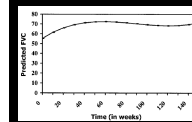
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Tacrolimus in Myositis-ILD (ASyS)

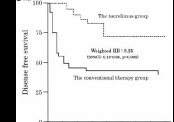
N = 13 refractory anti-Syn

25 pts: Tacro + steroid (9 pts with cyclozan)

24 pts: Steroid (9 pts with cyclozan or cyc)



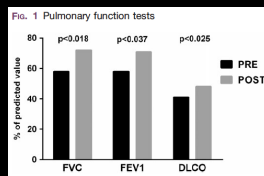
Wilkes & Oddis et al. 2005



Katayama et al. 2015

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Rituximab in Myositis-ILD (ASyS)



- N = 24 (anti-synthetase); retrospective
- 70% Failed IS + Pred; 30% Pred
- 10/12 acute ILD got cyclozan;
- 7 had >30% improvement in FVC%

Anderson et al. Rheumatology 2015, Norway

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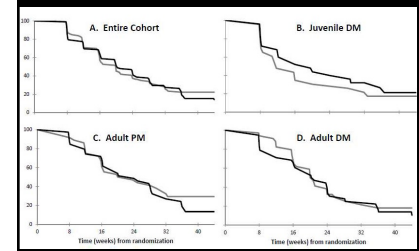
Rituximab in Myositis: A Double Blind Placebo Controlled RCT



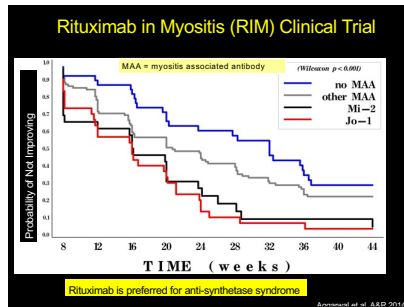
- Subjects randomly assigned, double-blind
- ½ subjects receive drug early (Rx Early) and ½ subjects receive drug 8 wks later (Rx Late)
- 200 patients were treated (75 PM, 75 DM, 50 JDM)

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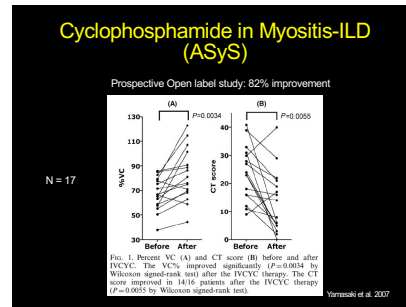
Primary Outcome: Myositis Response Criteria (IMACS DOI)



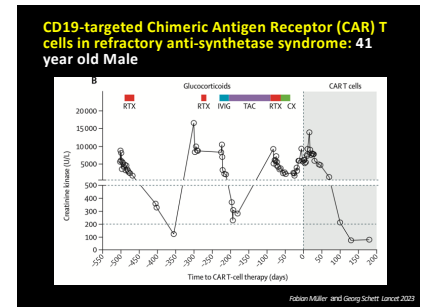
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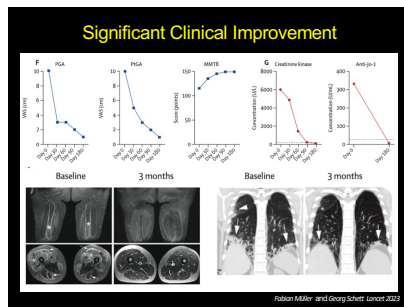
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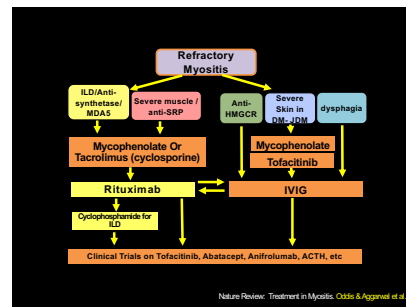
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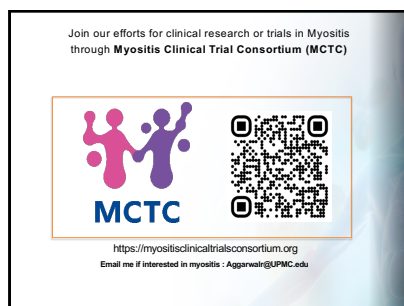
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