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EULAR Highlights 2024
Myositis

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COI

Research: AbbVie, Protagen, Novartis Biomedical; patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143)

Lecturing: Boehringer-Ingelheim, GSK, Novartis, Otsuka

Consulting: Novartis, Boehringer Ingelheim, Janssen-Cilag, GSK

Congress support: Medtalk, Pfizer, Roche, Actelion, Mepha, MSD

Advisory Boards: Boehringer-Ingelheim, Janssen-Cilag

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Content

- Auto-antibodies
- Treatment

Inflammatory Myopathies
Dermatomyositis
(Polymyositis)
Antisynthetase Syndrome
Immune-mediated necrotizing Myopathy
Cancer-associated Myositis
Overlap-Myositis (e.g. with systemic sclerosis, rheumatoid arthritis)
Secondary myositis (connective tissue disease, vasculitis, sarcoidosis)

Sporadic inclusion body myositis

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Auto-antibodies

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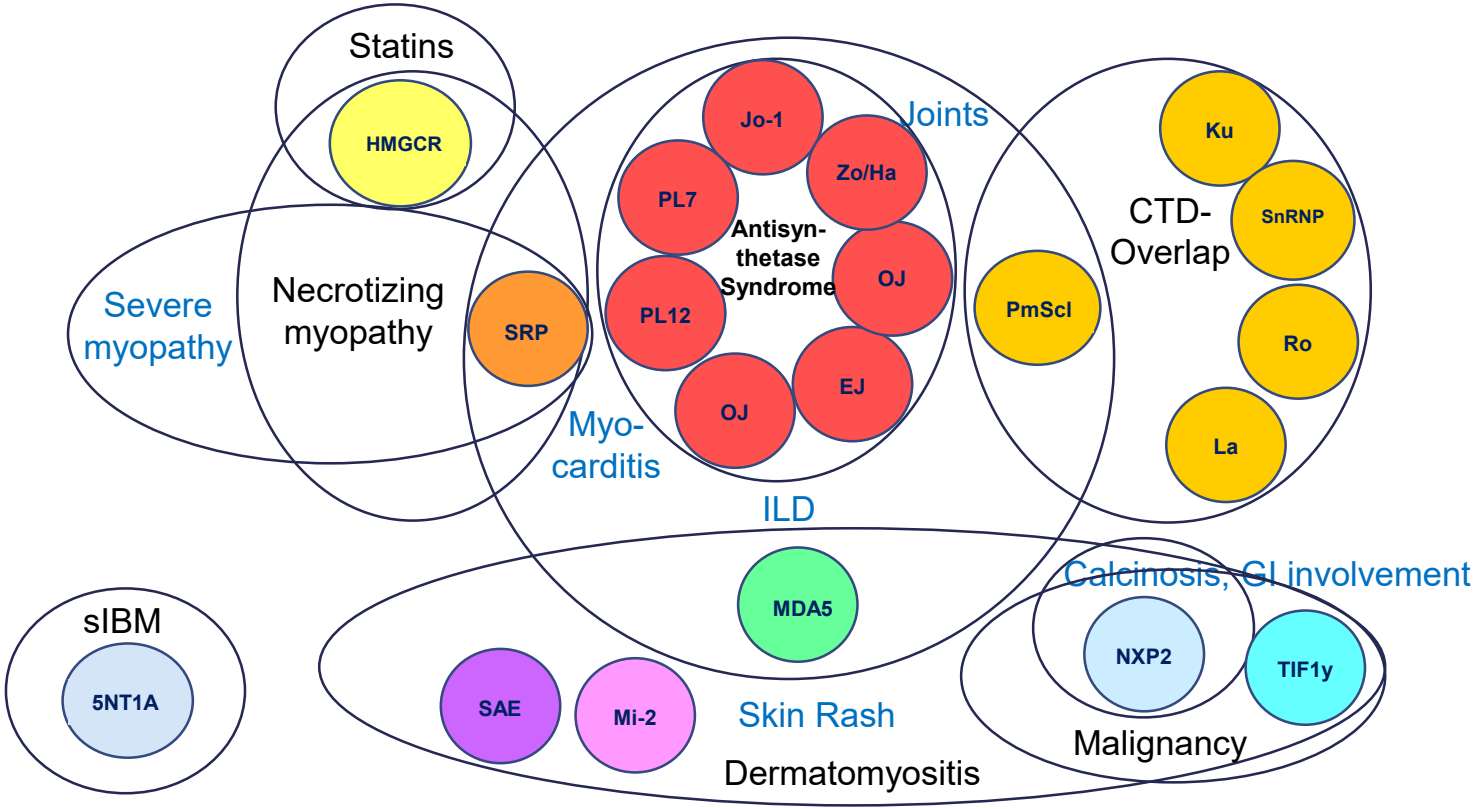
Disorders of the Myositis Spectrum



Adapted from Betteridge Z et al. J Intern Med. 2016 Jul;280(1):8-23

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Navigating Complexities of Multiple Positive Myositis Autoantibodies

Background

- Myositis-specific autoantibodies (MSAs) considered mutually exclusive
- Multiple positivities rare using immunoprecipitation (=reference standard)
- Techniques, favored in clinical practice, e.g. ELISA and Line Blot Immunoassay (LIA) associated with increased rates of multiple positivity and probability of false positivity

Aim

- To evaluate real-life prevalence and clinical meaning of multiple seropositivity for MSA and Myositis Associated Antibodies (MAAs) in the Classification Criteria of Anti-Synthetase Syndrome (CLASS) cohort

Loganathan A, et al. 10.1136/annrheumdis-2024-eular.3269

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Navigating Complexities of Multiple Positive Myositis Autoantibodies

Results

- Seropositivity for MSA/MAA confirmed in 2832 patients (67.8%)
- Multiple seropositivity by LIA in 43.7%, ELISA in 33.7%, IP in 24%
- True multiple seropositivity for MSAs in 7.9%, clinically presenting with corresponding characteristic features

Conclusions

- Validity of results of immunoassays should be evaluated by congruent indirect immunofluorescence staining (positivity for ANA/Hep2 cytoplasm, pattern matching antigen)
- If in doubt, another sample should be send out to another accredited lab

Loganathan A, et al. 10.1136/annrheumdis-2024-eular.3269

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Seronegative Myositis

Background

- Autoantibodies considered pathogenic key players in myositis
- Up to 20-40% of IIM patients, even those with typical clinical manifestations, test seronegative for known myositis-specific autoantibodies

Aim

- To detect novel autoantigens

Galindo-Feria AS, et al. doi/10.1093/rheumatology/keae317/7687810; Preger C, et al. https://doi.org/10.1016/j.jaut.2022.102951

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Seronegative Myositis

Results

- Novel autoantigen FHL1 (Four-and a-half-LIM-domain 1), expressed in cytoplasm of skeletal and heart muscle (FHL1)
  - Found in 27% of previously negatively tested patients with IIM (ELISA)
- Autogenic properties found for 16/19 cytoplasmic aaRs and aaRs complex interaction proteins in myositis patients
  - 33% of previously negatively tested patients (multiplex bead array assay, confirmed by ELISA & WB)

Conclusion

- Cytoplasmic auto-antibodies not yet detectable by commercial testing may account for “seronegativity” in myositis
- IIF should include both antinuclear and anticytoplasmic staining

Galindo-Feria AS, et al. doi/10.1093/rheumatology/keae317/7687810; Preger C, et al. https://doi.org/10.1016/j.jaut.2022.102951

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Pathogenicity of Auto-Antibodies

Background

- Auto-antibodies thought to be pathogenic by activating the immune system

Aim

- To evaluate whether myositis auto-abs interfere with their autoantigens within the muscles and thereby compromise the normal function of these proteins
- Methods
  - Confocal microscopy, bulk RNA sequencing, transfection of cultured myoblasts with human auto-antibodies, followed by bulk RNA sequencing

Pinal-Fernandez I, et al. medRxiv preprint doi: https://doi.org/10.1101/2024.01.15.24301339

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Pathogenicity of Auto-Antibodies

Results

- Auto-ab accumulation in myofibers within the same subcellular compartment as the autoantigen (e.g. nuclear for Mi2, PmScl, cytoplasmic for MDA5, aaRs, HMGCR; NXP2/TIFy although nuclear autoantigens dissociate into the cytoplasm)
- Associated with protein dysfunction (e.g. derepression of genes normally repressed by Mi2/NuRD, accumulation of RNAs degraded by the nuclear RNA exosome in patients with anti-PM/Scl auto-antibodies targeting this complex, activation of transcription of type IFNs by MDA5, overexpression of genes through aaR dysfunction in ASS, accumulation of lipids within myofibers of anti-HMGCR-positive patients)
- Transfected myoblasts recapitulated the transcriptomic phenotypes observed in human disease

Conclusion

- Auto-abs directly disrupt protein functions in muscle fibers, mechanism may be relevant in other tissues

Pinal-Fernandez I, et al. medRxiv preprint doi: https://doi.org/10.1101/2024.01.15.24301339

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Treatment

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Cellular Targeted Therapies – Clinical Trials

Target	Name	Trial	Phase	Results
B cells				
CD20	Rituximab	RIM	II	Negative
		RECITAL	II	Positive
		EvER-ILD	III	Positive
BAFF	Belimumab	NCT02347891	III	Negative
CD19	CAR T Cells	9 different trials	I/II	Recruiting
T cells				
CD80/CD86	Abatacept	ARTEMIS	II	Reassuring
		NCT02971683	III	Negative
		NCT03215927	II	In progress
Dendritic cells				
ILT7	Daxdilimab	NCT05669014	II	In progress

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Cellular Targeted Therapies – Additional Data

Rituximab

- Literature review: 48 studies (458 IIM patients): 78.3% rate of clinical response
- Meta-analysis of IIM-associated ILD: seven trials and 121 patients: overall improvement in 65%, complete response in 35%; improvement in muscle strength, skin involvement and pulmonary function
- Prospective study: 50 IIM patients: effectiveness of 86%, GC taper in 78.7%

Daratumumab

- Anti-CD38 monoclonal ab; 3 refractory cases with good response

CD19 CAR T Cells

- 3 patients with IIM; all had an ACR–EULAR major clinical response and normalization of CK levels after 3 months and maintained these responses; muscular functional normalized; extramuscular disease activity vanished

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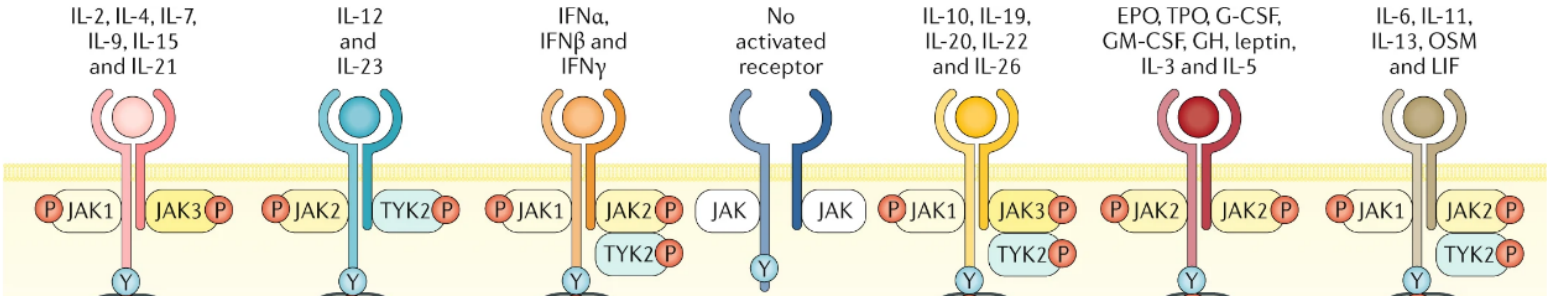
Small Molecules – Clinical Trials

Target	Name	Trial	Phase	Results
JAK1/3/(2)	Tofacitinib	NCT04966884	IV	Positive
JAK1/2	Baricitinib	NCT04972760	III	In progress
JAK1/TYK2	Brepocitinib	NCT05437263	III	In progress
TYK2	GLPG3667	GALARISSO	II	In progress



Salas, A et al. *Nat Rev Gastroenterol Hepatol* **17**, 323–337 (2020)

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Small Molecules – Additional Data

Recent meta-analysis on JAKi in IIM

- 7 publications with a total of 91 patients
- Ruxolitinib ≥ tofacitinib > baracitinib
- Effective regarding skin, muscle, and lung involvement

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Anti-Cytokine Therapies – Clinical Trials

Target	Name	Trial	Phase	Results
Cytokines				
Type I IFN receptor	Anifrolumab	NCT00979654	II	Negative
		D3463C00003	III	In progress
	PF-06823859	NCT03181893	II	Positive
IL-6	Tocilizumab	NCT04181762	II	Negative
IL-12/23	Ustekinumab	NCT03981744	III	Negative
IL-1	Anakinra	NCT01165008	II/III	Reassuring
IL-2	Aldesleukin	NCT05495321	III	In progress

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Anti-Cytokine Therapies – Additional Data

Anti-TNFα inhibitors

- Data from RCTs and open label studies conflicting; should not be used outside clinical trials

Tocilizumab (Anti-IL-6R)

- Data from open label studies rather disappointing; showed efficacy in small case series with refractory antisynthetase syndrome or rapidly progressing ILD (RP-ILD) or refractory IMNM

Anakinra (Anti-IL-1R)

- Used successfully in antisynthetase syndrome with myocardial involvement; systematic literature review identified 4 cases with improvement of muscular, lung and heart manifestations

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Diverse Targeted Therapies – Clinical Trials

Target	Name	Trial	Phase	Results
Complement pathway C5	Ravulizumab	NCT04999020	II/III	In progress
FC receptors FcRn	Nipocalimab Efgartigimod	NCT05379634 ALKIVIA	II II/III	In progress In progress

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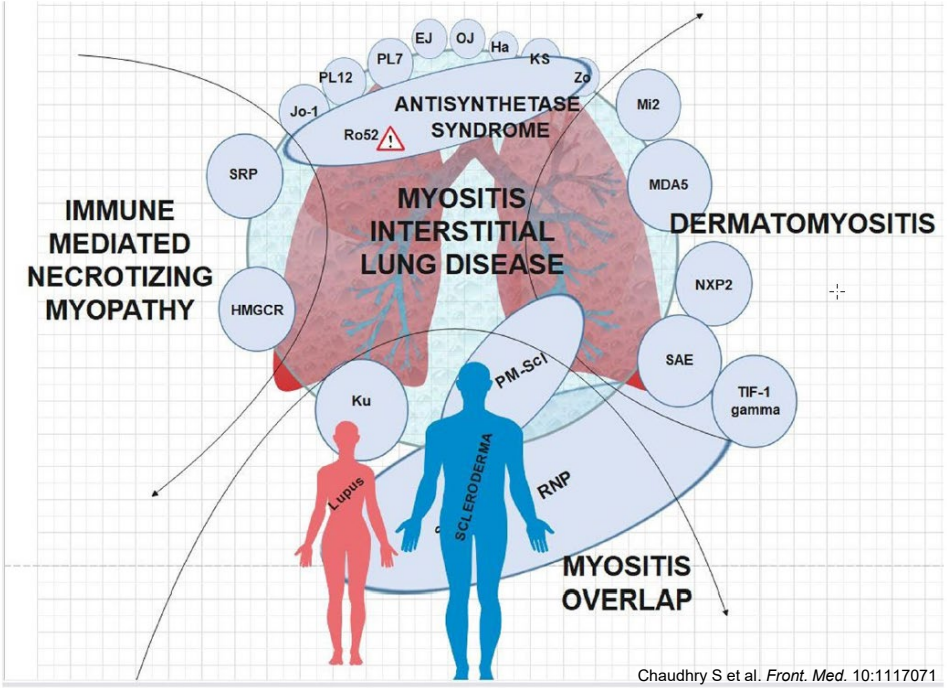
Anti-fibrotic Therapy in IIM-ILD



Chaudhry S et al. *Front. Med.* 10:1117071

- Nintedanib approved for patients with progressive fibrosing phenotype including patients with IIM-ILD (INBUILD trial)
- Pirfenidone may have survival benefit in subacute ILD
  - 2 trials in DM-associated ILD (NCT02821689, NCT03857854)

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Thank you for your attention!

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