# ACR 2017 SAN DIEGO HIGHLIGHTS - INFLAMMATORY MYOPATHIES

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Volos, 1-6-2018

- No disclosures

# Epidemiology

PM & DM

- Peak 5– 15 yrs & 30-50 yrs
- ♀ : ♂ = 2-3 : 1

IBM

- > 50yrs
- ♀ : ♂ = 1 : 3

# Current Classification

DM: Juvenile, Amyopathic.

Anti-synthetase syndrome

Necrotizing autoimmune: Statin, Malignancy, CTD - R

PM

Sporadic IBM

# ACR/EULAR 2017 Classification Criteria for Idiopathic Inflammatory Myopathies

| VARIABLE | SCORE POINTS | |
|---|---|---|
| | Without muscle biopsy data | With muscle biopsy data |
| 18 ≤ Age of onset of first symptom < 40 | 1.3 | 1.5 |
| Age of onset of first symptom ≥ 40 | 2.1 | 2.2 |
| **Clinical Muscle Variables** | | |
| Objective symmetric weakness, usually progressive, of the proximal upper extremities | 0.7 | 0.7 |
| Objective symmetric weakness, usually progressive, of the proximal lower extremities | 0.8 | 0.5 |
| Neck flexors are relatively weaker than neck extensors | 1.9 | 1.6 |
| In the legs proximal muscles are relatively weaker than distal muscles | 0.9 | 1.2 |
| **Skin variables** | | |
| Heliotrope rash | 3.1 | 3.2 |
| Gottron's papules | 2.1 | 2.7 |
| Gottron's sign | 3.3 | 3.7 |
| **Other Clinical Variables** | | |
| Dysphagia or esophageal dysmotility | 0.7 | 0.6 |
| **Laboratory Variables** | | |
| Elevated serum levels of creatine kinase (CK) or, Serum lactate dehydrogenase (LDH) or, Serum aspartate aminotransferase (ASAT) or, Serum alanine aminotransferase (ALAT) | 1.3 | 1.4 |
| Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity | 3.9 | 3.8 |
| **Muscle Biopsy Variables** | | |

# Myositis-specific antibodies and phenotype

| ANTIBODY | DISEASE ASSOCIATION | PREVALENCE |
|---|---|---|
| Anti-tRNA synthetases (Jo-1) | PM & DM, interstitial lung disease, "mechanic's hands"<br>Moderate response to RX | 25% |
| Anti-SRP (signal recognition protein) | PM acute onset/severe weakness; poor prognosis | 5% |
| Anti-Mi-2 | Older women, "shawl sign," good prognosis | 9-24% |
| PM/SCL | Polymyositis/scleroderma overlap | Rare |
| Anti-Mas | PM with rhabdo; chronic hepatitis | Rare |

# Anti-tRNA synthetase antibodies (ASA)

- Anti-Jo-1 (histidyl) 15-20% PM/DM
  - More myositis-specific
- Anti-PL-7 (threonyl) -17% of Japanese
- Anti-PL-12 (alanyl)
- Anti-EJ (glycyl)
- Anti-OJ (isoleucyl)
- Anti-KS (asparaginyl) 8 pts; 7/8 ILD
- Anti-ZO (phenylalanyl
- Anti-YRS (tyrosyl) most recent
- 99.9% of time only one of these but clinically similar

# Other Myositis specific abs

- **Anti-Signal recognition protein:** 4-6% IIM or necrotizing // severe disease or slowly progressive (little inflam, inner organ, CS-resistant, RA or SSc assoc) // disease activity???

- **Anti – MDA5 (melanoma differentiation gene 5):** Amyopathic DM + ILD + ↑↑ ferritin = poor prognosis

- **Anti – HMGCR:** necrotizing // statin assoc

- **cN1A:** 1/3 IBM, Sjögren, 1/5 SLE, 0-5% PM

# MRI

| T1 | T2 - STIR |
| --- | --- |
| Anatomy | Less clarity |
| Atrophy | Activity |
| Bone = dark | |
| **Light** = Fat, inflammation, edema | **Light** = active inflammation |
| **CHRONICITY** | **DISEASE ACTIVITY** |

# MIMICS

- Endocrine myopathies
  - hyper/hypothyroid, Acromegaly, Cushing's, Addison's, Hyper/hypocalcemia
- Drug or toxic myopathies
  - alcohol, colchicine, statins, chloroquine, amiodarone, etc.
- Metabolic myopathies – glycogen storage
- Mitochondrial myopathies
- Muscular dystrophies
  - Limb-girdle esp type 2B (dysferlinopathy)
  - Dystrophinopathy (Becker's and Duchenne's)
  - Facioscapulohumeral dystrophy
  - Myotonic disease
- Infectious myositis – viral, bacterial, parasites
- Neuropathies/neurologic syndromes – ALS, GBS, CIDP, MG
- Paraneoplastic syndromes
- Other connective tissue disorders
- Miscellaneous
  - amyloid, sarcoid, microemboli

Mammen, Curr Opin Rheum, 2017

# Corticosteroids

- **P.os:** No controlled trials, 25 % remission in 11 mo vs 75% of second-line on 2 yrs
- 1mg/kg/d – Max 80 mg
- No split unless needed
- Tapering?
- **I.V. :** 500 – 1000 mg x 3 / 5 d??? = ↑↑ CK, weak, dysphagia, lung.
- **Dissociative Cs = Vemorolone:** No Osteoporosis, adrenal, phase II Duchene

Mathur et al Am J Ther 22: 350-354, 2015

# 2nd line = When?

- Severe weakness
- Myocarditis, ILD
- CS Side effects risk: DM, Osteoporosis, Menopause, NeuroPs
- Relapse during CS
- Difficult to treat: Necrotizing

# Usual 2nd line

- HCQ
- AZA: 2mg/kg/d, TPMT ahead
- MTX: 10-30 mg/wk p.os / s.c.
- **IVIG:** Efficacy study-proven (Dalakas 1993), no side effects, safe & effective.

i. Steroid sparing if infection
ii. JDM
iii. Proximal dysphagia
iv. Acute worsening
v. Difficult rash

# 2nd line continues…

- **Mycophenolate mofetil:** 2-3 g/d, inhibits B- and T- cell prolif. by blocking purine synthesis
- 6/10 tapered CS (risk opportunistic inf) – ILD & CYC related (1) **but** skin improvement 10/12 (2), safe & effective (3)
- **Calcineurin inh: CIS** 3,5 mg/kg /d, case reports, **Tacrolimus** – review 2015 (4)
- **Cyclophosphamide:** Rapidly progressive ILD, vasculitis – Comb with RTX anti – synthetase & ILD (5)
- **Infliximab:** NIH – 40 wk, blinded 5mg/kg, non- resp =7,5 mg/kg. Placebo → INF after 16 wk.
- 3/6 INF pts MMT-8 improve at 16 wks, 0/6 placebo. Totally 4/12 at 40 wks.


(1) Rowin, Neurology, 2006
(2) Edge, Arch Derm, 2006
(3) Swigris, Chest, 2006
(4) Yonpeng G et al, Clin Rheumatol 34: 2097-2103, 2015
(5) Andersson H et al, Rheumatology54: 1420 – 1428, 2015

# RTX

- 6/7 DM pts, lonstanding, resistant. Open label, i.v.= myositis, rash, alopecia, ILD improvement, no serious AEs.(1)
- **RIM:** 76 DM / 76 PM, 48 JDM. 80% > 1 ab. 83% improvement wk 44, no difference in time.

- Refractory disease: 750 – 1000 mg q2w x 2 doses, repeat q 6-18 mo if worsening and/or ↑↑ CK.(2)

(1) Levine, Arth Rheum, 2015
(2) Fasano et al, Rheumatology , 2016

# Other Biologics

- Abatacept- case reports of effectiveness in refractory sick patients. Trial - ARTEMIS
  - Kerola A, Kauppi M. Clin Rheumatol 34:609-612, 2015
- Alemtuzumab – anti CD 52 – unlikely to be studied further – very suppressive
- Sifalimumab
  - Early studies of this anti-IFN-α
  - Suppressed IFN signature and correlated with clinical improvement
- Ruxolitinib
  - Janus kinase inhibitor
  - Case report in refractory DM
  - Pt had partial response to steroid, aza, IVIg and myophenolate
  - Had JAK2 mutation assoc myeloproliferative neoplasm.

# Calcinosis

## Risk factors

- Duration untreated
- Active disease
- Genetics: TNF–a–308A promoter, high TNF levels
- Race?
- Minor trauma (case reports)

## Medication - reports

- Probenecid: 250-500 mg qid
- Triamcinolone inj: In deposits
- Aluminum hydroxide: 15-20 ml TID – QID
- IVIG: 3 pts, 2m/kg/mo x 3-6 mo
- CIS: 3 pts, 5-6 mg/kg/d x 3-6 mo
- IFX: 2 pts, 3-5 mg/kg x 2-10 mo
- Colchicine: infl, not deposits – 0,5 TID / QID
- Diltiazem: 240–480mg QD
- Abatacept
- Sodium thiosulphate
- Biphosphonates?

# Malignancy and myositis

- **Incidence: DM**: 6-45%, (recent 14,8% - SIR 4,66), **PM** 0-28% (recent 9,89%, SIR 1,75)
- RR: ♂ DM 5,29, PM 1,62 ♀ DM 4,56, PM 2,02
- Ovarian, stomach overrepresented
- 1-2 yr time frame: before, same time or follow
- ↑↑↑ >50 yr, DM sine myositis, necrotizing, abs protein 155 (TIF 1-γ)
- ↓↓↓ If Abs, ILD, associated CTD

Quiang et al. Risk of malignancy in DM and PM: A systemic review and meta-analysis. J Cutan Med Surg 2017 21 (2) 131-136

# Malignancy associated

- Rapid onset, biopsy necrotizing, high CKs. Raynaud (-).
- Blind work up 10-15% // CT 25-30% // PET equivalent (small study) // surgery??

# Inclusion Body Myositis

- Refractory PM
- ♂, elderly
- Insidious, painless, muscle weakness, slow progression
- Distal, asymmetric muscle involvement (foot drop).
- Proximal dysphagia – cricopharyngeal achalasia?
- Forearm flexors, quadriceps, intrinsic muscles of hands

# IBM treatment

- Refractory
- PZN, MTX, AZA: small reports
- 3 mo IVIG in severe dysphagia??? (short term meds)
- **RecentTrials:**
- Oxandrolone 5mg bid - WBC, LFTs, PSA check
- Arimoclomol in mice = disappointing in humans
- Myostatin targeting degeneration = disappointing
- **Follistatin** , myostatin-like = further investigation needed

Schmidt, Curr Opin Rheumatol, 2017

# Statin myopathy prevention

- Use lower doses
- Carefully to elderly, women
- DM, CRF pts at higher risk : withhold dose during major surgery
- Check drug interactions

# Necrotizing Autoimmune Myopathy

- Macrophage mediated autoimmune response
- Usually have anti –SRPs
- Have anti –HMG-CoA R: though not all exposed to statins (!!), no improvement in symptoms after statin stop as expected if statin induced
- Necrosis >>inflammation
- Treatment: CS, MTX, AZA< MMF, IVIg

Troyanov et al. Atorvastatin-induced necrotizing autoimmune myositis. An emerging dominant entity in patients with autoimmune myositis presenting with a pure polymyositis phenotype. Medicine 2017 96:3

# ↑↑ CK without myopathy

- **Race:** B>W, ♂>♀
- **Exercise:** 8-24 hrs after, baseline 72 hrs later / intensity, duration, higher in utrained / LFTs & LDH rise / can be asymptomatic
- **Muscle injury:** IM injection, EMG, surgery
- **Motor neuron disease:** ALS, spinal muscular atrophy
- Metabolic myopathies or dystrophies
- Occupation
- Idiopathic hyper CKmias

# TIPS

- PM = very low incidence, almost exclusion diagnosis!
- Finger flexor weakness = usually in IBM, rare in IIM.
- Quick control = x10 rising from chair / Baseline can be 0 / Pts are their own control!

Am J Med 78:77-81, 1985

- Jo -1 synthetase abs = in longstanding disease better answer to treatment
- Hypo >> hyper, check even if TSH normal!

# TIPS TREATMENT I

- Usually DMARDs added right away!
- **RTX - IVIG** with 2-3 weeks interval = one drug negates the other!
- TPMT predicts **only** bone-marrow originated toxicity, not peripheral.
- **Tacrolimus:** 10mg x 2 and up titrating, don't check levels
- **CYC**: 3 doses of the EURO-LUPUS regimen / can be used in ILD deteriorating, then switch to MMF.
- **TNFi come back:** INF, ADA.

# TIPS TREATMENT II

- **RTX:** RA regimen = 1g with 15 days interval, repeat every 6-8 mo **if** ↑↑ CPK, symptoms.
- **HCQ:** Skin not muscle
- **Bisphosphonates:** Careful in children
- **Minocycline:** No data in IIM

- **No response:** Change medication
- **Partial response:** Add on a smaller dose

# DD

- **Statin-induced myopathy:** switch to pravastatin = no muscle infiltration, but less effective.
- Statins can be used in IIM.
- Rest 3 days after exercise / few days after i.m. injection to repeat CK.
- Don’t forget idiopathic ↑↑ CK

# ACR 2017 SAN DIEGO HIGHLIGHTS - AUTOINFLAMMATORY

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# NF-kb mediated autoinflammatory disease

- Autosomal dominant
- Loss of function of A20 → NF-kb
- 7 families with 17 pts
- Polyarthritis, recurrent fever, ulcers, pericarditis
- HLA – B51 = 2/5 tested
- Early onset (<10yrs)
- Remitting/relapsing course

# JAK kinases in IFN-mediated

- Mendelian Autoinflammatory Interferonopathy
- CANDLE = Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature syndrome
- SAVI = STING (beta interferon)-associated vasculopathy with onset in infancy: protein from TMEM173 gene, mutation & gain of function

- **Baricitinib:** <20kg = 6mg TID, 20-40kg = 6mg BID, >40kg= 8mg BID
- ↓↓ IFNα-stimulated STAT-1 phosphorylation in a dose-dependent manner.
- More frequent dosing = half life shorter than in adults
- Need for higher doses

# CLUSTER study: Canakinumab in colchicine resistant FMF, HIDS, MKD, TRAPS

- Classic TRAPS = all responders.

# Serum IL-18 as biomarker sJIA & MAS / Recombinant 18BP

- IL-18 as IL-1 positive feedback loop
- Tadekinig alpha=recombinant binding protein of IL-18, given in 2 mg/kg dose every 48hrs despite continuous IL-1 inhibition.
- > 50% PZN reduction

- 5 yr old boy, 2 MAS episodes, easily controlled with methylprednisolone.
- Lung involvement, therapy discontinued. Severe MAS!

# Ferritin to ESR ratio: MAS vs sJIA flare

| Ferritin | ↑↑↑ MAS | ↑ sJIA |
|---|---|---|
| ESR | ↓↓↓ MAS | ↑↑ sJIA |

- ESR elevated in coagulopathy, fibrinogenemia
- 2016 EULAR/ACR sJIA/MAS criteria

- Cut point 21.5 = sensitivity 82%, specificity 78%

# Microbiota

- Dysbiosis caused by antibiotics = decreased diversity, competition,function
- Finn study: Clindamycin stronger correlated.
- Breast fed and older siblings-bifidobacteria (more beneficial).
- Antibiotics >> Siblings >> Caesarian > Breast fed

- ERA: ↑ Bacteroides, Enterococcus, Klebsiella, ↓ Prevotella
- Why? Immune process, dysregulation, treatment effect, dietary changes?
- Increased intestinal permeability in JIA, SpA, IBD.


Thank you!
SAMSUNG
5 STAR
NO