Teaching Course: Neuromuscular diseases: Advances in the diagnosis and treatment of immune-mediated neuromuscular disorders, WCN 2019

The role of auto-antibodies in idiopathic inflammatory myopathies.

Kristl Claeys

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Kristl.Claeys@uzleuven.be

UZ Leuven | Herestraat 49 B - 3000 Leuven | www.uzleuven.be tel. +32 16 33 22 11 | UNIVERSITY HOSPITALS LEUVEN

Learning objectives

- Auto-antibodies and muscle biopsy are important in the diagnosis of IIM, with direct prognostic relevance and direct impact on therapeutic decisions, e.g.:
  - No therapy in sIBM
  - Search for tumour in DM, search for ILD in ASS, etc.

- Inflammatory myopathy can occur without the presence of inflammatory infiltrates in muscle tissue (NAM)
  Role of myositis-specific antibodies
  DD muscular dystrophy !
  Treatment !

- Inflammatory infiltrates in muscle tissue are not necessarily due to myositis, but can occur in other (hereditary) muscle diseases (e.g. FSHD, LGMD R2: No treatment)

Idiopathic inflammatory myopathies (IIM)

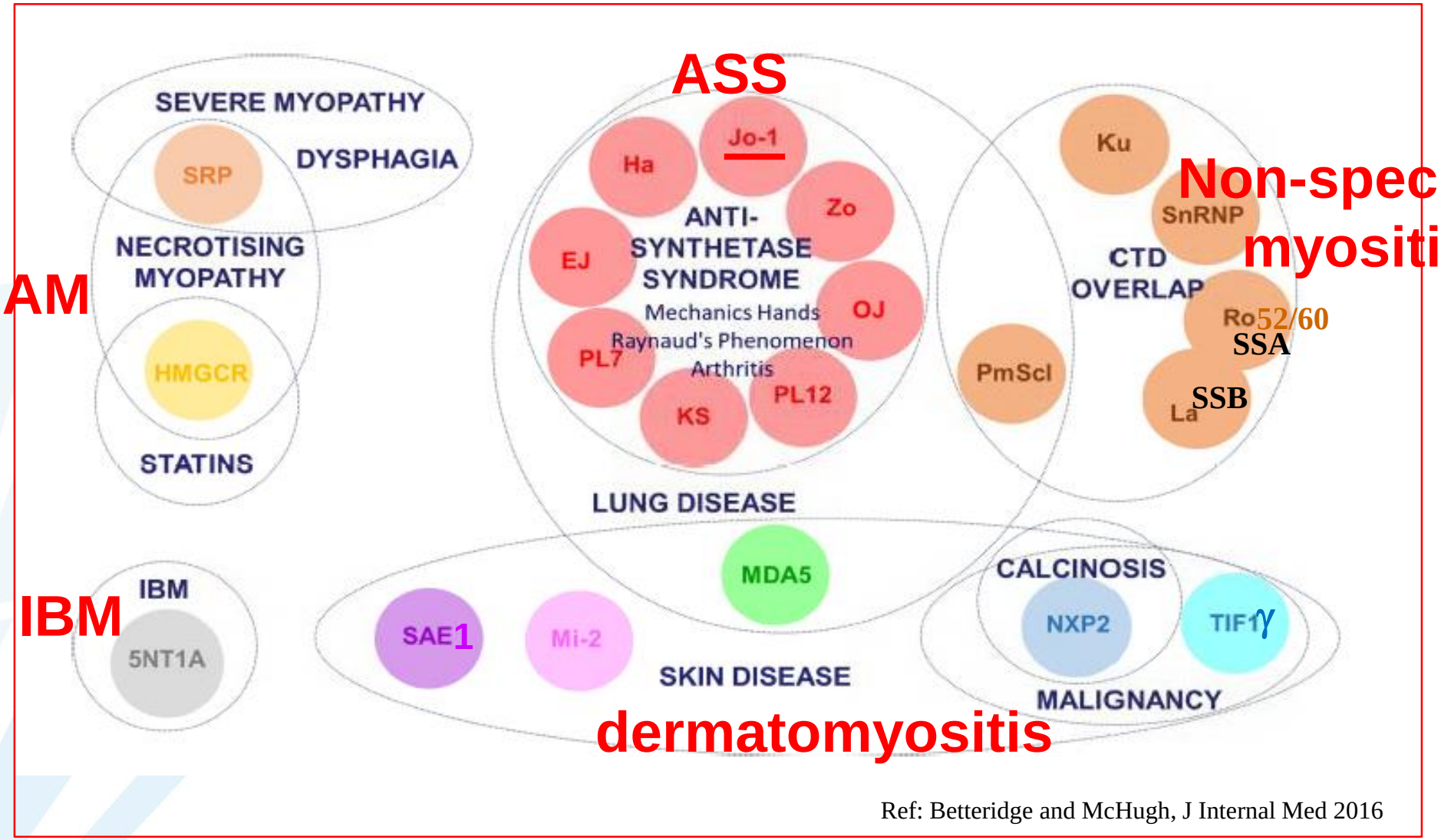
- **Heterogeneous** group of rare **autoimmune** diseases affecting **skeletal muscles**

  But also various other organs may be involved (skin, lung, heart, joints)

- **Classifications:**
  - Bohan and Peter (1975): **PM** and **DM**
  - Griggs and Askanas (1991): **IBM**
  - Love (1991): first attempt to classify myositis based on **MSAs**
  - Troyanov (2004): novel serological classification of IIM
    myositis-specific antibodies (**MSAs**)
    incl. anti-synthetase syndrome (**ASS**)
  - ENMC (2004): clinico-pathological criteria,
    necrotizing autoimmune myopathy (**NAM**)
  - Pestronk criteria (2011): histopathological classification
  - EULAR-ACR classification (2017)

Auto-antibodies in IIM

- Myositis-**associated** antibodies (**MAA**): also in systemic diseases (CTD)
  - Myositis-**specific** antibodies (**MSA**): specific for IIM



Ref: Betteridge and McHugh, J Internal Med 2016

Classification in IIM

Classification in 5 groups:

- Dermatomyositis
- Non-specific (‘overlap’) myositis
- Antisynthetase syndrome (ASS)
- Necrotising auto-immune myopathy (NAM)
- Inclusion body myositis (IBM)

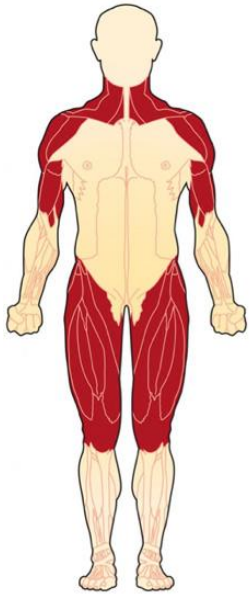
Importance of classification in IIM

Importance of classifying IIM:

- Distinct diseases
- Distinct pathomechanisms
- Different risks of associated cancer
- Different comorbidities
- Different responses to immunosuppressive treatment
- Different prognosis
- Improving stratification in clinical trials
- Facilitating diagnosis in atypical cases

Dermatomyositis: Summary

- Adults (DM), children (JDM); F > M
- **Subacute** onset (weeks to months)
- **Symmetrical** and **proximal** muscle **weakness** ± myalgia



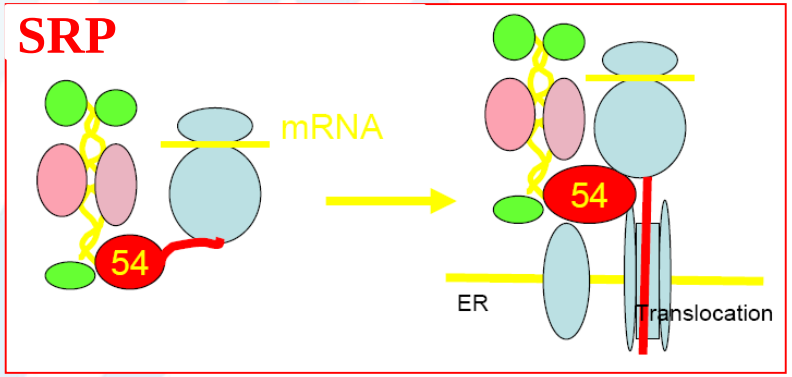
- Involvement of other organs possible:
  - Skin changes
  - Interstitial lung disease (ILD)
  - Pericarditis
  - Dysphagia

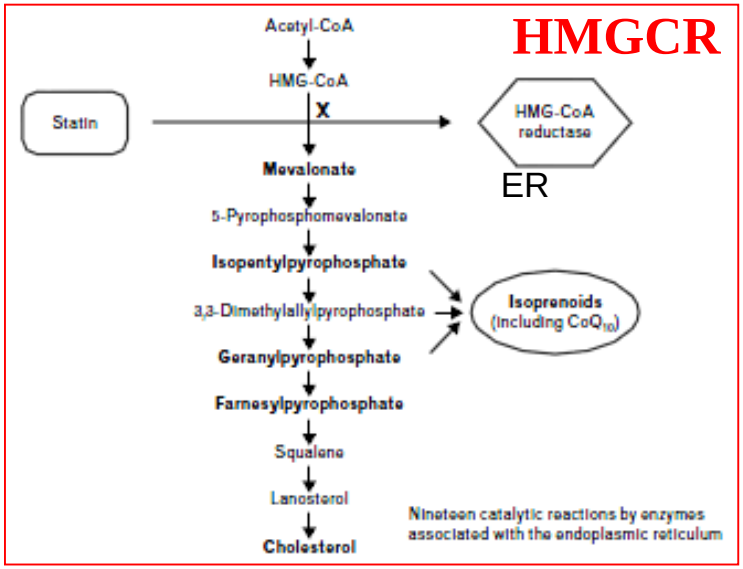
- **Serum-CK**: 1-50N
- Presence of **MSAs** (TIF1γ, NXP2, Mi2, SAE1, MDA5): 50-80%
- Association with **malignancy** possible (DM 6-45%; TIF1γ, NXP2)

- **Treatment**: steroids, immunosuppressive therapy

Necrotizing auto-immune myopathy: summary

- NAM, also: immune-mediated necrotizing myopathy (IMNM)
- 20% of IIM
- Antibodies against:
  - ✓ **SRP** = signal recognition particle
  - ✓ **HMGCR** = 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase (65% use of statins)
  - ✓ 30-40%: AB not known





Necrotizing auto-immune myopathy: summary

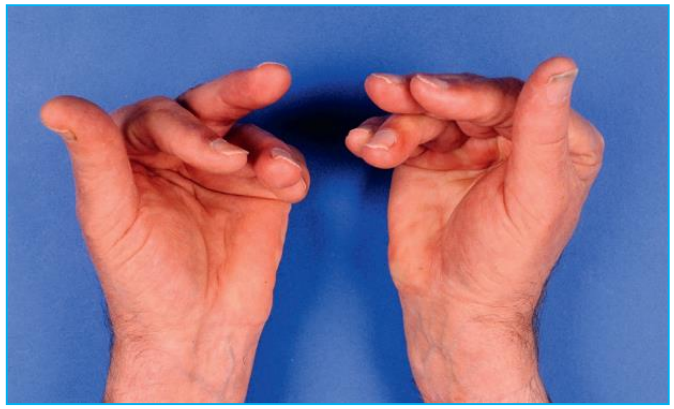
- Subacute progressive symmetrical proximal muscle weakness ± myalgia
- Dysphagia, ILD (SRP), cardiac (SRP)
- Association with malignancy possible (SRP 5%)
- **Very high serum-CK** (3000-25000 U/l)
- Muscle biopsy: **necrosis, no inflammatory infiltrates !**
- DD rhabdomyolysis, hereditary muscular dystrophies, toxic myopathies !
- Immunosuppressive **therapy** (often resistant)

Antisynthetase syndrome (ASS): summary

- Antibodies against aminoacyl-tRNA-synthetases:
  - 25-30 % of IIM
  - **Jo1** (histidyl), PL-7, PL-12, EJ, OJ, KS, Zo, Ha
- Clinical presentation ASS:
  - ◊ Myositis
  - ◊ Non-erosive arthritis
  - ◊ Mechanic's hands
  - ◊ Interstitial longfibrosis (ILD); 70-89% (anti-Jo1)
  - ◊ Cardiac involvement
  - ◊ Raynaud phenomenon
  - ◊ Fever, weight loss
- Association with malignancy possible (Jo1: 12%)
- Immunosuppressive **therapy** (often resistant)

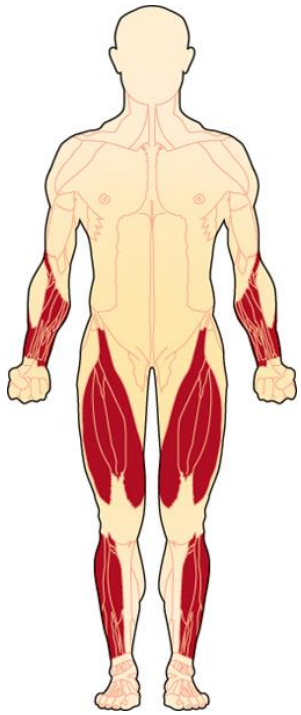
Inclusion body myositis (IBM): summary

- Onset mainly > 50 y; M >> F
- Chronic progressive weakness of
  quadriceps, **finger flexors**,
  foot dorsiflexors
- Often asymmetrical
- **Dysphagia (>>>)**

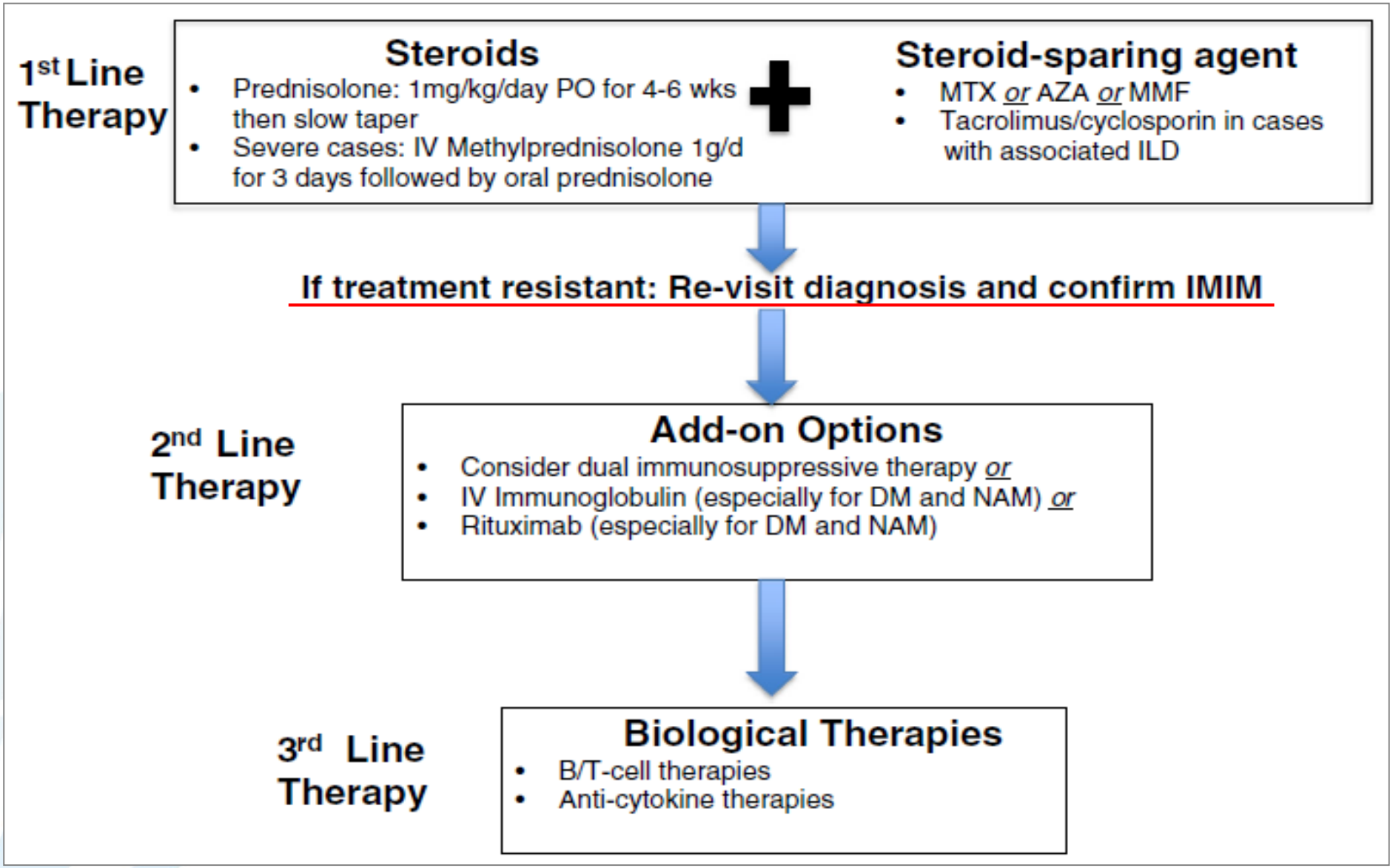


- Serum-CK: 1-12N
- Presence of **NT5C1A-antibodies** in 34%
- No association with cardiac involvement or ILD
- No association with malignancy

- **NO treatment !**



Treatment of IIM (except IBM): Overview



Ref: Needham and Mastaglia, Neurotherapeutics 2016

Differential diagnoses of IIM

- Vascularitis, CTD
- Viral/bacterial/fungal myositis
- Granulomatous myositis
- Polymyalgia rheumatica
- Limb-girdle muscular dystrophies (LGMD)
- Facio-Scapulo-Humeral muscular dystrophy (FSHD)
- Toxic myopathies
- Metabolic / Mitochondrial myopathies
- Myofibrillar myopathies, hereditary IBM (GNE, VCP)
- …

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