Understanding necrotizing myopathy

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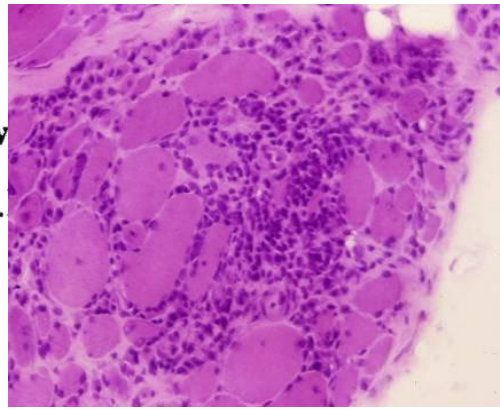
First myositis classification

344 THE NEW ENGLAND JOURNAL OF MEDICINE February 13, 1975

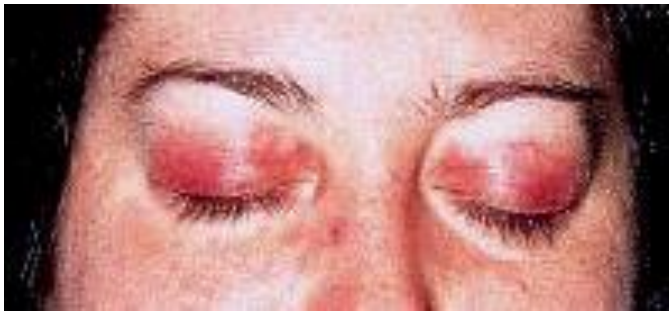
MEDICAL PROGRESS

POLYMYOSITIS AND DERMATOMYOSITIS (First of Tw

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



1. Symmetrical proximal muscle weakness;
2. Muscle biopsy abnormalities :
    1. Muscle fiber destruction and regeneration;
    2. Perivascular and interstitial inflammatory infiltrates with muscle fiber destruction.
3. Elevation of CPK, Transaminases, LDH or aldolase activity;
4. Myogenic electromyography changes;
5. Typical skin rash.



- DEFINITE: any 4 of the criteria
- PROBABLE: any 3 of the criteria

NEUROLOGICAL PROGRESS

Inclusion Body Myositis and Myopathies

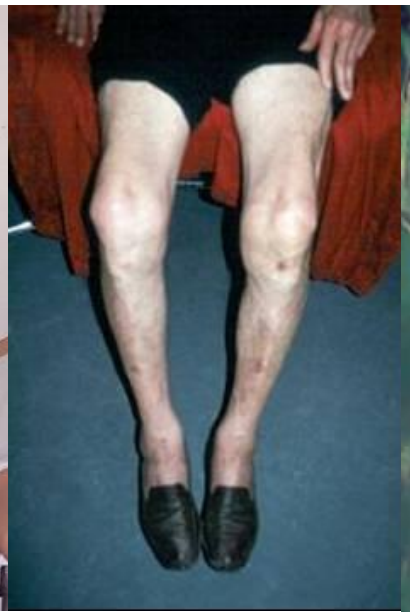
Robert C. Griggs, MD,* Valerie Askanas, MD, PhD,† Salvatore DiMauro, MD,‡ Andrew Engel, MD,§ George Karpati, MD,¶ Jerry R. Mendell, MD,** and Lewis P. Rowland, MD††

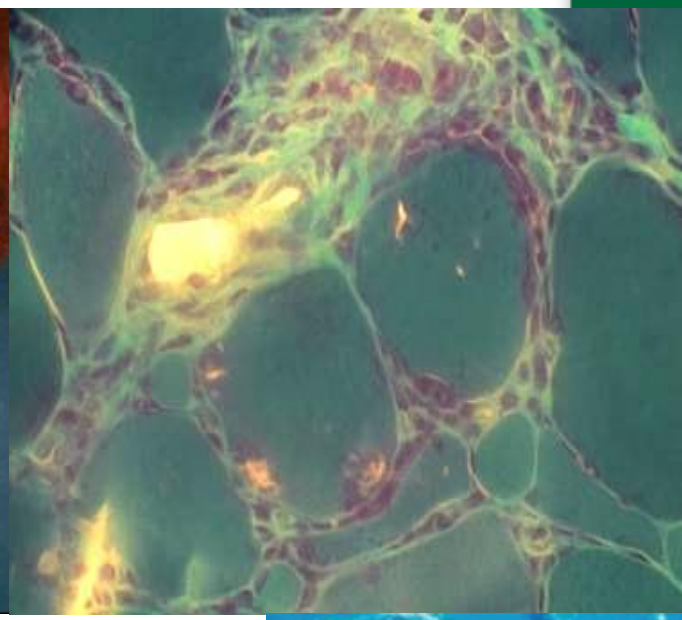
Neurology, 1995

Neurology 2014

Evaluation and construction of diagnostic criteria for inclusion body myositis

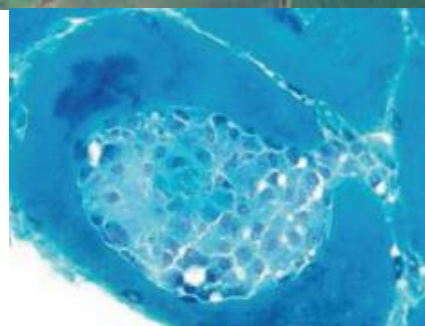
Thomas E. Lloyd, MD, PhD
Andrew L. Mammen, MD, PhD
Anthony A. Amato, MD
Michael D. Weiss, MD
Merrilee Needham, MBBS
Steven A. Greenberg, MD





- Finger flexor **or** quadriceps weakness, **and**
- Endomysial inflammation, **and**
- Invasion of nonnecrotic muscle fibres **or** rimmed vacuoles

→ 90% sensitivity and 96% specificity



IMNM

PERGAMON

Neuromuscular Disorders 14 (2004) 337–345

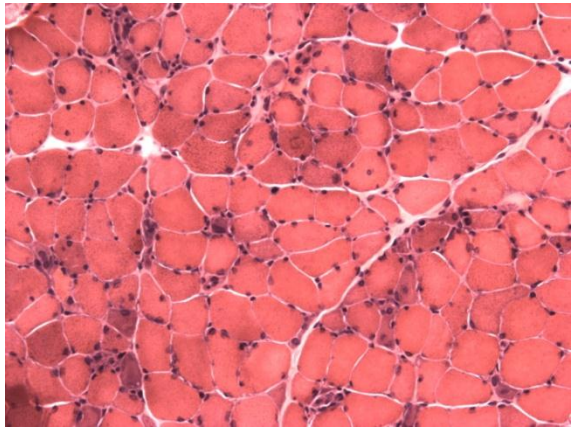
www.elsevier.com/locate/nmd

Workshop report

119th ENMC international workshop: Trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, The Netherlands

Jessica E. Hoogendijk[a,*], Anthony A. Amato[b], Bryan R. Lecky[c], Ernest H. Choy[d], Ingrid E. Lundberg[e], Michael R. Rose[f], Jiri Vencovsky[g], Marianne de Visser[h], Richard A. Hughes[i,1]

Immune-mediated necrotizing myopathy



1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3) EMG, MRI, auto-Abs
4. Muscle biopsy criteria include *g*, and exclude all others

Necrosis + regeneration without inflammation

2017 European League Against Rheumatism/ American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups

Table 1 Demographic data of the International Myositis Classification Criteria Project cohort

	IIM (n=976)	Comparators (n=624)
Sex, n (%)		
Female	652 (66.8)	369 (59.1)
Male	324 (33.2)	255 (40.9)
Adult onset disease*, n (%)	727 (74.5)	509 (81.6)
Childhood onset disease*, n (%)	249 (25.5)	115 (18.4)
Age at onset of symptoms, median (IQR), years	44.0 (14.7–57.0)	41.0 (20.0–56.0)
Age at diagnosis, median (IQR), years	45.5 (16.2–59.3)	45.0 (25.8–58.0)

- One unique MSA: anti-Jo1
- 3 subgroups: (J)DM, PM, IBM

Table 4 Performance of the EULAR/ACR classification criteria for IIM and existing classification and diagnostic criteria for IIM

Performance (%)	EULAR/ACR classification criteria for IIM*		Bohan and Peter† [7 8]	Tanimoto *et al*† [10]	Targoff *et al*† [11]	Dalakas and Hohlfeld† [14]	ENMC Hoogendijk *et al*† [15]
	Without muscle biopsy	With muscle biopsy					
Mean (95% CI)							
Sensitivity	87 (84 to 90)	93 (89 to 95)	98 (96 to 99)	96 (94 to 97)	93 (90 to 95)	6 (5 to 8)	52 (48 to 55)
Specificity	82 (77 to 87)	88 (83 to 93)	55 (50 to 61)	31 (25 to 37)	89 (84 to 92)	99 (98 to 100)	97 (95 to 98)

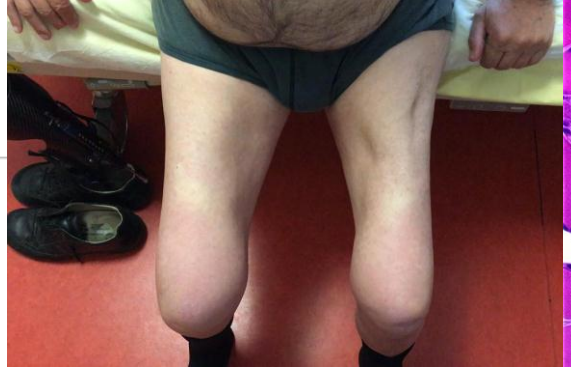
www.imm.ki.se/biostatistics/calculators/iim

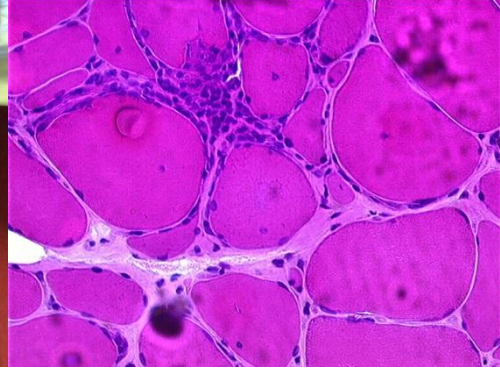
Classification Criteria for Idiopathic Inflammatory Myopathies

About the Criteria | About the Webcalculator | Download Excel Worksheet

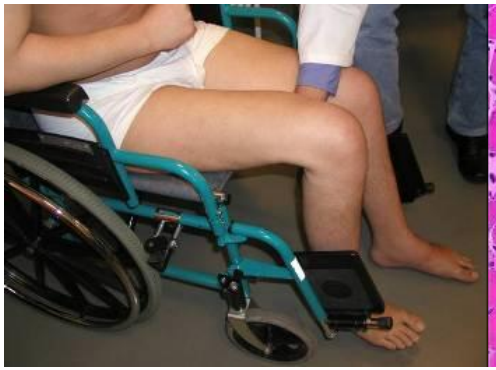
Score range	0 – 20.7
Probability (min – max)	0 – 100%
Classification	
Subgroup	

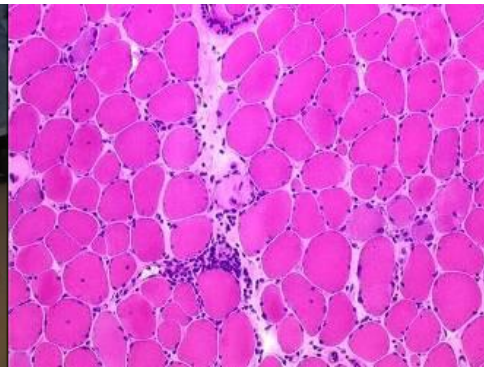
		Yes	No
Age of onset of first symptom	0 – 17	☐	
	18 – 39	☐	
	40+	☐	
Objective symmetric weakness, usually progressive, of the proximal upper extremities		☐	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities		☐	☐
Neck flexors are relatively weaker than neck extensors		☐	☐
In the legs proximal muscles are relatively weaker than distal muscles		☐	☐
Heliotrope rash		☐	☐
Gottron's papules		☐	☐
Gottron's sign		☐	☐
Dysphagia or esophageal dysmotility		☐	☐
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity		☐	☐
Elevated serum levels of creatine kinase (CK) or lactate dehydrogenase (LDH) or aspartate aminotransferase (ASAT/AST/SGOT) or alanine aminotransferase (ALAT/ALT/SGPT)		☐	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		☐	☐





1) 74 yo man with proximal and distal weakness with dysphagia, invaded fibers but no vacuoles at the muscle biopsy.
Score of 7, with a probability of 64% : IIM type PM.
But IBM!





2) 22 yo man with proximal weakness, with endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers.
Score of 9.2, with a probability of 94%: definite IIM subtype PM.
But dysferlinopathy (LGMD2B)!

Actual classification of myositides

- Dermatomyositis, 30% paraneoplastic
- Inclusion body myositis

- Polymyositis

- Overlap myositis (Troyanov)
  - Myositis associated to a connective tissue disease
  - Myositis with associated Abs (PmScl, Ku …)
  - Myositis with specific Abs (anti-synthetases, anti-SRP…)
- Immune mediated necrotizing myopathies (Hoogendijk) with anti-SRP+, anti-HMGCoA Reductase+ (post-statines), or paraneoplastic

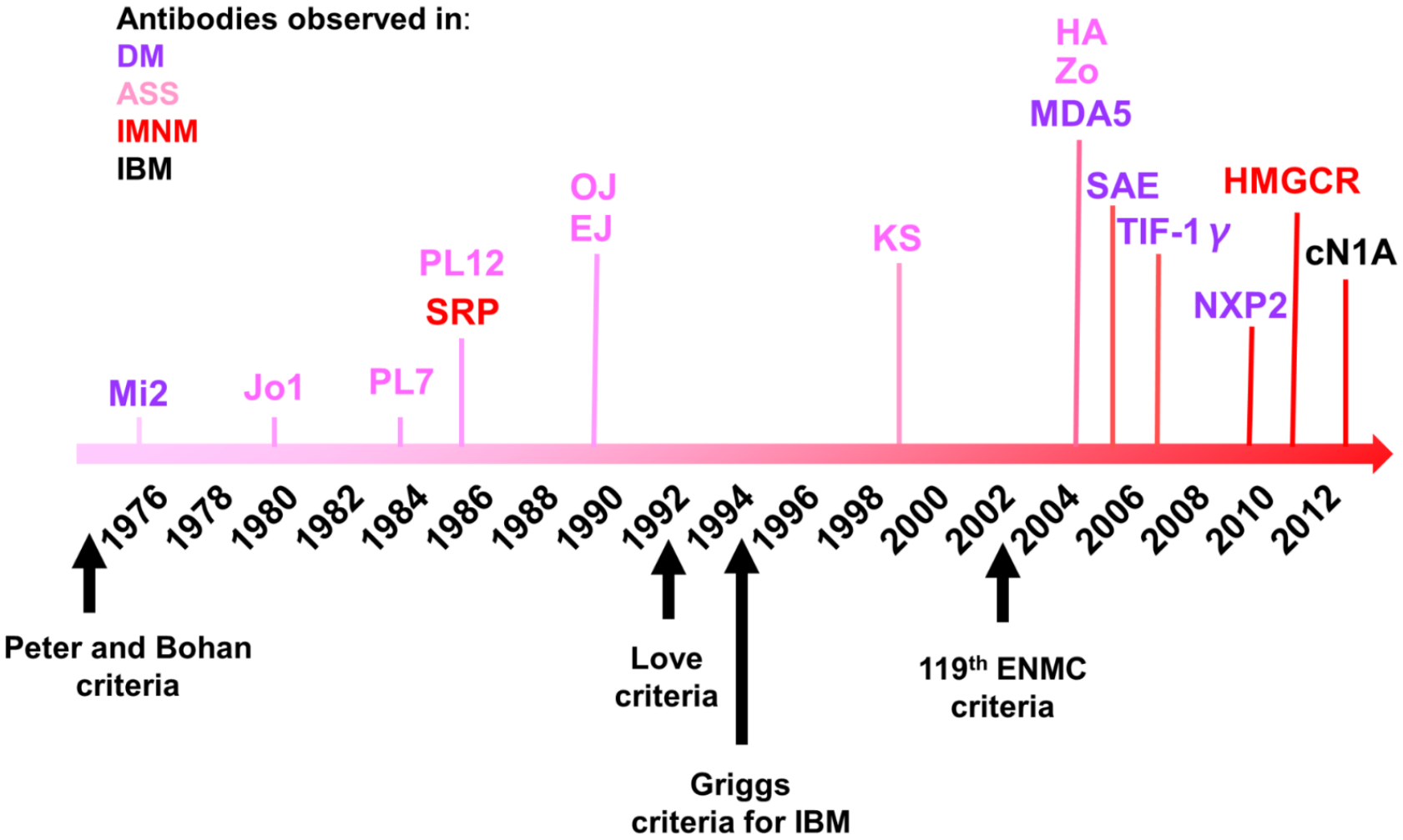
CME

Polymyositis

An overdiagnosed entity

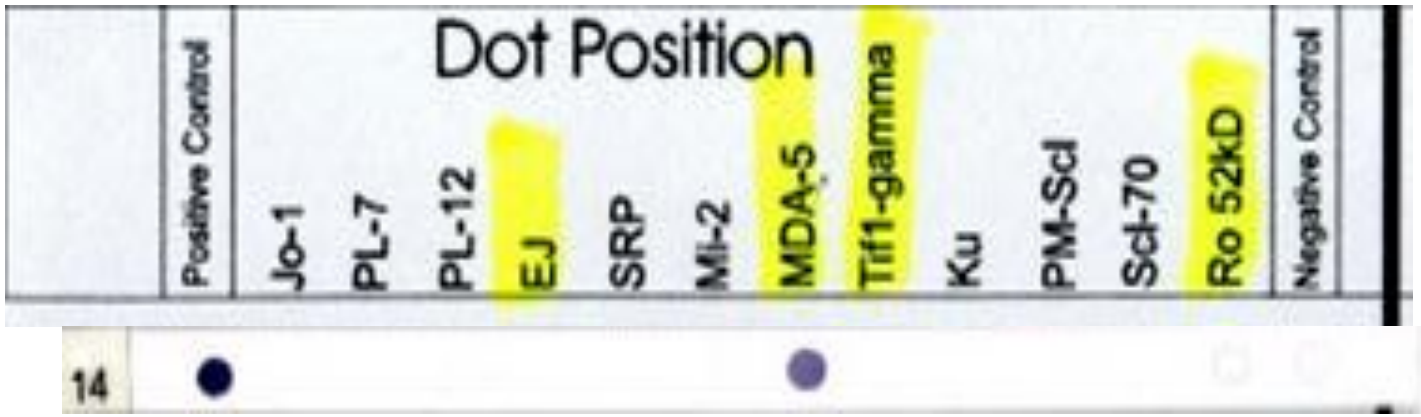
M.F.G. van der Meulen, MD; I.M. Bronner, MD; J.E. Hoogendijk, MD, PhD; H. Burger, MD, PhD; W.J. van Venrooij, PhD; A.E. Voskuyl, MD, PhD; H.J. Dinant, MD, PhD; W.H.J.P. Linssen, MD, PhD; J.H.J. Wokke, MD, PhD; and M. de Visser, MD, PhD

Myositis specific auto-antibodies

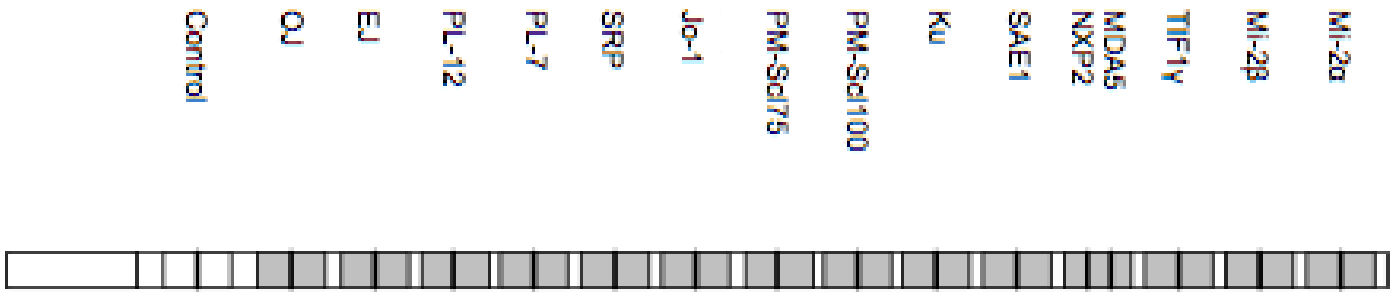


Benveniste, Curr Opin Neurol, 2016

Commercial line dot assays



12 Abs



15 Abs

Clinic Rev Allerg Immunol
DOI 10.1007/s12016-015-8510-y

A Comprehensive Overview on Myositis-Specific Antibodies: New and Old Biomarkers in Idiopathic Inflammatory Myopathy

Minoru Satoh[1] · Shin Tanaka[2] · Angela Ceribelli[3,4] · S. John Calise[5] · Edward K. L. Chan[5]

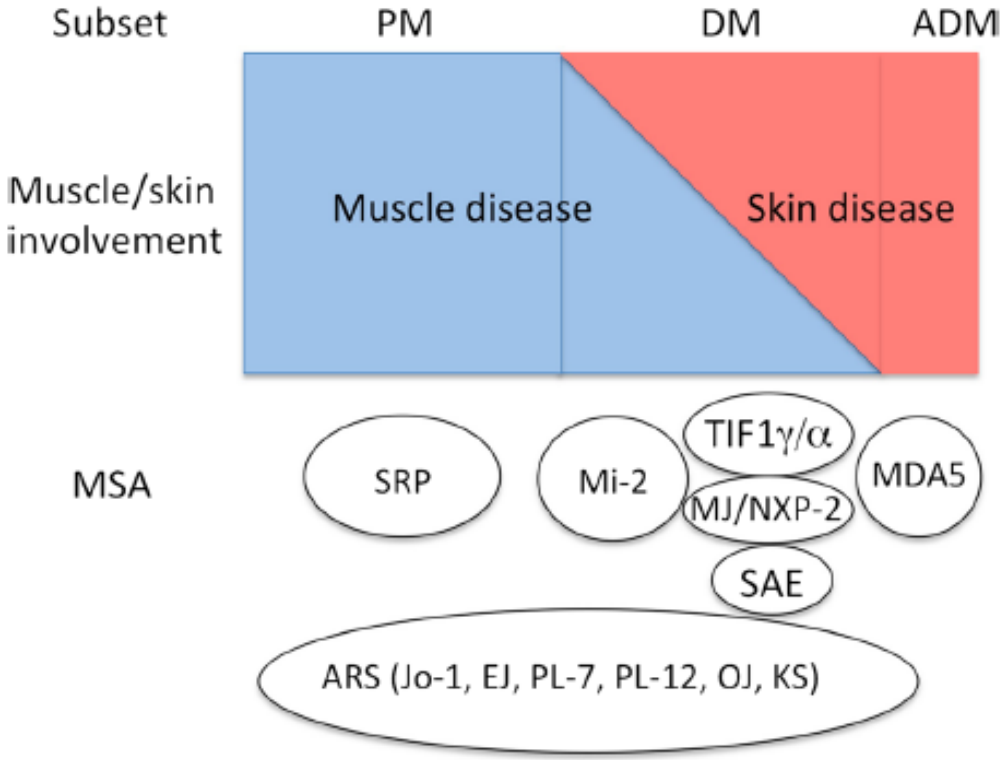


Fig. 1 A summary of the association of myositis-specific autoantibodies with the spectrum of muscle and skin involvements in different subsets of PM/DM

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

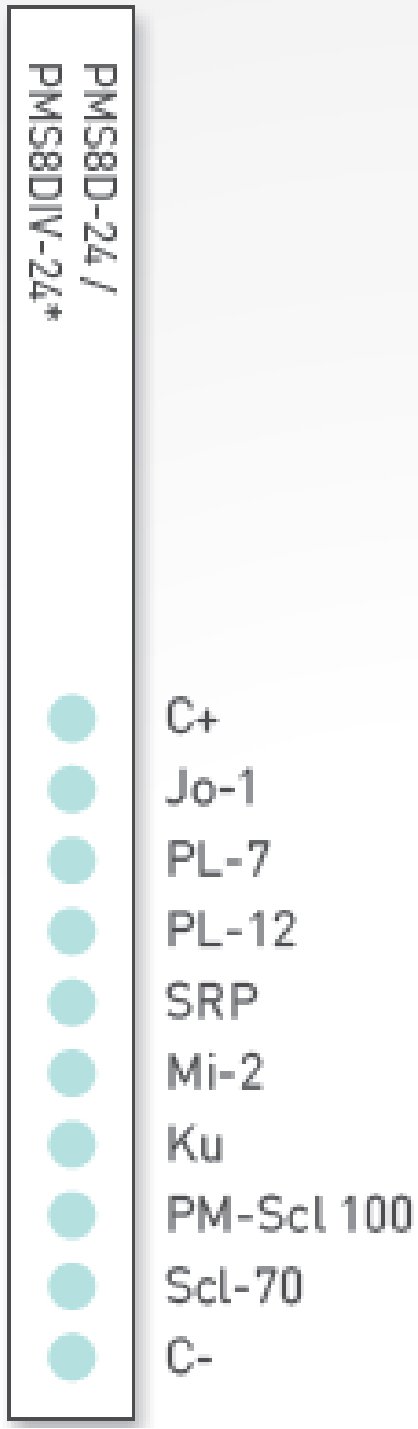
INSTITUT DE MYOLOGIE
INNOVER POUR GUERIR

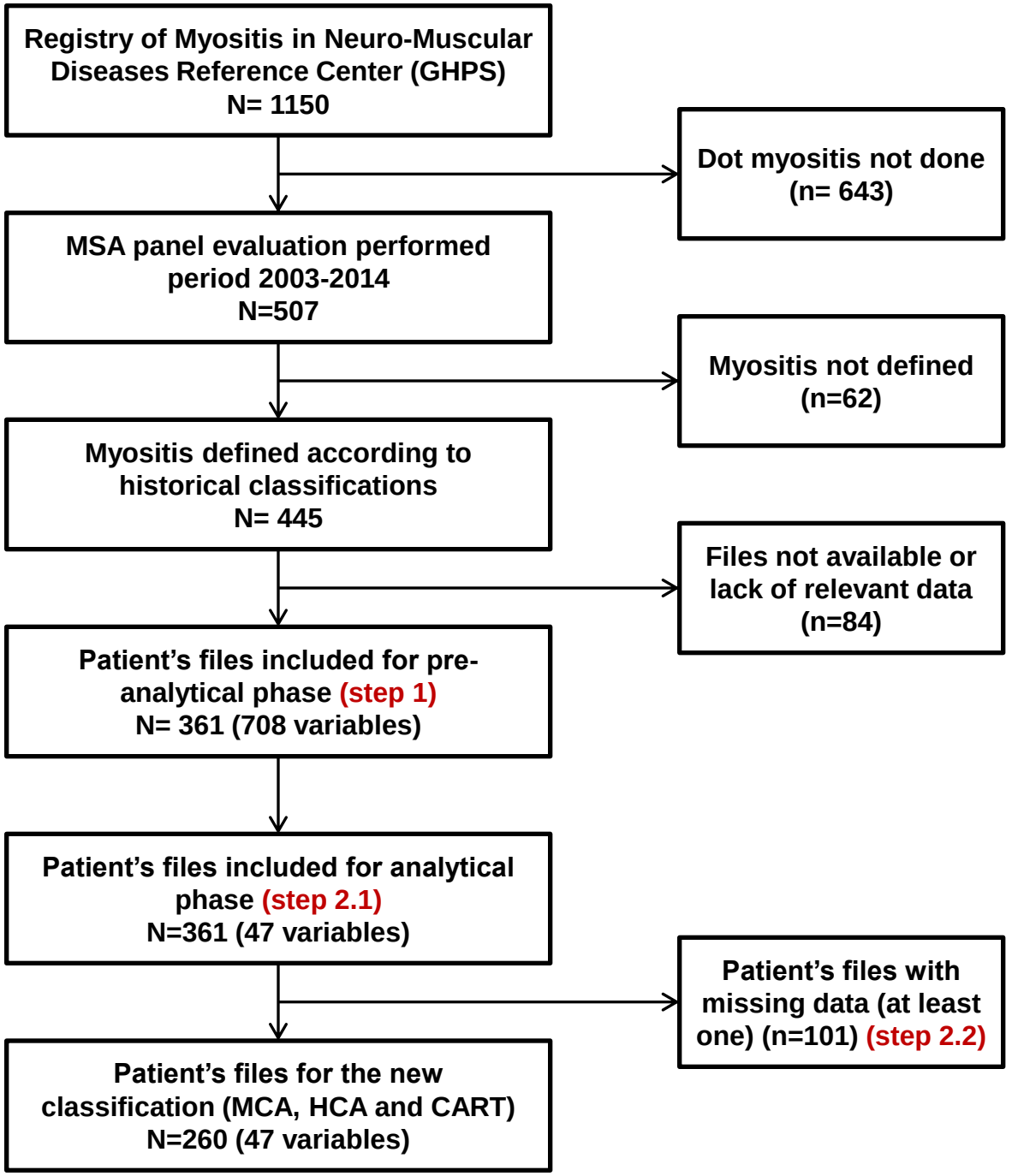
JAMA Neurology | Original Investigation

Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies

Kubéraka Mariampillai, PhD; Benjamin Granger, MD; Damien Amelin, MSc; Marguerite Guiguet, PhD; Eric Hachulla, MD; François Maurier, MD; Alain Meyer, MD; Aline Tohmé, MD; Jean-Luc Charuel, PharmD; Lucile Musset, PharmD; Yves Allenbach, MD; Olivier Benveniste, MD

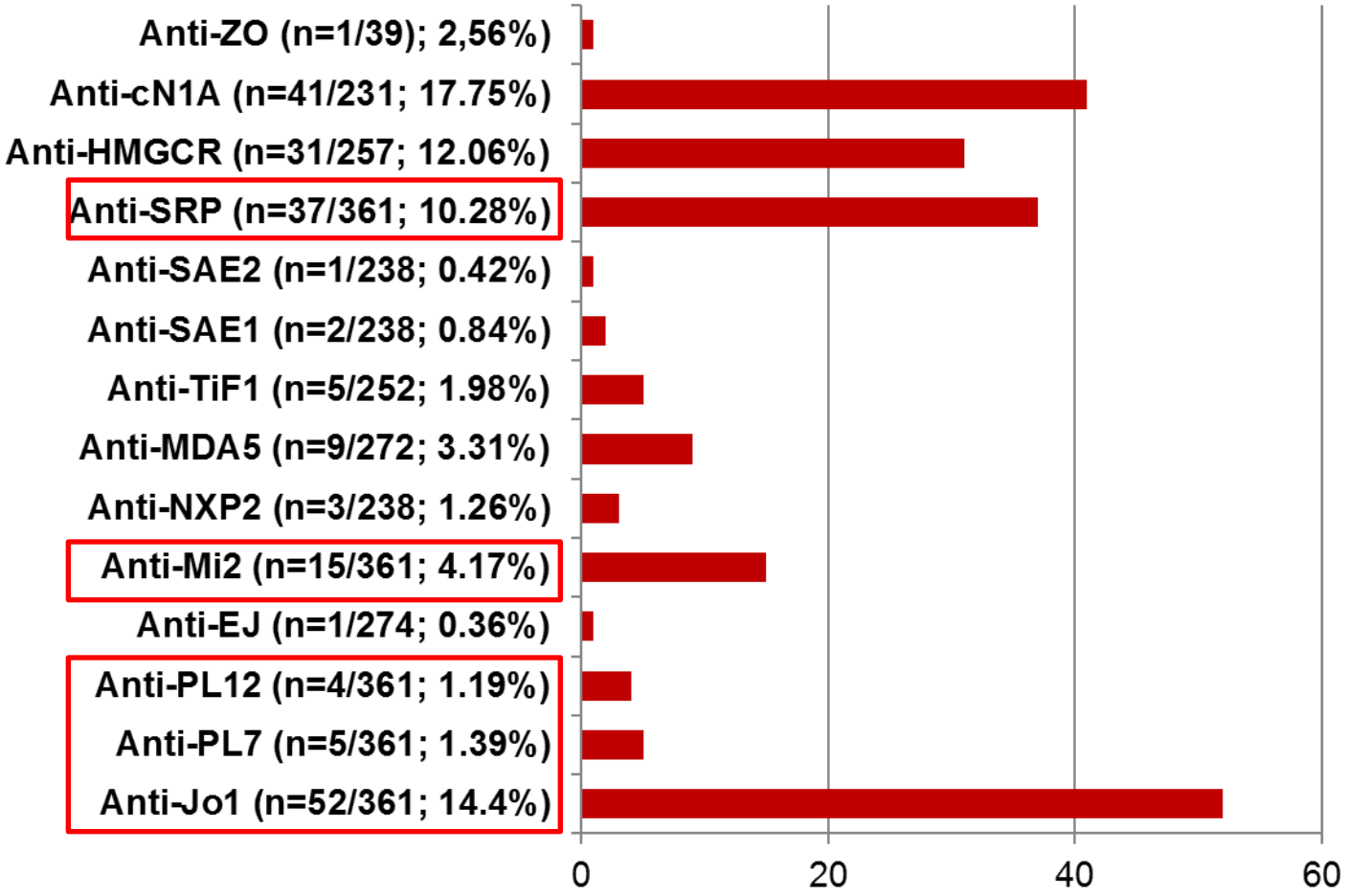
In press


PMS8D-24 /
PMS8DIV-24*
C+
Jo-1
PL-7
PL-12
SRP
Mi-2
Ku
PM-Scl 100
Scl-70
C-


Registry of Myositis in Neuro-Muscular Diseases Reference Center (GHPS)
N= 1150
Dot myositis not done
(n= 643)
MSA panel evaluation performed
period 2003-2014
N=507
Myositis not defined
(n=62)
Myositis defined according to historical classifications
N= 445
Files not available or lack of relevant data
(n=84)
Patient's files included for pre-analytical phase (step 1)
N= 361 (708 variables)
Patient's files included for analytical phase (step 2.1)
N=361 (47 variables)
Patient's files with missing data (at least one) (n=101) (step 2.2)
Patient's files for the new classification (MCA, HCA and CART)
N=260 (47 variables)

Step1 : pre-analytic phase

- Presence of MSA: 207/361 patients (57.34%)

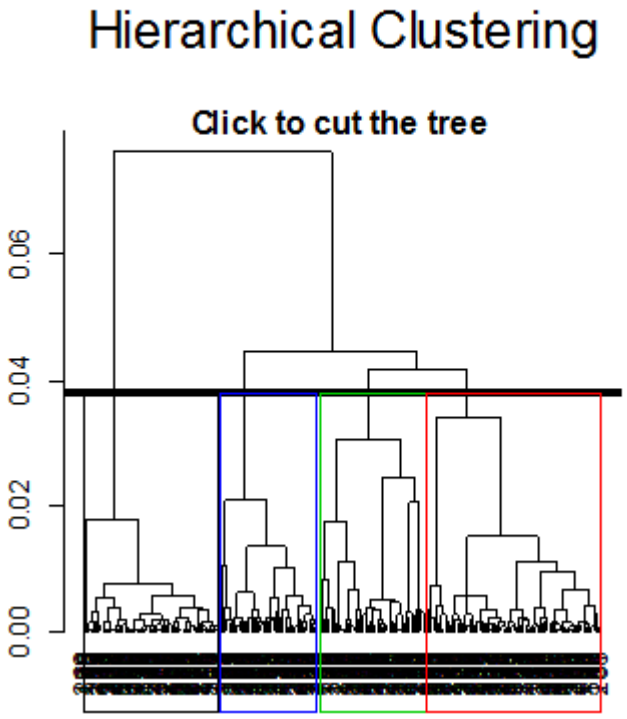


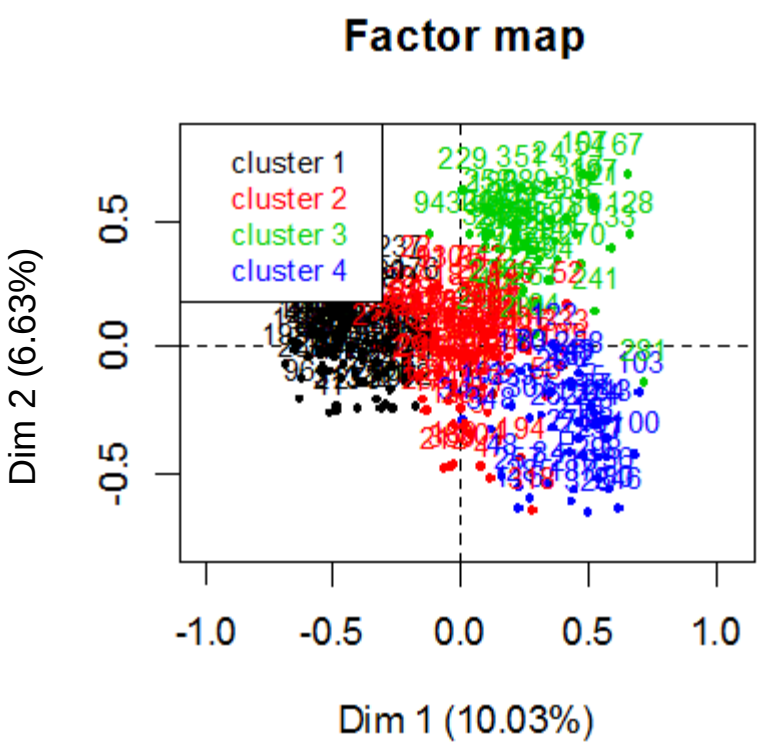
Step 2: analytic phase

- 47 variables used for multiple correspondence analysis (260 patients):

Type of variables	Variables selected
Sociodemographic variables	patient number, gender, age at diagnosis, ethnicity
Skin lesions variables	Skin lesions criteria, shawl signs, typical DM skin rash, heliotrope rash, alopecia, calcinosis, limb edema, panniculitis, skin ulcers and mechanic's hands
Biological variables	CK level (highest), anti-synthetase autoantibodies (grouping anti-Jo1, anti-PL7 and anti-PL12), anti-Jo1, anti-Mi2, anti-SRP, ANA, anti-Ku, anti-PmScl, anti-RNP, anti-Scl70, anti-Sm, anti-SSARo52, anti-SSARo60, anti-SSB
Histological variables	necrotic fibers, mitochondrial abnormalities, perifascicular atrophy, vacuolated fibers, inflammatory infiltrates, inflammatory infiltrate invading non-necrotic fibers and perivascular infiltrates
Muscular variables	Proximal/distal/axial muscle weakness, swallowing troubles, Manual muscle testing (MRC scale) for the deltoids, psoas, quadriceps and finger flexors,
Extra-muscular variables	cancer (± 3 years of the myositis diagnosis), arterial hypertension, Raynaud's phenomenon, lung specific involvement, arthritis/arthralgia,

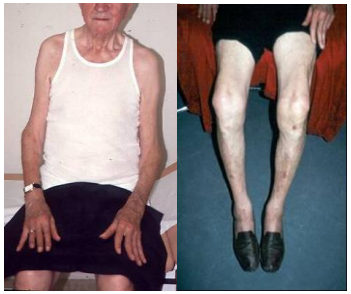
Step2: Hierarchical Cluster Analysis (HCA)



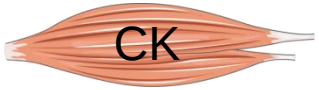


HCA: cluster 1 (n=77, 29.6%)

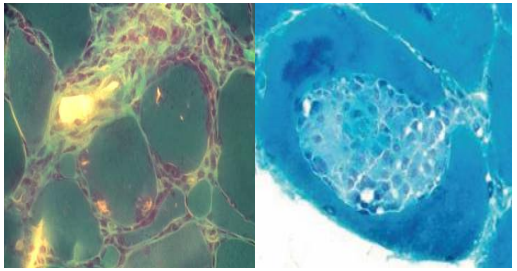
IBM (n=72, 93.51%; p<0.0001)



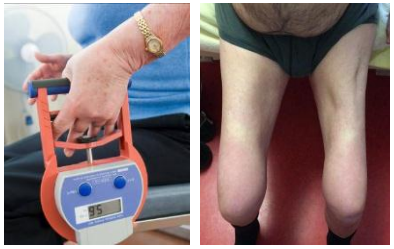
- Men (n=74, 96.11%; p<0.0001)
- Caucasian origin (n=63, 81.82%; p<0.0001)
- ≥ 60 yo (n=58, 75.32%; p<0.0001)



- 160 IU/L ≤ CK ≤ 793 IU/L (n=33, 42.86%; p<0.0001)



- Inflammatory infiltrates (n=77, 100%; p<0.0001)
- **Vacuolated fibers** (n=62, 80.52%; p<0,00001)
- invaded fibers (n=52, 67.53%; p<0.0001)

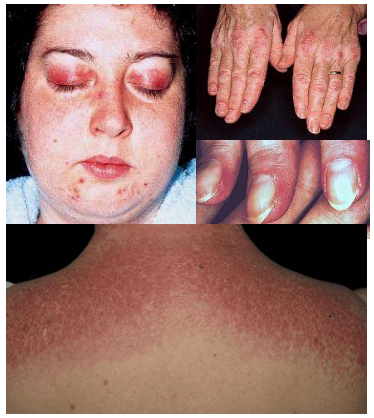


- **Fingers flexors ≤ 3** (n=48, 62.34%; p<0,00001)
- Quadriceps ≤ 3 (n=47, 61.04%), p<0.0001)
- Deltoïd=5 (n=28, 36.36%; p < 0.0001)
- Swallowing troubles (n=59; 76.62%; p = 0.0001)

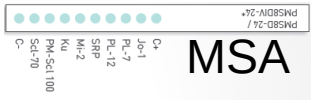
- No skin, lung, Raynaud, arthritis, MSA …

HCA: cluster 2 (n=52, 20%)

DM (n=43, 82.69%; p < 0.0001)

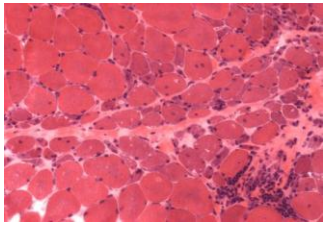


- Age at diagnosis ≤ 40 (n=19, 36.54%; p <0.0001)
- **DM skin rash** (n=46, 88.46%), **heliotrope rash** (n=39, 75%), **shawl sign** (n=42, 80.77%; p<0,00001)
- Limb eodema (n=18, 34.62%; p<0,0001), Skin ulcers (n=9, 17.31%; p<0.0001), Alopecia (n=10, 19.23%; p=0.001), Panniculitis (n=4, 7.69%; p=0.002), Calcinosis (n=5, 9.62%; p=0.0007)



- **Anti-Mi2** (n=10, 19.23%; p<0.00001)

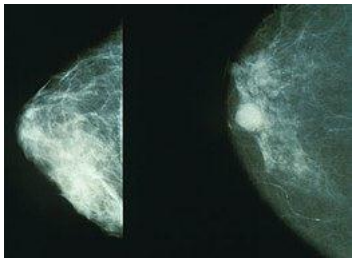
+ Anti-MDA5 (n=3, 8.11%; p=0.02) **+ anti-TiF1gamma** (n=2, 5.56%; p=0.04) **+ Anti-SAE1** (n=2, 6.06%; p=0.05)



- Perifascicular atrophy (n=29, 55.77%; p<0,0001),
- Inflammation (n=46, 88.46%; p<0,0001) with perivascular infiltrates (n=35, 67.31%; p<0.0001)

- Deltoïds ≤ 3 (n=29, 55.77%; p < 0.0001)

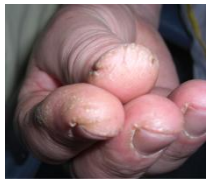
- Cancer (n=11, 21.15%; p=0.02)



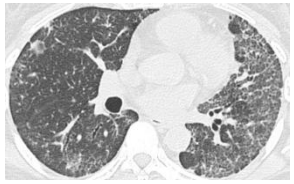
HCA: cluster 3 (n=40, 15.39%)

ASyS (n=36; 90%) **or PM** (n=38, 95%) **and 2 DM** (p < 0.0001)

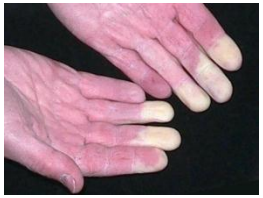
- Age at diagnosis ≤ 40 yo (n=15, 37.5%; p<0.0001)
- African origin (n=9, 22.5%; p<0.0001)



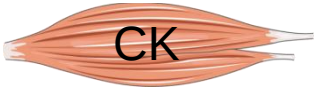
- **Mechanic's hands** (n=22, 55%; p < 0.00001)



- ILD (n=34, 85%; p<0.0001), FVC≤70 (n=19, 55.88%; p=0.0002)



- Raynaud phenomenon (n=17, 42.5%; p < 0.0001)
- Arthritis/arthralgia (n=36, 90%; p < 0.0001)



- ≥7000 IU/L (n=15, 37.5%; p<0.0001)

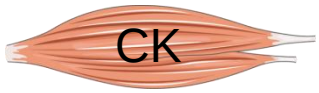
- **Anti-Jo1** (n=31, 77.5%; p<0.00001)

+ anti-PL7 (n=3, 7.5%; p=0.02), **anti-PL12** (n=2, 5%; p=0,05)

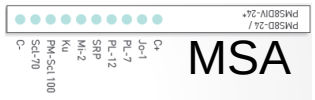
HCA: cluster 4 (n=91, 35%)

IMNM (n=53, 58.24%; p<0,0001) or **PM** (n=21, 23.08%; p < 0.0001)

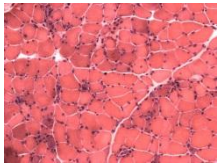
- Women (n=66, 72.53; p < 0.0001)
- Asian origin (n=17, 18.68%; p < 0.0001)



- **≥ 2300 IU/L** (n=58, 63.74%; p<0.00001)



• **Anti-SRP** (n=23, 25.27%; p<0.00001), anti-Ku (n=5, 5.49%; p= 0.03)
+ Anti-HMGCR (n=20, 28.57%; p<0.0001)



- **No muscle inflammation** (p<0,00001), vacuoles, perifascicular atrophy, nor mitochondrial abnormalities

- Psoas ≤3 (n= 57, 62.64%; p=0.02), Quadriceps = 5 (n=40, 43.96%; p<0.0001)
- Fingers flexors = 5 (n= 59, 64.84%; p<0.0001)

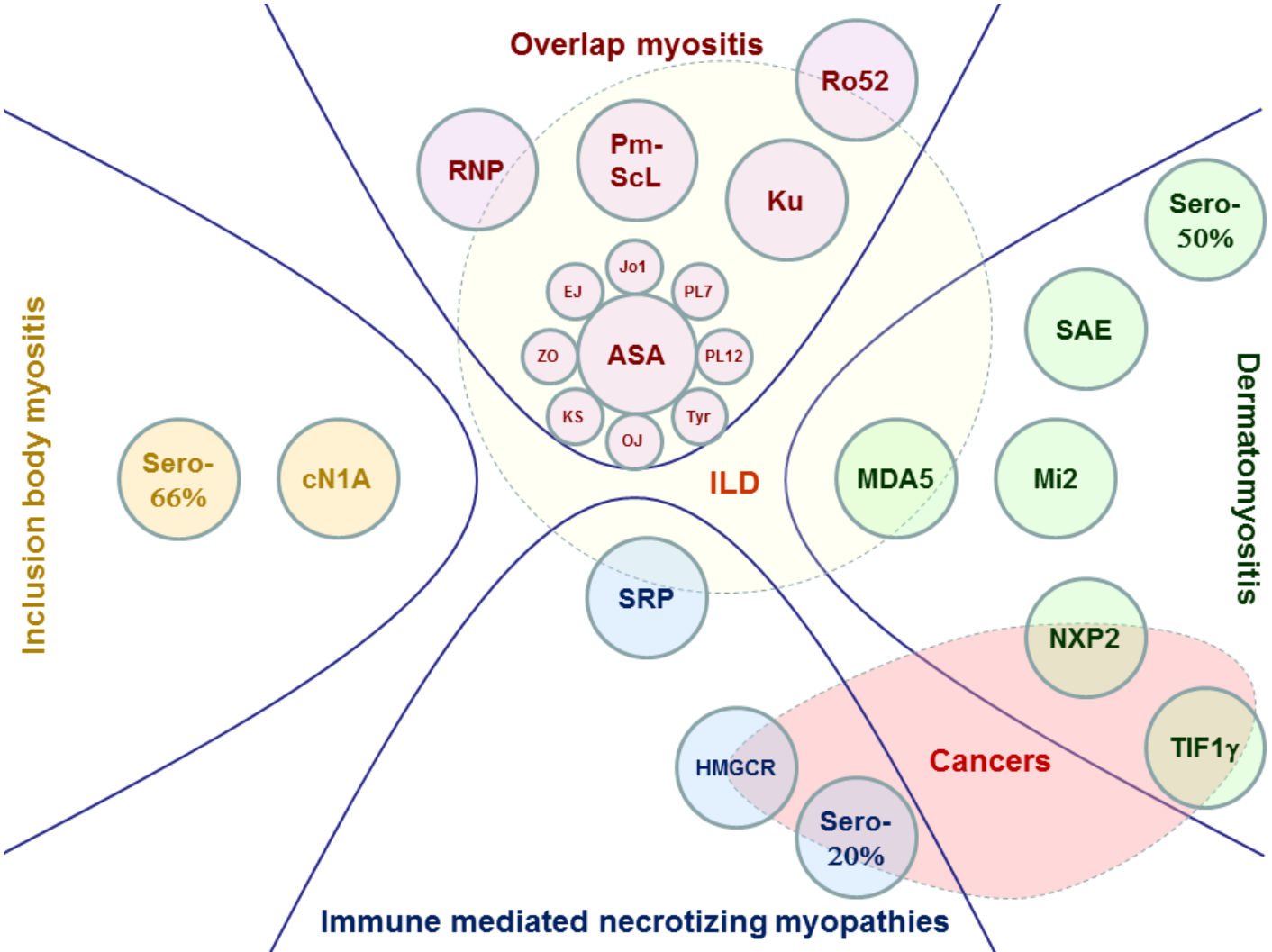
- No skin lesion

CURRENT OPINION

Advances in serological diagnostics of inflammatory myopathies

Volume 29 • Number 5 • October 2016

Olivier Benveniste[a,b], *Werner Stenzel*[c], *and Yves Allenbach*[a,b]

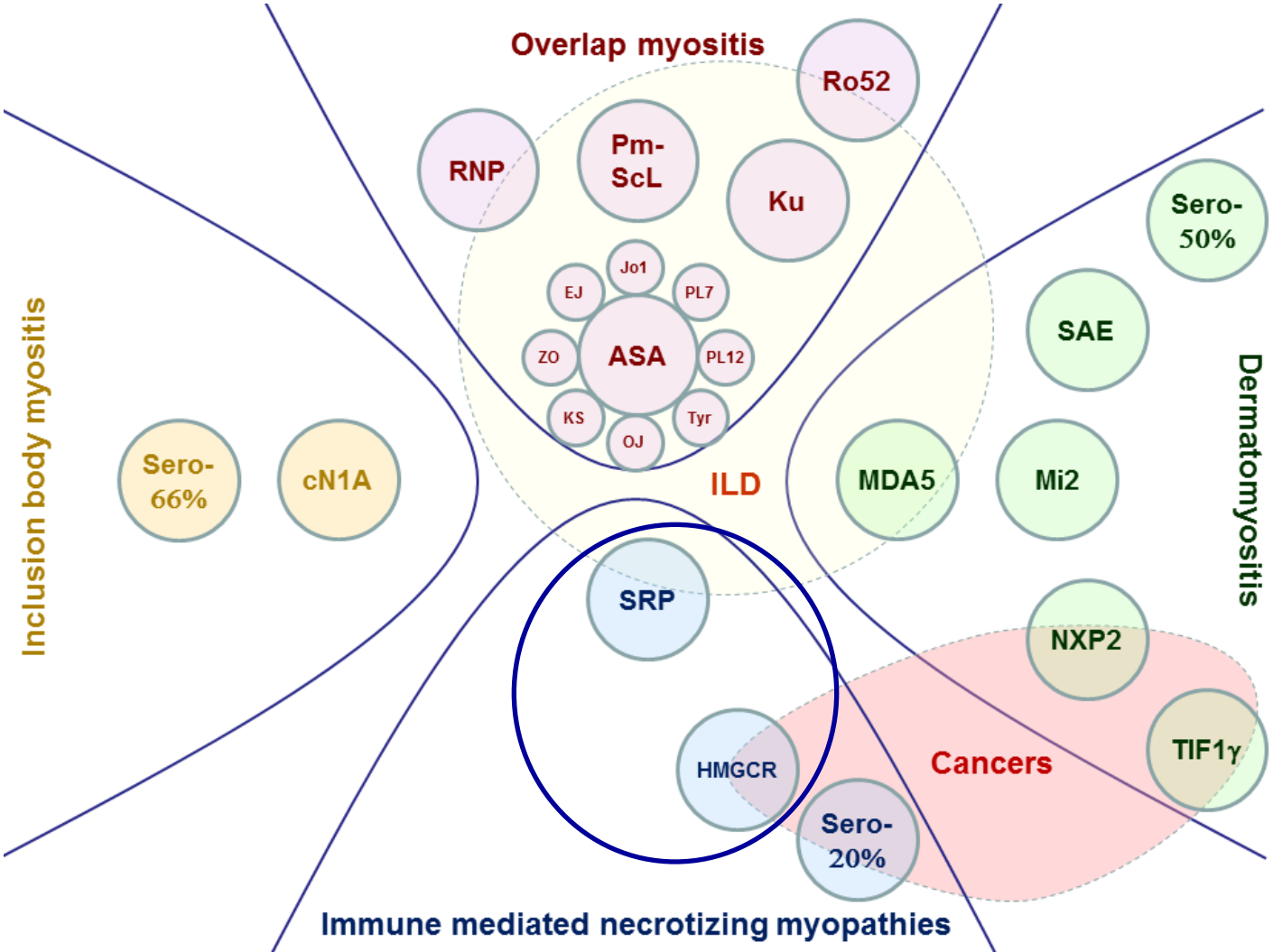


CURRENT OPINION

Advances in serological diagnostics of inflammatory myopathies

Volume 29 • Number 5 • October 2016

Olivier Benveniste[a,b], *Werner Stenzel*[c], *and Yves Allenbach*[a,b]



First series of cases

ANTIBODY TO SIGNAL RECOGNITION PARTICLE IN POLYMYOSITIS

IRA N. TARGOFF, ARTHUR E. JOHNSON, and FREDERICK W. MILLER

Arthritis and Rheumatism, Vol. 33, No. 9 (September 1990)

- 13 patients PM
- « Some of these cases were unusually severe and/or of rapid onset »
- « Anti-SRP antibodies may serve as a marker for a second (after Jo1), distinct subgroup of adult PM »

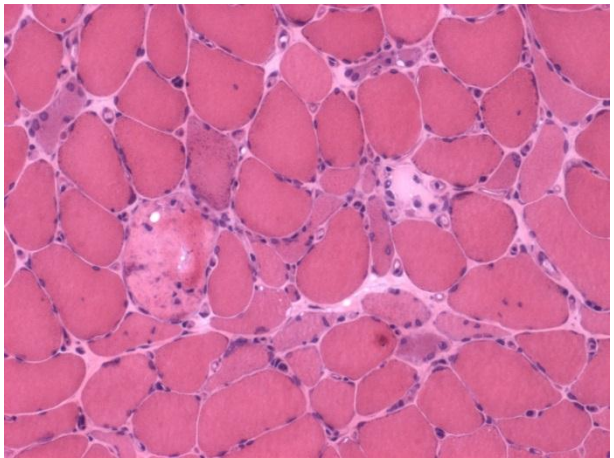
Myopathy with antibodies to the signal recognition particle: clinical and pathological features

T Miller, M T Al-Lozi, G Lopate, A Pestronk

J Neurol Neurosurg Psychiatry 2002;**73**:420–428

- 7 patients with severe myopathy
- ± cardiomyopathy (30%)
- High CK level (> 10 000 U/L)
- Sometimes skin rash or interstitial lung disease
- Muscle fiber necrosis and regeneration and little or no inflammation

HE



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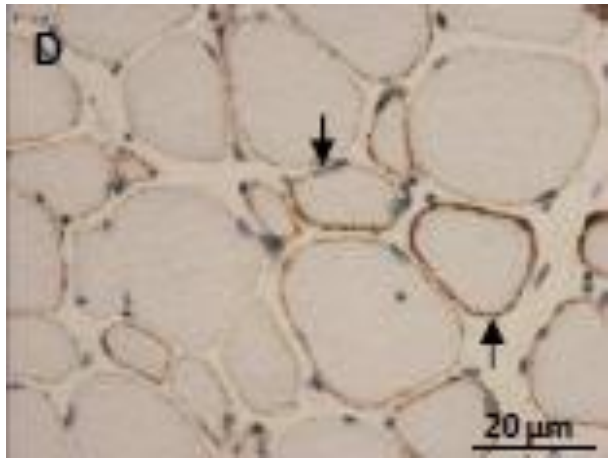


A Novel Autoantibody Recognizing 200-kd and 100-kd Proteins Is Associated With an Immune-Mediated Necrotizing Myopathy

Arthritis, Sept 2010

Lisa Christopher-Stine, Livia A. Casciola-Rosen, Grace Hong, Tae Chung, Andrea M. Corse, and Andrew L. Mammen

- 225 patients with an IIM (muscle biopsies + sera)

- 38 IMNM
  - 4 anti-synthetases
  - 6 anti-SRP
  - 16 anti-p200/100

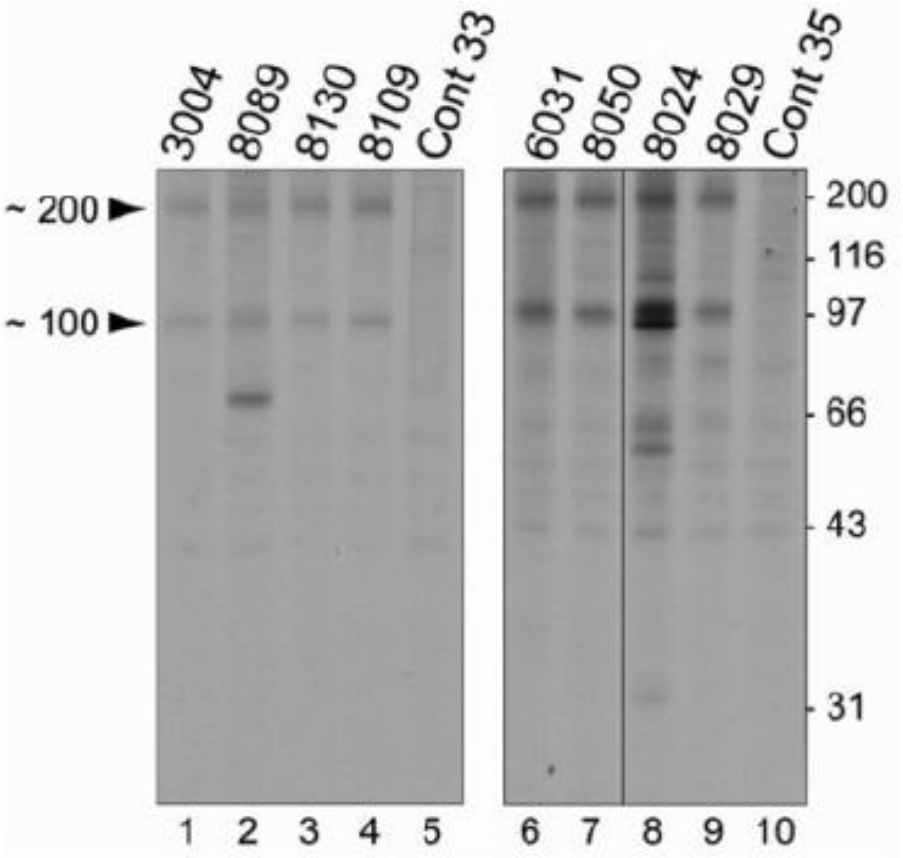


Table 1. Clinical features of the patients with anti-200/100 autoantibodies*

Demographics	
No. of patients	16
Mean age at disease onset, years	54
Female sex	63
White race	56
Nonwhite race	44
Deceased	0
Clinical feature	
Subjective muscle weakness	100
Proximal weakness on examination	100
Wheelchair use	25
Interstitial lung disease	0
Malignancy	13
Raynaud's phenomenon	13
Rash	44
Myalgias	75
Arthralgias	50
Dysphagia	63
Statin use	63
Laboratory findings	
Initial CPK level, mean IU/liter	8,702
Maximum CK level, mean IU/liter	10,333
ANA positivity (>1:160)	6
Elevated ESR	38
Elevated C-reactive protein level	6
Anti-Ro positive	0
Anti-La positive	0
Thigh MRI features	
Normal findings on thigh MRI	0
Muscle edema	100
Atrophy	75
Fatty replacement	67
Fascial edema	25
EMG findings	
Irritable myopathy	88
Nonirritable myopathy	13
Normal	0

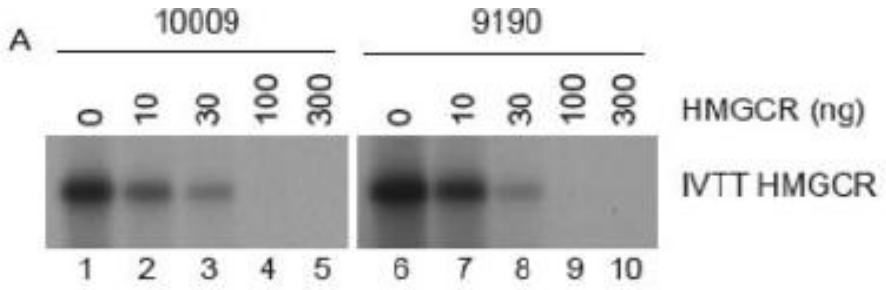
ARTHRITIS & RHEUMATISM
Vol. 63, No. 3, March 2011, pp 713–721
DOI 10.1002/art.30156

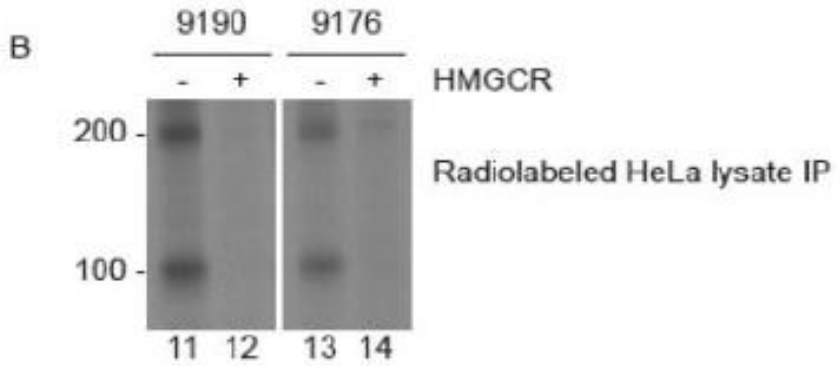
Autoantibodies Against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase in Patients With Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, Tae Chung, Lisa Christopher-Stine, Paul Rosen, Antony Rosen, Kimberly R. Doering, and Livia A. Casciola-Rosen

- ELISA HMGCoAR: 100% + patients anti-p200/100
- Specificity:

Immunoprecipitation





W blot

Arthritis Care & Research
Vol. 64, No. 2, February 2012, pp 269–272
DOI 10.1002/acr.20662

ORIGINAL ARTICLE

Rarity of Anti–3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Antibodies in Statin Users, Including Those With Self-Limited Musculoskeletal Side Effects

ANDREW L. MAMMEN,[1] KATHERINE PAK,[1] EMMA K. WILLIAMS,[1] DIANE BRISSON,[2] JOE CORESH,[1] ELIZABETH SELVIN,[1] AND DANIEL GAUDET[2]

N = 1966 with 763 now under statines, 322 had statines, 881 no statines

Table 1. Familial hypercholesterolemia subjects' characteristics*

	Statin tolerant (n = 47)	Statin intolerant (n = 51)	*P*
Sex, M/F	26/21	29/22	0.878
Age, years	57.8 ± 11.1	56.5 ± 10.2	0.56
CK, units/liter	105.09 ± 47.34	131.44 ± 71.07	0.038

Anti-HMGCR Autoantibodies in European Patients With Autoimmune Necrotizing Myopathies

Inconstant Exposure to Statin

Yves Allenbach, MD, PhD, Laurent Drouot, MSc, Aude Rigolet, MD, Jean Luc Charuel, PharmD, Fabienne Jouen, MD, Norma B. Romero, MD, Thierry Maisonobe, MD, Odile Dubourg, MD, Anthony Behin, MD, Pascal Laforet, MD, PhD, Tania Stojkovic, MD, Bruno Eymard, MD, PhD, Nathalie Costedoat-Chalumeau, MD, PhD, Emmanuelle Campana-Salort, MD, Anne Tournadre, MD, Lucile Musset, MD, Brigitte Bader-Meunier, MD, Isabelle Kone-Paut, MD, PhD, Jean Sibilia, MD, PhD, Laurent Servais, MD, PhD, Olivier Fain, MD, Claire Larroche, MD, Elisabeth Diot, MD, PhD, Benjamin Terrier, MD, PhD, Raphael De Paz, MD, Antoine Dossier, MD, Dominique Menard, MD, Chafika Morati, MD, Marielle Roux, MD, Xavier Ferrer, MD, Jeremie Martinet, PharmD, Sophie Besnard, MD, Remi Bellance, MD, Patrice Cacoub, MD, PhD, Laurent Arnaud, MD, PhD, Bernard Grosbois, MD, PhD, Serge Herson, MD, Olivier Boyer, MD, PhD, and Olivier Benveniste, MD, PhD, on behalf of the French Myositis Network

TABLE 1. Characteristics of 45 Anti-HMGCR+ Patients

Characteristic	
Age, yr; mean	48.9 ± 21.9
Sex ratio (M:F)	0.36
Statin exposure	44.4% (n = 20)
Muscular involvement	
Muscular deficit	97.7% (n = 44)
Subacute onset	64.4% (n = 29)
Progressive onset	33.3% (n = 15)
Severe deficit (≤3)	75.5% (n = 34)
Myalgia	53.3% (n = 24)
Dysphagia	26.7% (n = 12)
CK level	6941 ± 8802 IU/L
Extraskeletal muscular involvement	
Weight loss	20% (n = 9)
Interstitial lung disease	2.2% (n = 1)
Cardiac insufficiency	2.2% (n = 1)
Arthralgia	11.1% (n = 5)
Raynaud phenomenon	11.1% (n = 5)

TABLE 3. Treatments Used for NAM Patients

Patient Number	First-Line Treatment	Number of Treatment Intensification	Disease-Modifying Antirheumatic Drugs	Treatment Duration (Months)
2	CT + IVIg + MTX	0	none	3
3	CT + MTX	0	none	1
4	MTX + CT	0	none	3
6	CT + MTX + PE + IVIg	1	CT/MTX/RTX	3
7	CT + MTX	0	none	3
8	CT + MTX	2	CT/MMF/TACRO/PE/MTX/IVIg	24
9	CT + MTX + PE + IVIg	0	none	18
11	CT	5	CT/AZA/MTX/CYC/MMF/IVIg	114
12	CT + IVIg	4	CT/AZA/MTX/RTX/PE/IVIg	41
13	CT + MTX	4	CT/IVIg/RTX	42
14	CT + IVIg + MTX	2	CT/AZA/IVIg/RTX	40
16	CT + IVIg	4	CT/MTX/IVIg/MMF/RTX	62
17	CT + MTX	1	CT/MTX	36
18	CT + MTX	0	none	4
19	CT + IVIg + MTX	0	none	1
20	CT + EDX	0	none	3
21	CT + MTX	3	CT/AZA	80
22	CT	5	CT/IVIg/AZA/MTX/RTX	180
23	CT	6	CT/IVIg/MTX/AZA/MMF	90
24	CT	1	CT/AZA	34
25	CT	10	CT/IVIg/AZA/CYC/TACRO/RTX	120
26	CT + MTX	1	IVIg	18
27	CT	1	CT/IVIg/PE/MTX	5
28	CT + IVIg + MTX	2	IVIg	8
29	CT	2	MTX/PE/IVIg/RTX	11
30	CT + IVIg	1	CT/EDX	23
31	CT	1	IVIg	12
32	IVIg	0	none	7
33	IVIg	0	none	7
34	CT + MTX	3	CT/MTX/IVIg/MMF/RTX/AZA	42
35	CT	3	CT/MMF	89
36	CT	3	CT/EDX/IVIg	36
37	CT + MTX + IVIg	0	CT/MTX/IVIg	4
38	CT + MTX	1	CT/MTX/IVIg	3
39	CT	1	IVIg	50
40	CT	1	CT/AZA	6
41	CT	1	MTX	84
42	CT + MTX	0	none	11
43	CT + MTX	1	CT/MTX	12

Allenbach Y, Medicine, 2014

IMNM, HMGCR and muscle strength

RHEUMATOLOGY

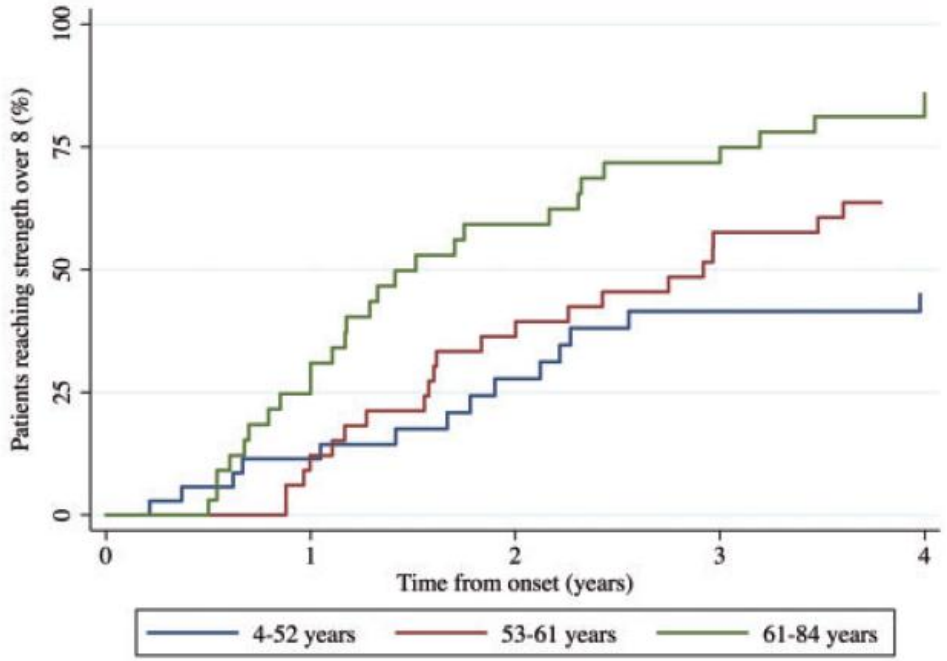
Original article

doi:10.1093/rheumatology/kew470

More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy

Eleni Tiniakou[1,*], Iago Pinal-Fernandez[2,*], Thomas E. Lloyd[3], Jemima Albayda[1], Julie Paik[1], Jessie L. Werner[1], Cassie A. Parks[2], Livia Casciola-Rosen[1], Lisa Christopher-Stine[1,3] and Andrew L. Mammen[1,2,3]

Patient characteristic	4–52 years (n = 35)	53–61 years (n = 35)	61–84 years (n = 34)
Statin exposure	40	89	97
Sex (female)	63	66	47
Caucasian	60	71	85
African American	29	17	12
Other races	11	11	3



IMNM and severity

Neuromuscular

RESEARCH PAPER *J Neurol Neurosurg Psychiatry* 2016;**87**:1038–1044

Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy

Yurika Watanabe,[1] Akinori Uruha,[2,3] Shigeaki Suzuki,[1] Jin Nakahara,[1] Kohei Hamanaka,[2,4] Kazuko Takayama,[2] Norihiro Suzuki,[1] Ichizo Nishino[2]

Table 2 Comparison between anti-SRP and anti-HMGCR antibodies

Findings, number (%)	Anti-SRP (n=68)	Anti-HMGCR (n=45)	p Value
Female	40 (59)	31 (69)	0.28
Age at examination (years)	55.2±16.1	56.4±18.8	0.74
Statin exposure	3 (4)	8 (18)	0.019
Chronic progression	17 (25)	11 (24)	0.95
Muscle weakness			
Legs dominant	52 (76)	32 (71)	0.52
Severe involvement	43 (63)	11 (24)	<0.0001
Laterality	12 (18)	6 (13)	0.68
Distal dominant	1 (1)	0 (0)	0.41
Neck weakness	48 (71)	20 (44)	0.0055
Dysphagia	46 (68)	20 (44)	0.014
Facial involvement	3 (4)	1 (2)	0.54
Cardiac involvement	1 (1)	0 (0)	0.41
Respiratory insufficiency	8 (12)	0 (0)	0.017
Muscle atrophy	46 (68)	20 (44)	0.014

IMNM and MRI

Ann Rheum Dis 2016;**0**:1–7.

Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity

Iago Pinal-Fernandez,[1] Maria Casal-Dominguez,[2] John A Carrino,[2] Arash H Lahouti,[2] Pari Basharat,[2] Jemima Albayda,[2] Julie J Paik,[2] Shivani Ahlawat,[2] Sonye K Danoff,[2] Thomas E Lloyd,[2] Andrew L Mammen,[1,2] Lisa Christopher-Stine[2]

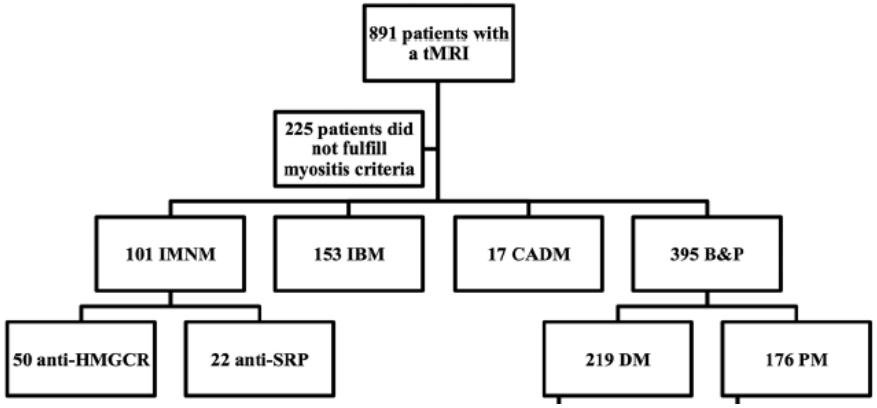


Table 2 Extent of thigh MRI findings among clinical subsets

	IMNM							
	Total (n=101) Mean (SD)	HMGCR (n=50) Mean (SD)	SRP (n=22) Mean (SD)	IBM (n=153) Mean (SD)	PM (n=176) Mean (SD)	DM (n=219) Mean (SD)	CADM (n=17) Mean (SD)	Total (n=666) Mean (SD)
Oedema	55.5 (32.2)***	58.9 (31.8)	65.8 (28.9)	48.1 (24.6)***	29.4 (30.5)***	30.1 (36.7)***	6.1 (18.5)***	37.3 (33.5)
Atrophy	23.2 (28.7)**	21.7 (28.9)*	38.2 (30.2)*	32.2 (26.7)***	12.7 (24.6)*	5.7 (16.7)***	2.5 (7.4)*	16.2 (25.5)
Fatty replacement	38.0 (33.1)*	34.4 (30.9)	49.1 (31.2)	50.1 (27.3)***	28.3 (31.1)	17.5 (27.0)***	7.1 (12.8)**	30.7 (31.6)
Fascial oedema	6.2 (15.1)*	5.1 (15.2)	6.0 (12.2)	6.0 (12.0)**	5.8 (11.8)**	16.5 (24.3)***	8.6 (17.0)	9.5 (18.1)

Table 4 Multivariate analysis of the extent of the different thigh MRI features (percentage of muscles involved) in patients with anti-HMGCR-associated myositis compared with those with anti-SRP-associated myositis using fractional probit regression

	Oedema dy/dx (95% CI)	Atrophy dy/dx (95% CI)	Fatty replacement dy/dx (95% CI)	Fascial oedema dy/dx (95% CI)
IMNM autoantibody group (anti-SRP vs anti-HMGCR)	6.92 (–9.74 to 23.58)	19.18 (6.52 to 31.84)**	17.64 (0.59 to 34.70)*	6.59 (–1.38 to 14.56)
Age at onset (10 years)	–2.04 (–7.33 to 3.25)	0.28 (–4.69 to 5.25)	0.06 (–5.53 to 5.65)	1.35 (–1.85 to 4.56)
Time from onset to MRI (logarithm of months)	–21.98 (–35.02 to –8.93)***	11.21 (–2.96 to 25.38)	20.50 (6.34 to 34.66)**	–2.32 (–9.08 to 4.45)
Sex (female)	–10.63 (–26.29 to 5.04)	5.06 (–8.39 to 18.50)	–2.68 (–17.65 to 12.30)	–6.19 (–13.14 to 0.76)
Race (referenced to white patients)				
Black	8.41 (–8.93 to 25.75)	4.42 (–8.56 to 17.40)	11.98 (–4.41 to 28.37)	–4.47 (–10.05 to 1.10)
Other races	6.18 (–16.62 to 28.97)	16.62 (–11.24 to 44.48)	–24.72 (–48.05 to –1.39)*	–3.18 (–9.81 to 3.45)

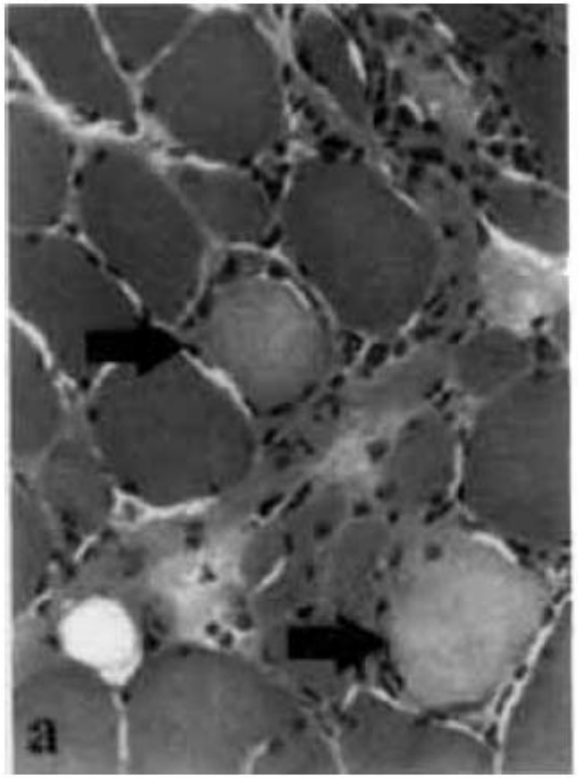
Paraneoplastic necrotizing myopathy

Clinical and pathologic features

Michael I. Levin, MD; Tahseen Mozaffar, MB, BS; Muhammed Taher Al-Lozi, MD; and Alan Pestronk, MD

Neurology. 1998 Mar;50(3):764-7.

HE



C5b9

4 cases with cancer

- Lung
- Bladder
- Gastric
- Colon

IMNM, MSA and cancers

in Advance Access published April 17, 2016

BRAIN 2016: Page 1 of 5 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REPORT

High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody

Yves Allenbach,[1,2] Jeremy Keraen,[1] Anne-marie Bouvier,[3] Valérie Jooste,[3] Nicolas Champtiaux,[1] Baptiste Hervier,[1] Yoland Schoindre,[1] Aude Rigolet,[1] Laurent Gilardin,[1] Lucile Musset,[4] Jean-Luc Charuel,[4] Olivier Boyer,[5] Fabienne Jouen,[5] Laurent Drouot,[5] Jeremie Martinet,[5] Tanya Stojkovic,[6] Bruno Eymard,[6] Pascal Laforêt,[6] Antony Behin,[6] Emmanuelle Salort-Campana,[7] Olivier Fain,[8] Alain Meyer,[9] Nicolas Schleinitz,[10] Kuberaka Mariampillai,[1,2] Aurelie Grados[1] and Olivier Benveniste[1,2]

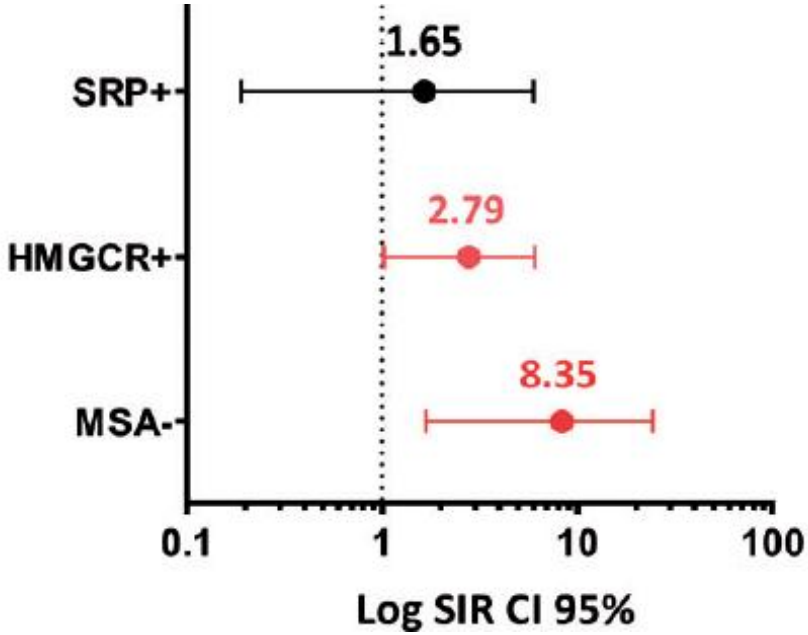


Table 1 Patients' characteristics

	MSA− patients *n* = 14	Anti-HMGCR+ patients *n* = 52	Anti-SRP+ patients *n* = 49	P-values
Age (years) at diagnosis of myopathy	53 ± 15	50 ± 22	47 ± 17	0.6
Statin exposure (%)	7.1 (1/14)	46.1 (24/52)	19.1 (5/26)	**0.004**
Percentage female (%)	73	73.1	67.3	0.8
Muscle strength (MRC)	2.9 ± 1	2.8 ± 0.9	2.1 ± 1.3	**0.0006**
Creatine kinase level (I.U/l)	10 156 ± 14 658	7012 ± 5944	8453 ± 6547	0.39
Dermatomyositis rash (%)	0 (0/14)	0 (0/37)	2.3 (1/44)	0.46

For muscle strength evaluation muscle manual testing was performed using MRC scale (0–5). The mean score of the weakest muscles is represented.
MRC = Medical Research council

IMNM, MSA and cancers

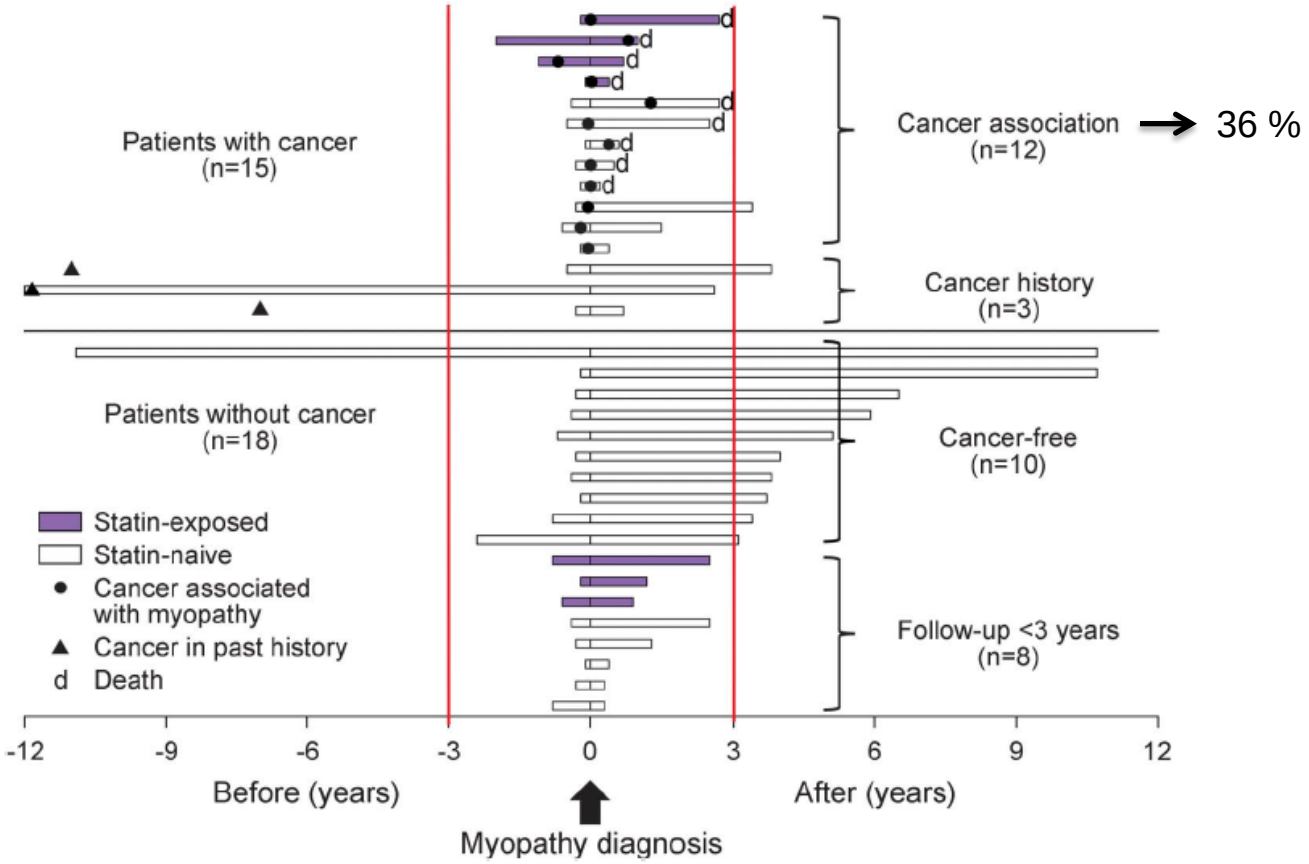
Cancer association as a risk factor for anti-HMGCR antibody-positive myopathy

OPEN

Masato Kadoya, MD

Neurol Neuroimmunol Neuroinflamm 2016;3:e290; doi: 10.1212/NXI.0000000000000290

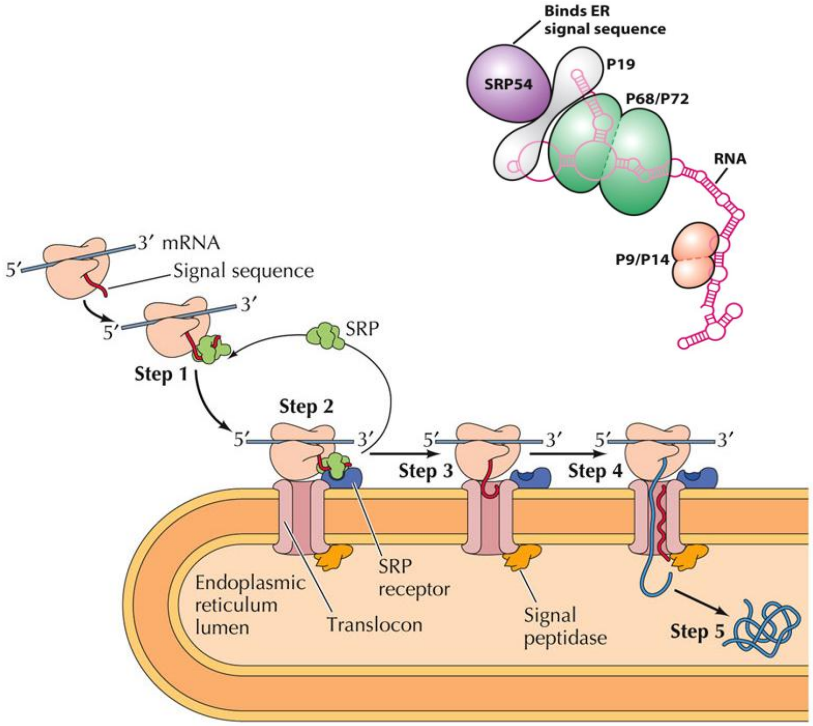
Figure 1 Follow-up periods of 33 anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody (HMGCR Ab+) myopathy patients in relation to cancer or statin exposure

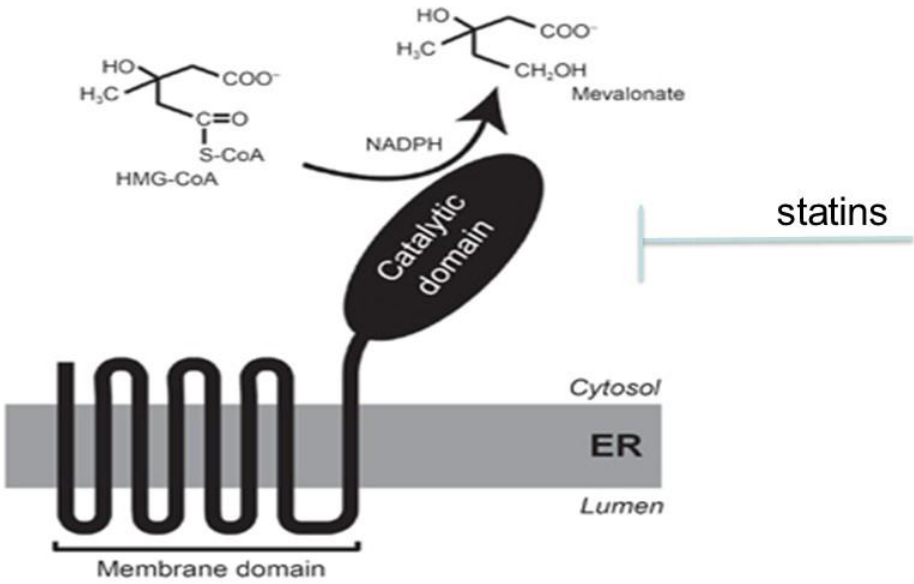


→ 36 %

	SRP	HMGCR
Muscular deficit	++++	+++
CK	++++	+++
MRI	++++	+++
Cardiac	+	-
ILD	+	-
Arthralgia	+	-
Malignancy	-	+

SRP and HMGCR functions

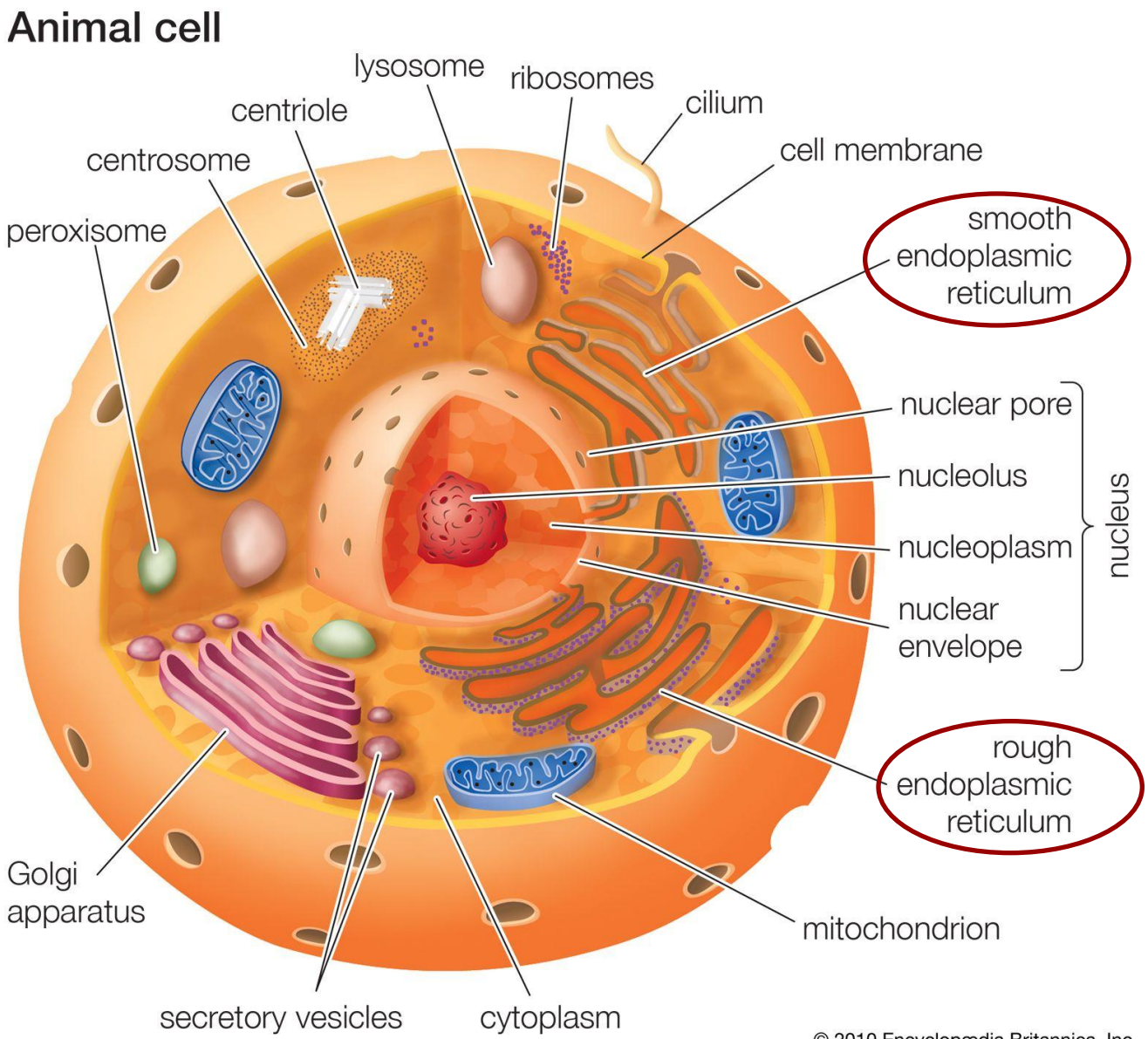




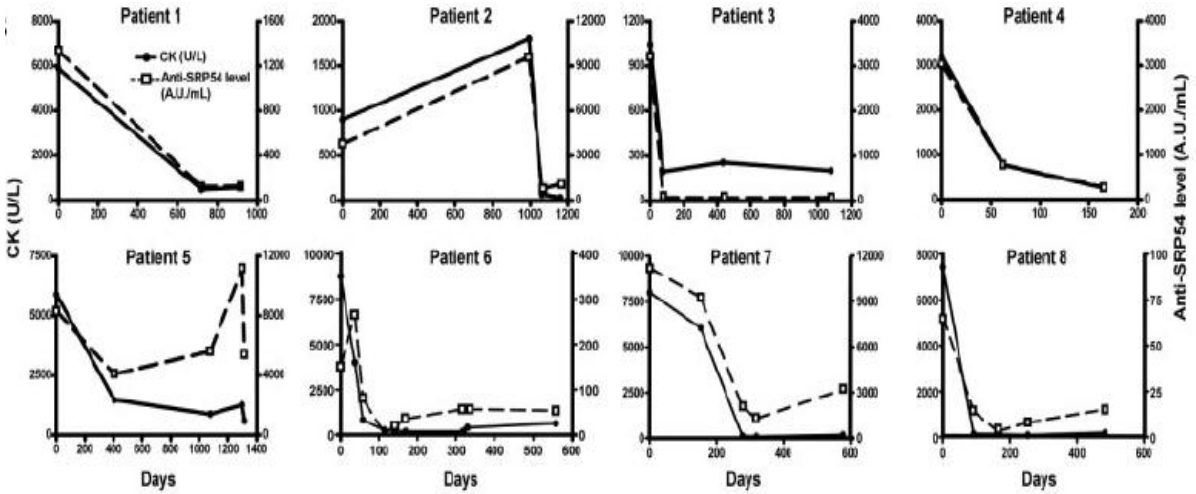
Signal Recognition Particule (SRP)

3-hydroxy-3-methylglutaryl-CoA-reductase (HMGCR)

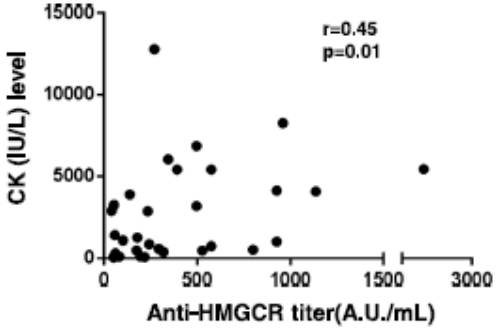
SRP and HMGCR location



Correlations between CK and Ab titer levels



Benveniste et al; Arthritis, 2011



Allenbach et al; Medicine, 2014

Necrosis in anti-SRP$^+$ and anti-HMGCR$^+$ myopathies

Role of autoantibodies and complement

Yves Allenbach, MD, PhD,* Louiza Arouche-Delaperche, PhD,* Corinna Preusse, PhD, Helena Radbruch, MD, Gillian Butler-Browne, PhD, Nicolas Champtiaux, MD, PhD, Kuberaka Mariampillai, MSc, Aude Rigolet, MD, Peter Hufnagl, PhD, Norman Zerbe, Damien Amelin, Thierry Maisonobe, MD, Sarah Louis-Leonard, MD, Charles Duyckaerts, MD, PhD, Bruno Eymard, MD, PhD, Hans-Hilmar Goebel, MD, Cecile Bergua, MSc, Laurent Drouot, PhD, Olivier Boyer, MD, PhD, Olivier Benveniste, MD, PhD,† and Werner Stenzel, MD†

Correspondence
Dr. Allenbach
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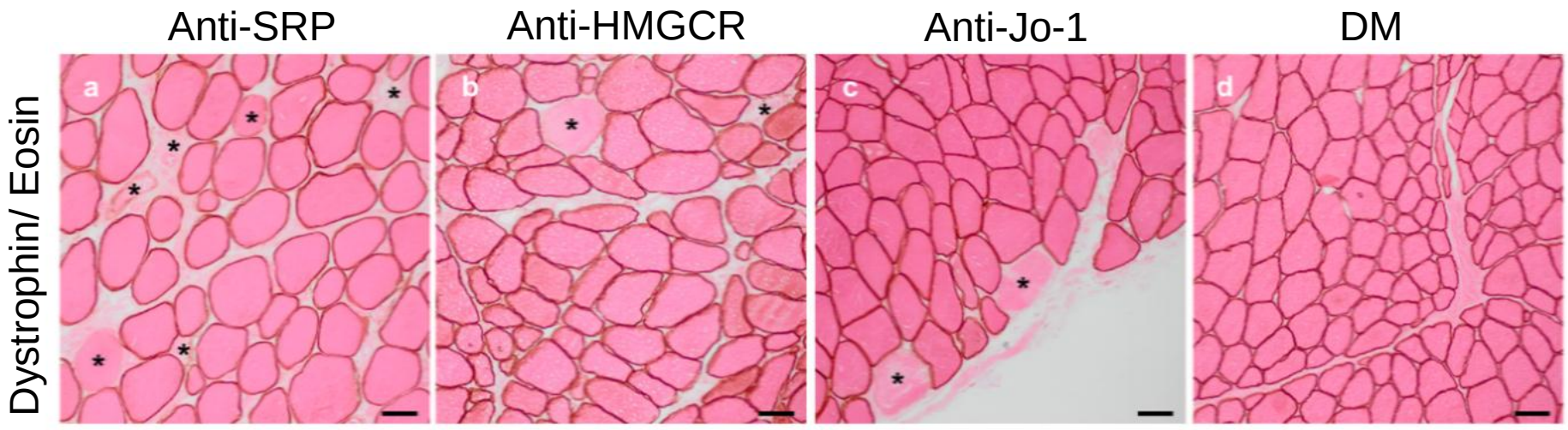
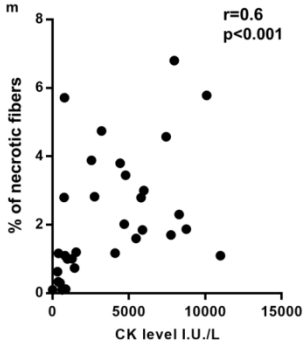
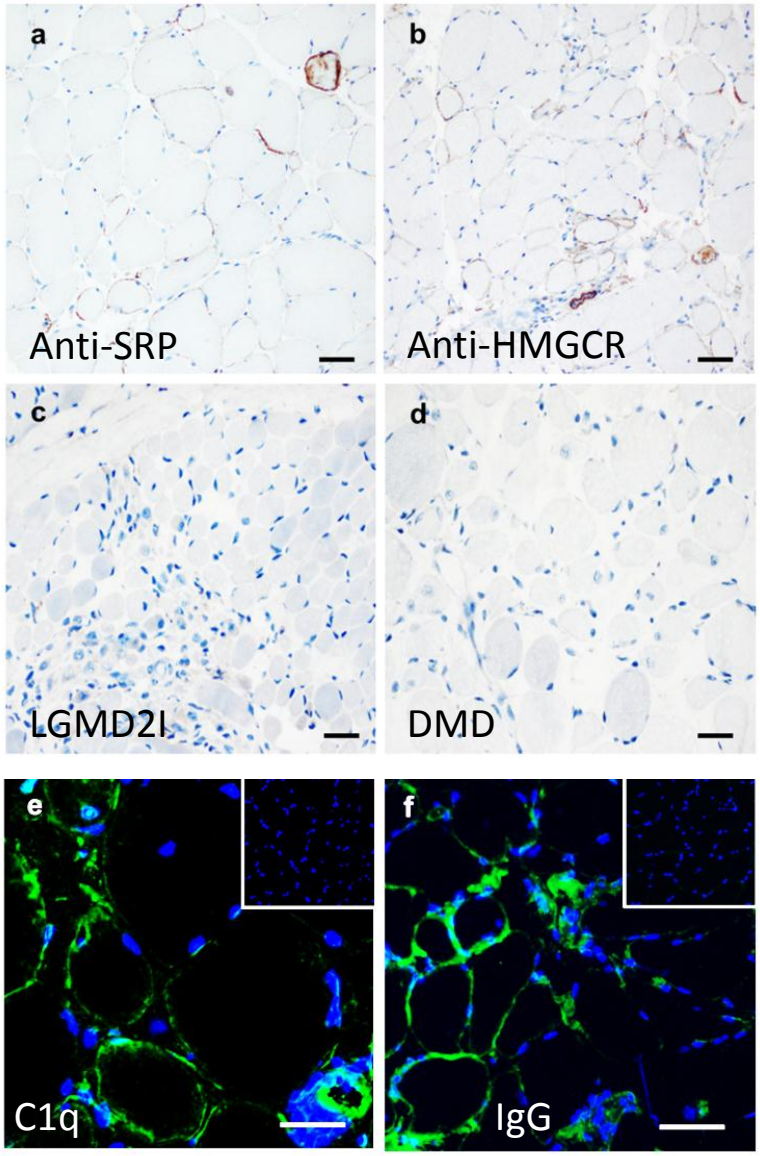
Neurology® 2018;90:e507-e517. doi:10.1212/WNL.0000000000004923

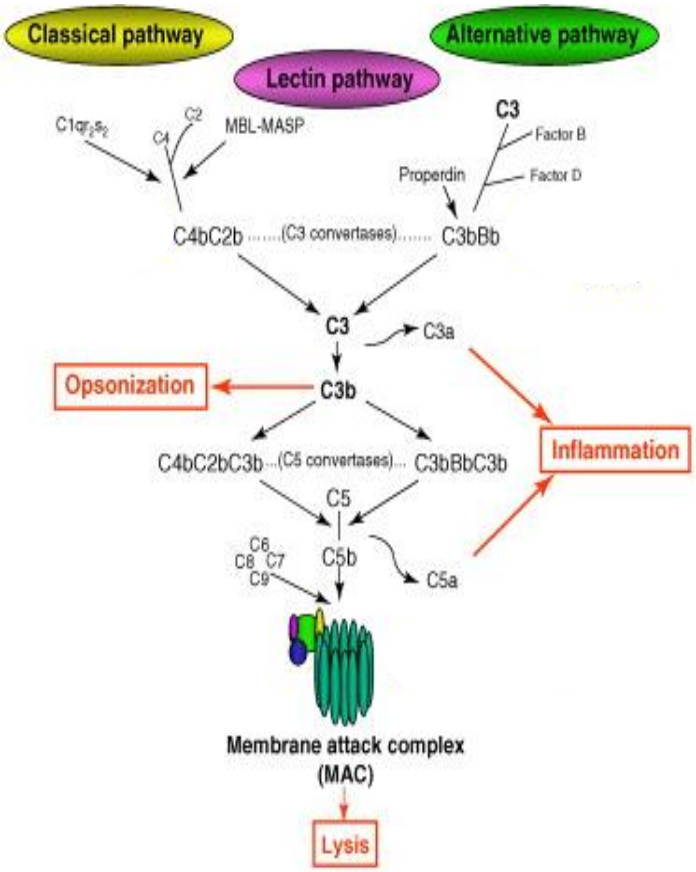




Fiber necrosis : role of the complement

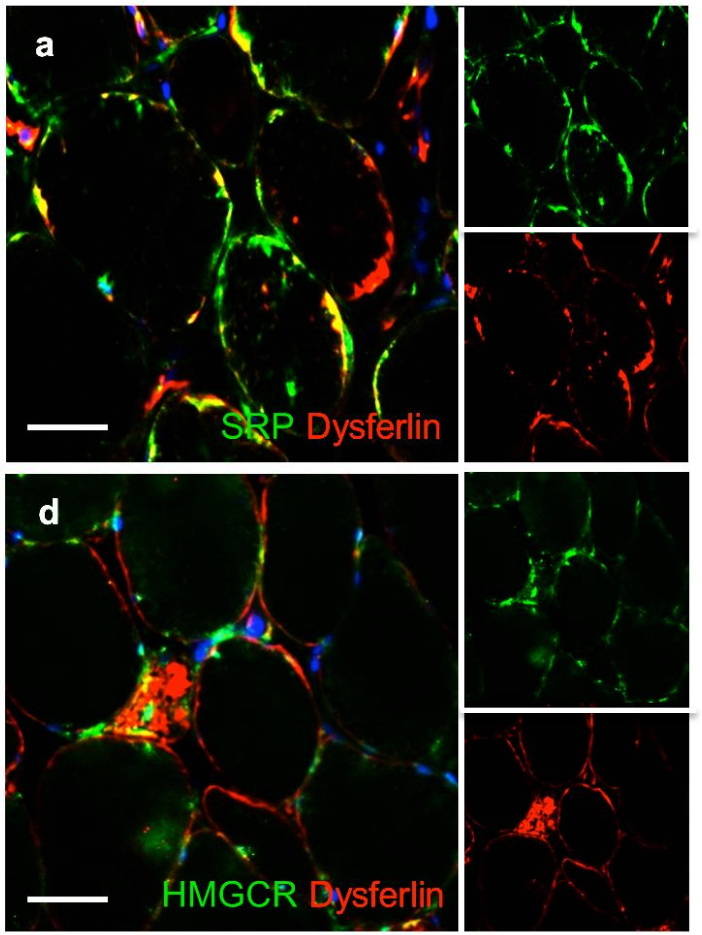
C5b9

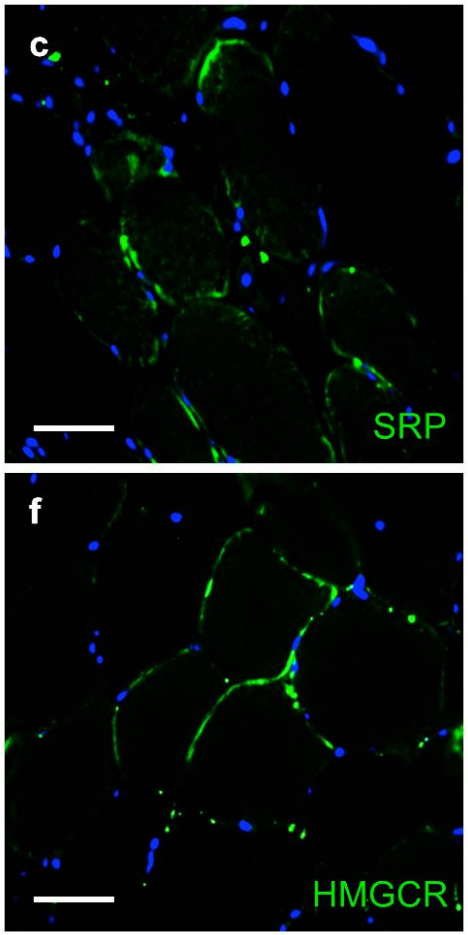




Y Allenbach Neurology 2018

How these Abs can reach their intracytosolic targets?

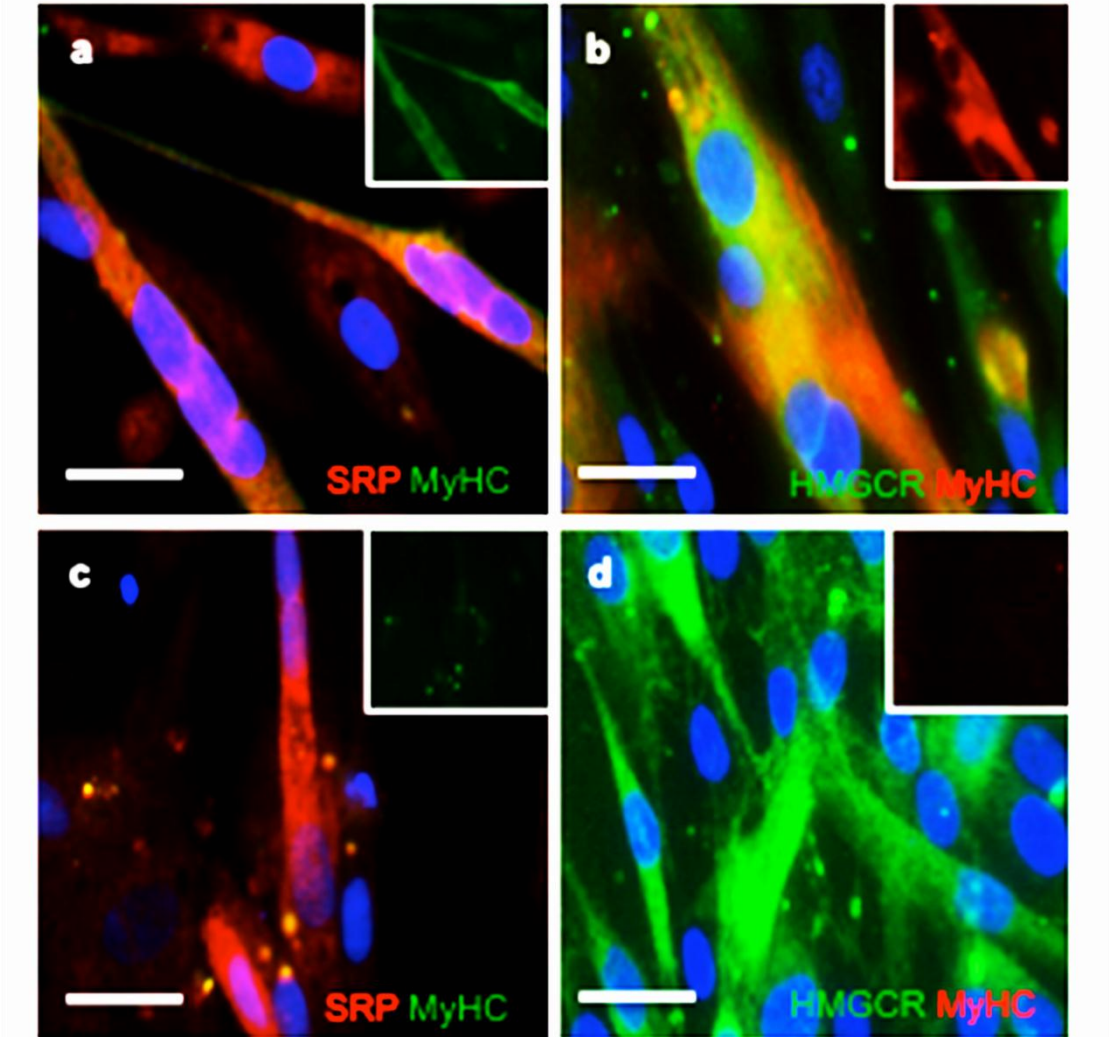




Commercial anti-SRP polyclonal Ab
Commercial anti-HMGCR monoclonal Ab

Patient's purified anti-SRP
Patient's purified anti-HMGCR

On young myotubes

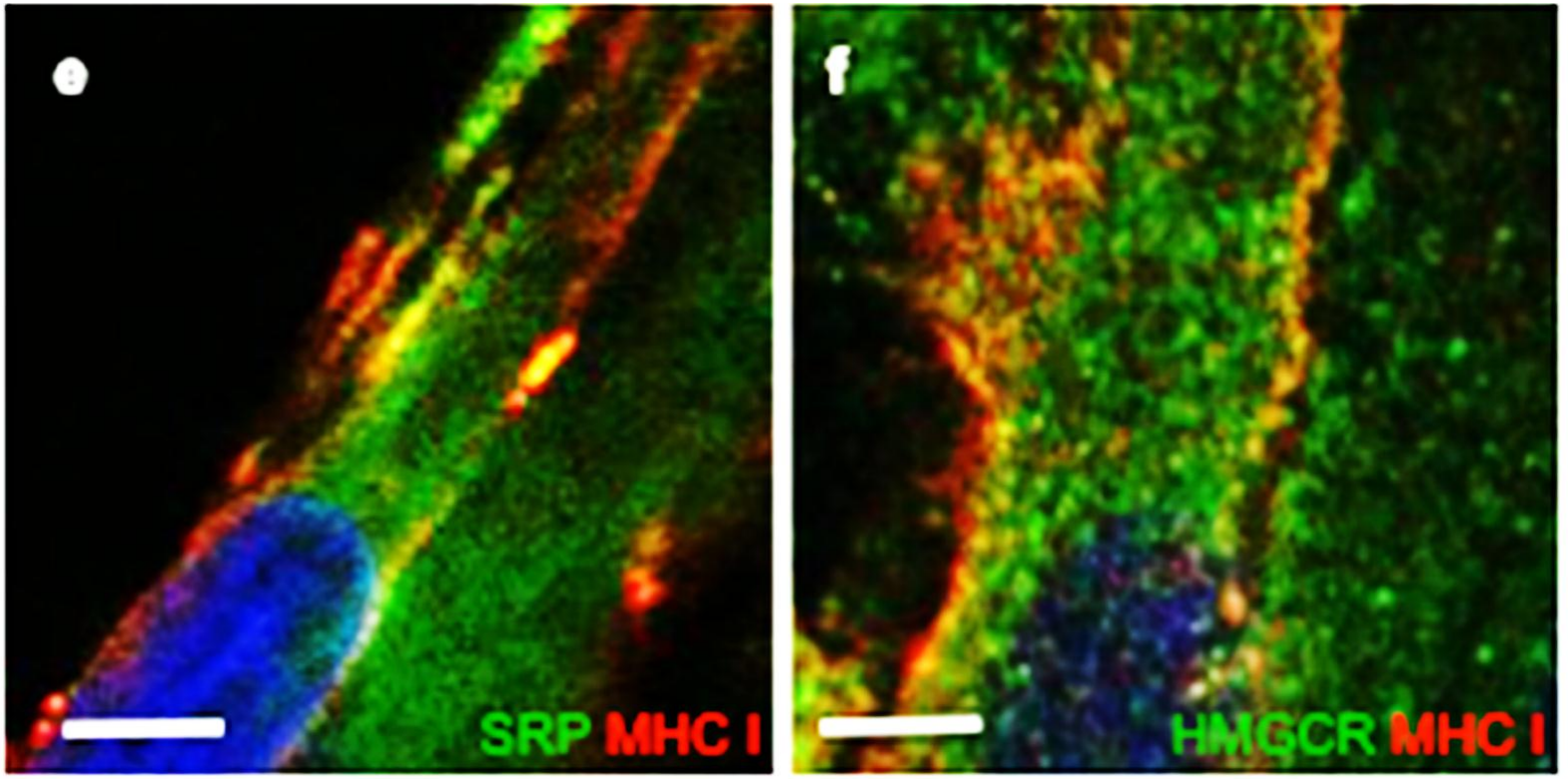


Patient's purified anti-SRP or HMGCR

L Arouche-Delaperche Ann. Neurol 2017

On young non permeabilized myotubes

Confocal microscope



Patient's purified anti-SRP

Patient's purified anti-HMGCR

Anti-SRP and anti-HMGCR reach their targets at the membrane surface

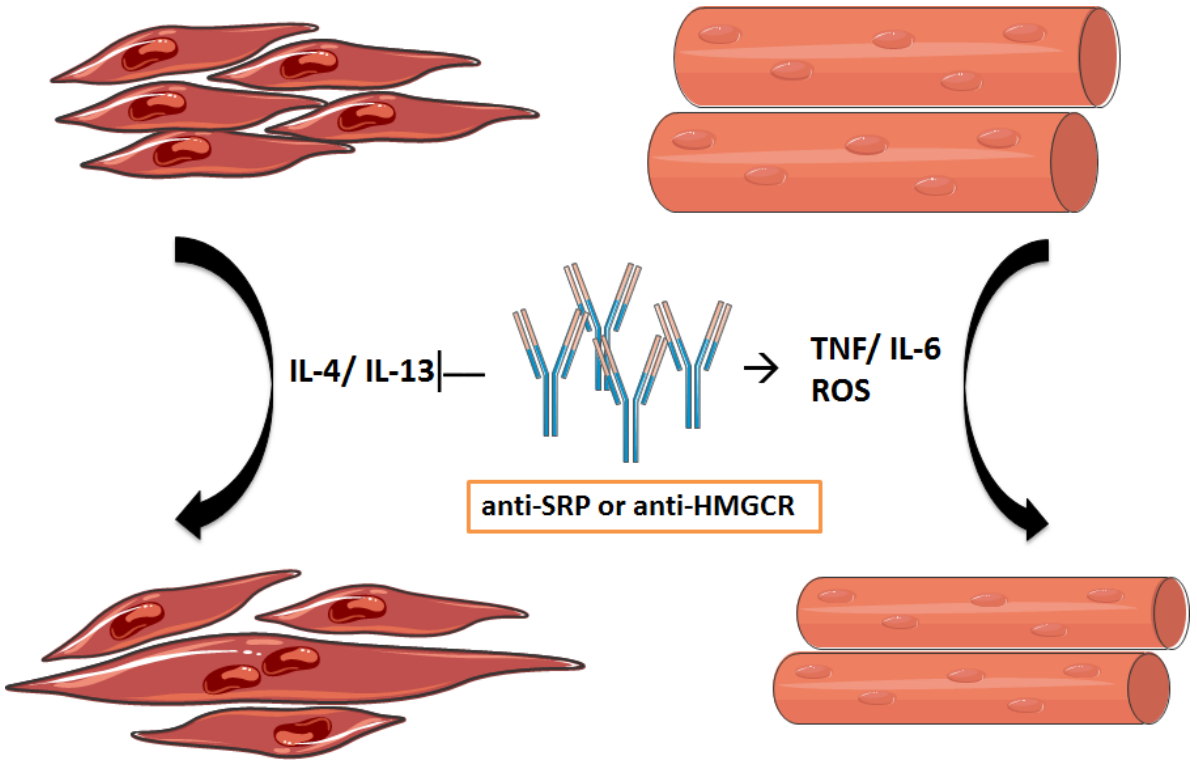
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

Volume 81, Issue 4
April 2017
Pages 538–548

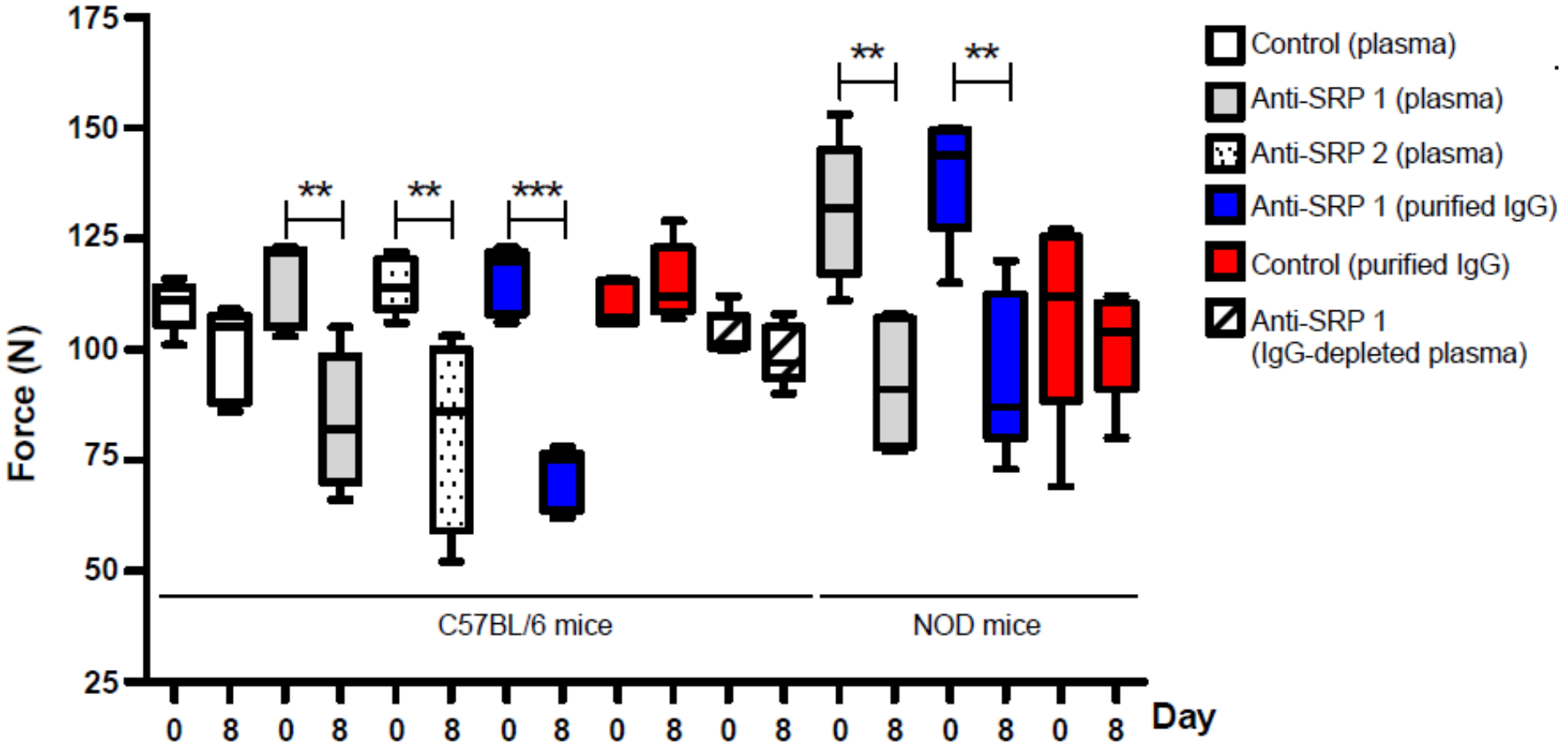
Research Article

Pathogenic role of anti–signal recognition protein and anti–3-Hydroxy-3-methylglutaryl-CoA reductase antibodies in necrotizing myopathies: Myofiber atrophy and impairment of muscle regeneration in necrotizing autoimmune myopathies

Louiza Arouche-Delaperche PhD, Yves Allenbach MD, PhD , Damien Amelin MSc, Corinna Preusse PhD, Vincent Mouly PhD, Wladimir Mauhin MD, Gaelle Dzangue Tchoupou MSc, Laurent Drouot PhD, Olivier Boyer MD, PhD, Werner Stenzel MD, PhD, Gillian Butler-Browne PhD, Olivier Benveniste MD, PhD

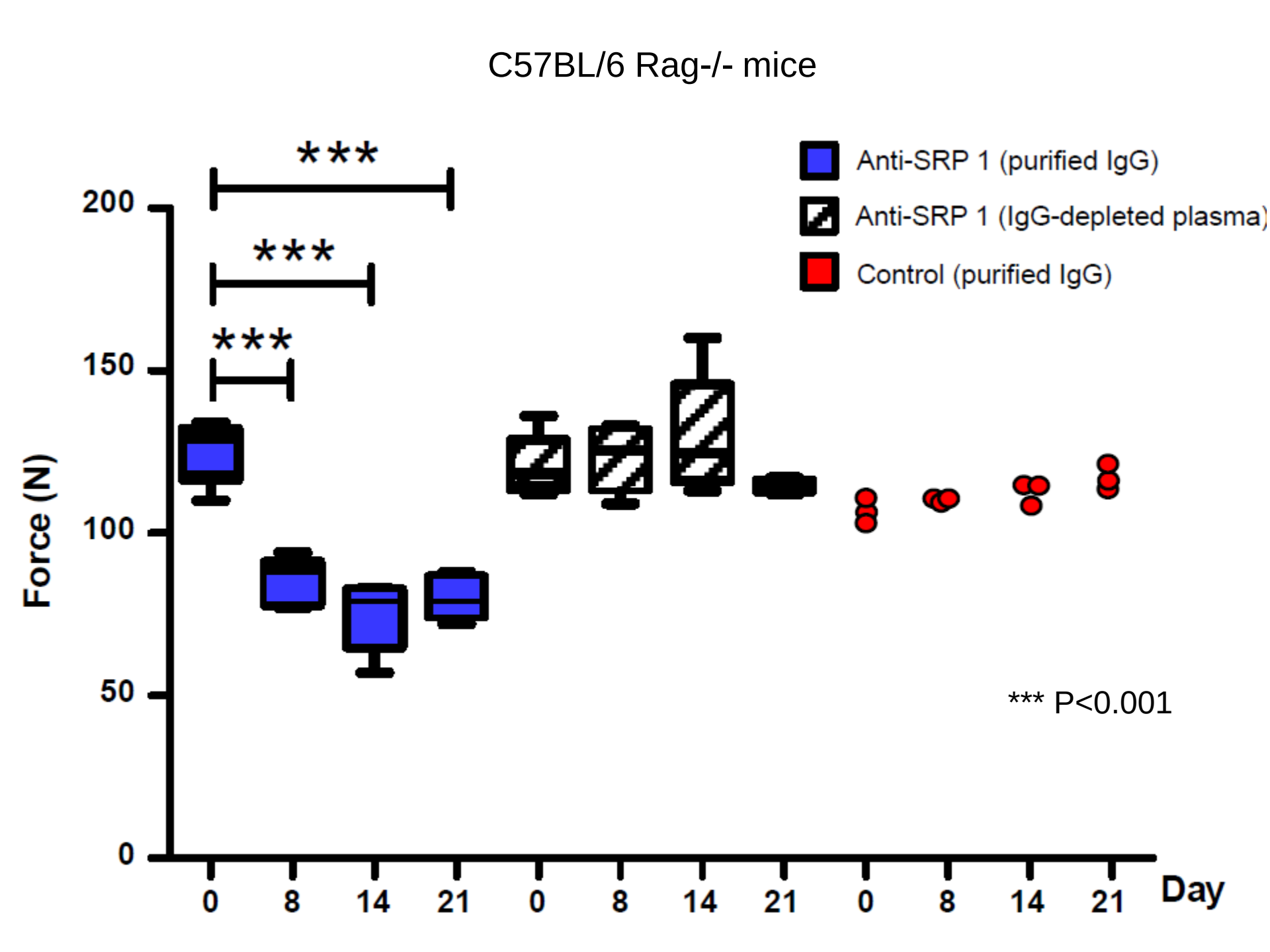


Passive transfer of anti-SRP Abs in mice



** P<0.01, *** P<0.001

O Boyer et al., Rouen, France

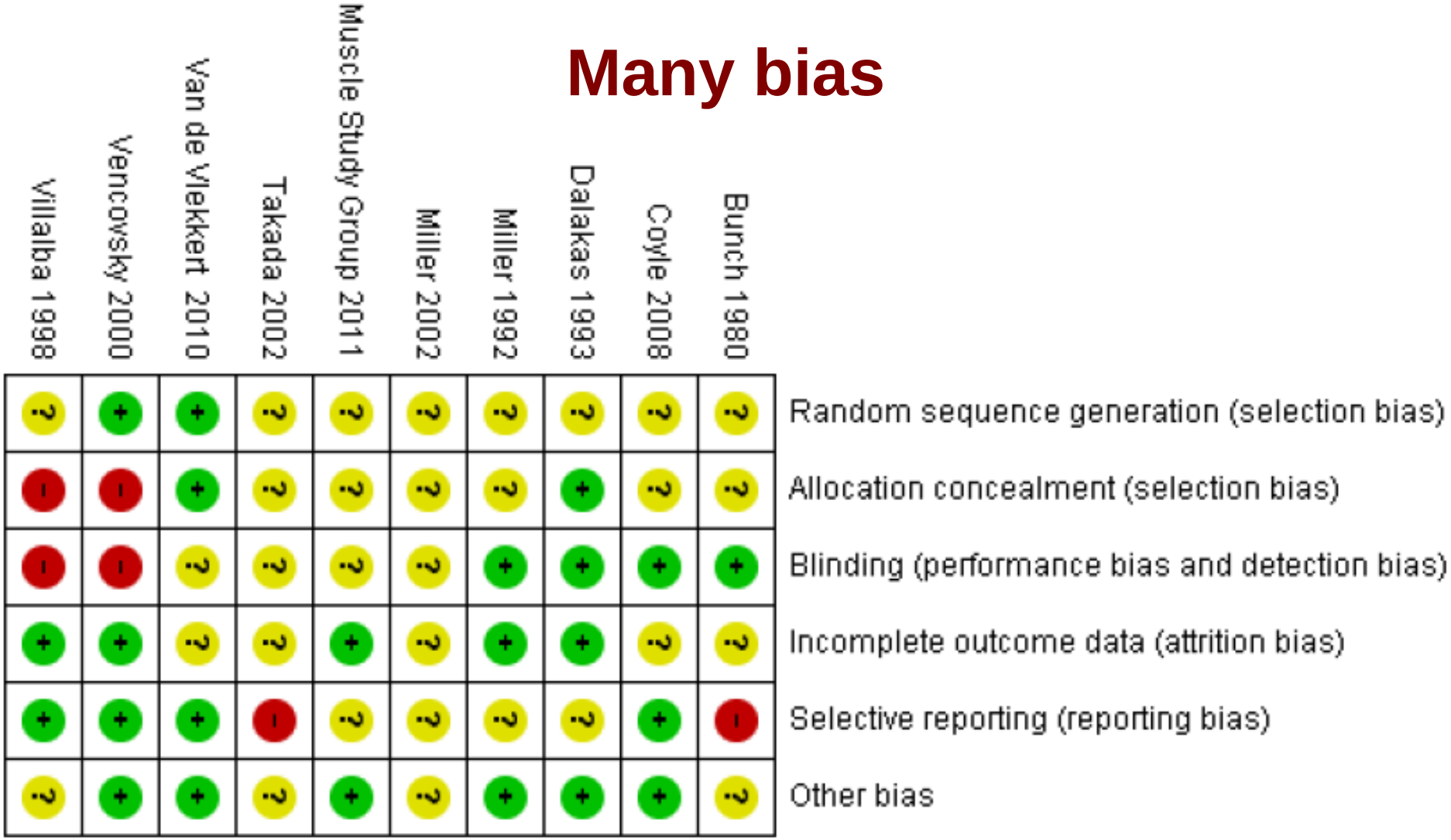

C57BL/6 Rag-/- mice
Anti-SRP 1 (purified IgG)
Anti-SRP 1 (IgG-depleted plasma)
Control (purified IgG)
***
***
***
Force (N)
200
150
100
50
0
0
8
14
21
0
8
14
21
0
8
14
21
Day
*** P<0.001

Only 10 Randomised Controlled Trials (RCT)

Authors, year	type	N	Intervention	Efficacy at x months
Dalakas, 1993	DM	15	IVIg vs pbo	Yes at 3
Miller, 1992	PM/DM	39	PE, leukap vs pbo	No at 1
Muscle Stud Gp, 2001	DM	16	Etanercept vs pbo	No at 12
Takada, 2002	DM	13	Eculizumab vs pbo	Yes? at 2
Coyle, 2008	PM/DM	18	Infliximab vs pbo	No at 3
Bunch, 1980	PM	16	Pred+ AZA vs pbo	No at 3
Villalba, 1998	PM/DM	30	MTX vs MTX+AZA	Yes at 6
Vencovsky, 2000	PM/DM	36	Pred+CSA vs MTX	Equival at 6
Miller, 2002	PM/DM	28	Pred+MTX vs AZA	Equival at 12
Van de Vlekkert, 2010	PM/DM	62	Pred vs Dexa	Equival at 18

Different outcomes: MMT on 5 to 13 point scale on 18 to 26 muscle groups

Many bias



Conclusion: lack of high quality RCTs that assess the efficacy and toxicity of immunosuppressants

Gordon PA et al. Cochrane Database of Systematic Reviews 2012, Issue 8.

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324
DOI 10.1002/art.37754

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

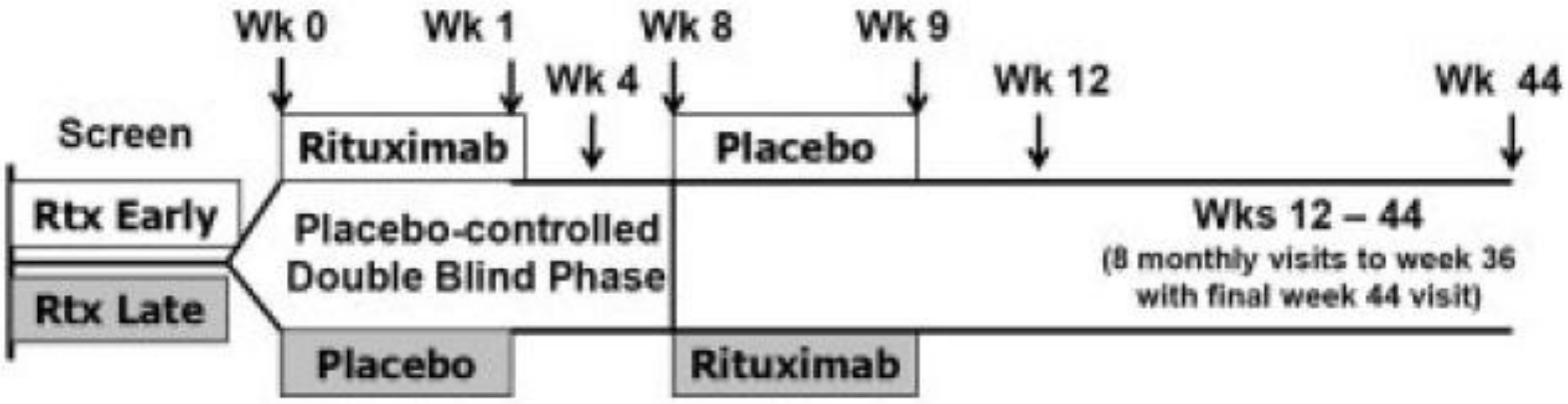
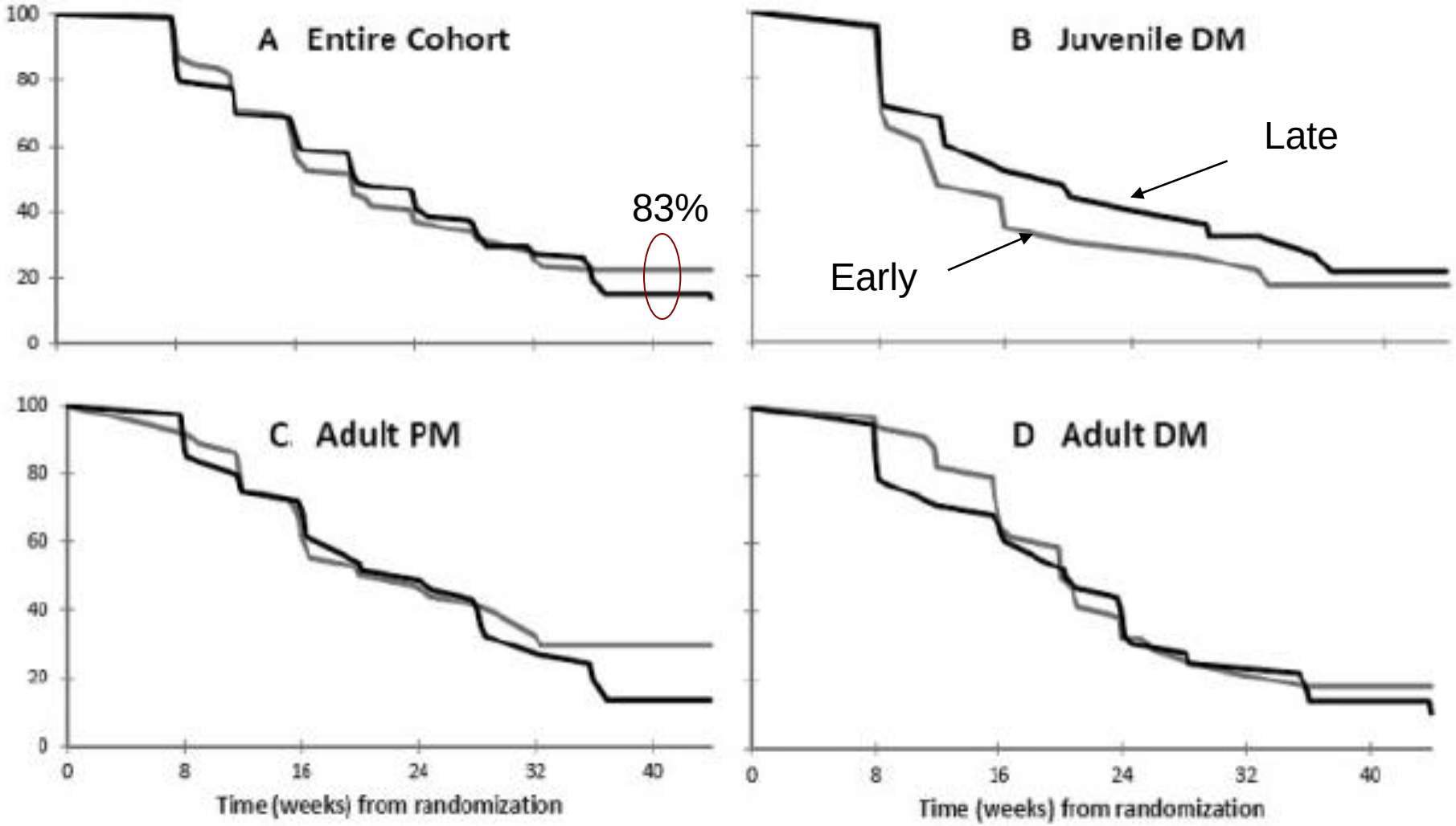


Table 1. Baseline demographic and clinical characteristics and core set measures, by treatment group*

Characteristic	Rituximab early (n = 96)	Rituximab late (n = 104)
No. (%) Caucasian	62 (65)	81 (78)
Age, mean ± SD years	43 ± 18.2	40 ± 18.4
No. (%) female	68 (71)	78 (75)
IIM subset		
PM	37	39
DM	36	40
Juvenile DM	23	25
Disease duration, mean ± SD years	5.2 ± 6.5	5.4 ± 6.0
Prednisone dosage, mean ± SD mg/day	19.7 ± 12.1	21.4 ± 14.4
No. (%) taking noncorticosteroid immunosuppressive agents	84 (88)	89 (86)
Myositis autoantibody, no. (%) positive		
Antisynthetase	16 (18)	16 (16)
Anti–signal recognition particle	13 (14)	12 (12)
DM-associated†	33 (37)	38 (38)
Other autoantibody‡	8 (9)	16 (16)
None of the above	20 (22)	19 (19)
No. with undefined autoantibody§	6	3
Mean MMT-8 ratio¶	71	71.7
Mean global assessment, by VAS (0–100 mm scale)		
Physician's	51.4	49.2
Patient's/parent's	65.4	65.6
Mean HAQ/C-HAQ disability index (range 0–3)	1.55	1.53
Muscle enzyme, mean ± SD ×ULN#	9.5 ± 14.9	5.5 ± 9.0
Mean extramuscular score, by VAS (0–100 mm scale)	27.4	30.7



Median time to achieving a DOI of 20 weeks in both groups (much longer than the 8 weeks of placebo controlled double blind phase)

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 3, March 2014, pp 740–749
DOI 10.1002/art.38270

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]

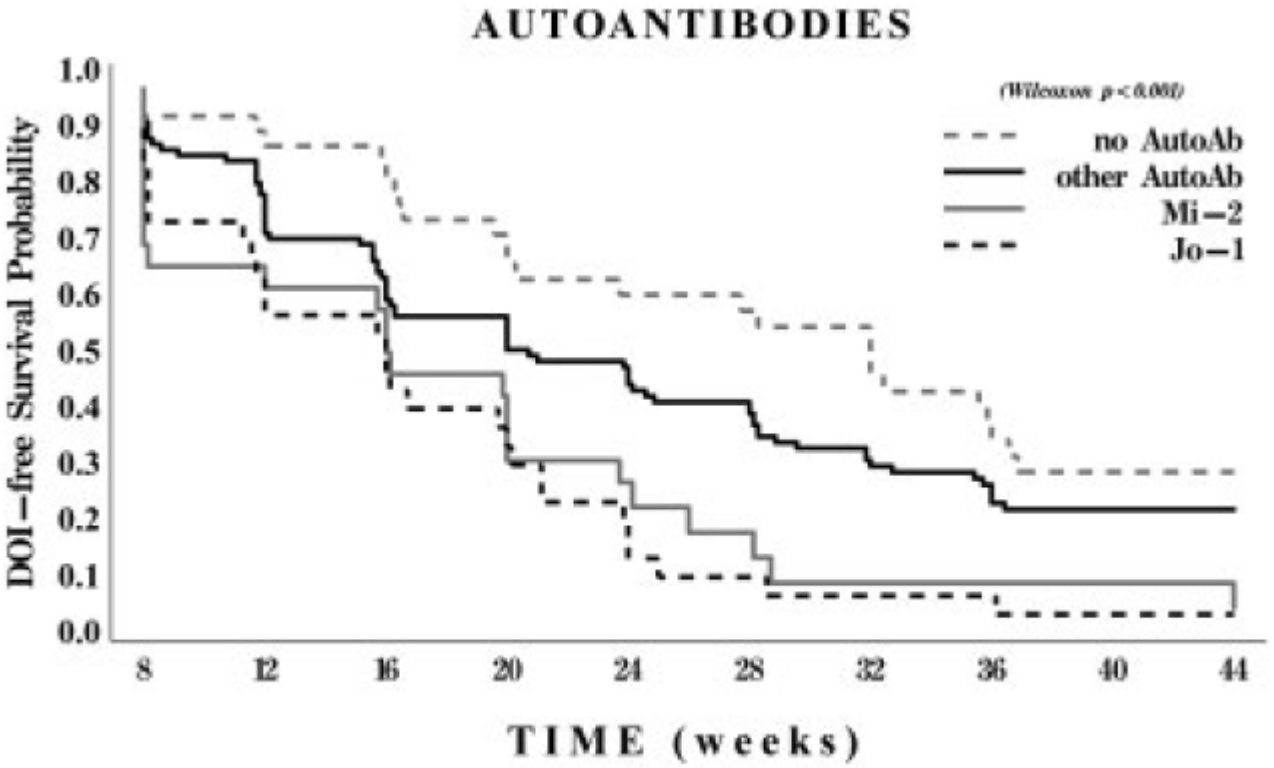


Figure 1. Kaplan-Meier curves for probability of meeting the definition of improvement (DOI) according to myositis autoantibody

Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial

Lancet 2016; 387: 671–78

Nicolino Ruperto, Angela Pistorio*, Sheila Oliveira*, Francesco Zulian, Ruben Cuttica, Angelo Ravelli, Michel Fischbach, Bo Magnusson, Gary Sterba, Tadej Avcin, Karine Brochard, Fabrizia Corona, Frank Dressler, Valeria Gerloni, Maria T Apaz, Claudia Bracaglia, Adriana Cespedes-Cruz, Rolando Cimaz, Gerard Couillault, Rik Joos, Pierre Quartier, Ricardo Russo, Marc Tardieu, Nico Wulffraat, Blanca Bica, ınay, ıl Trials

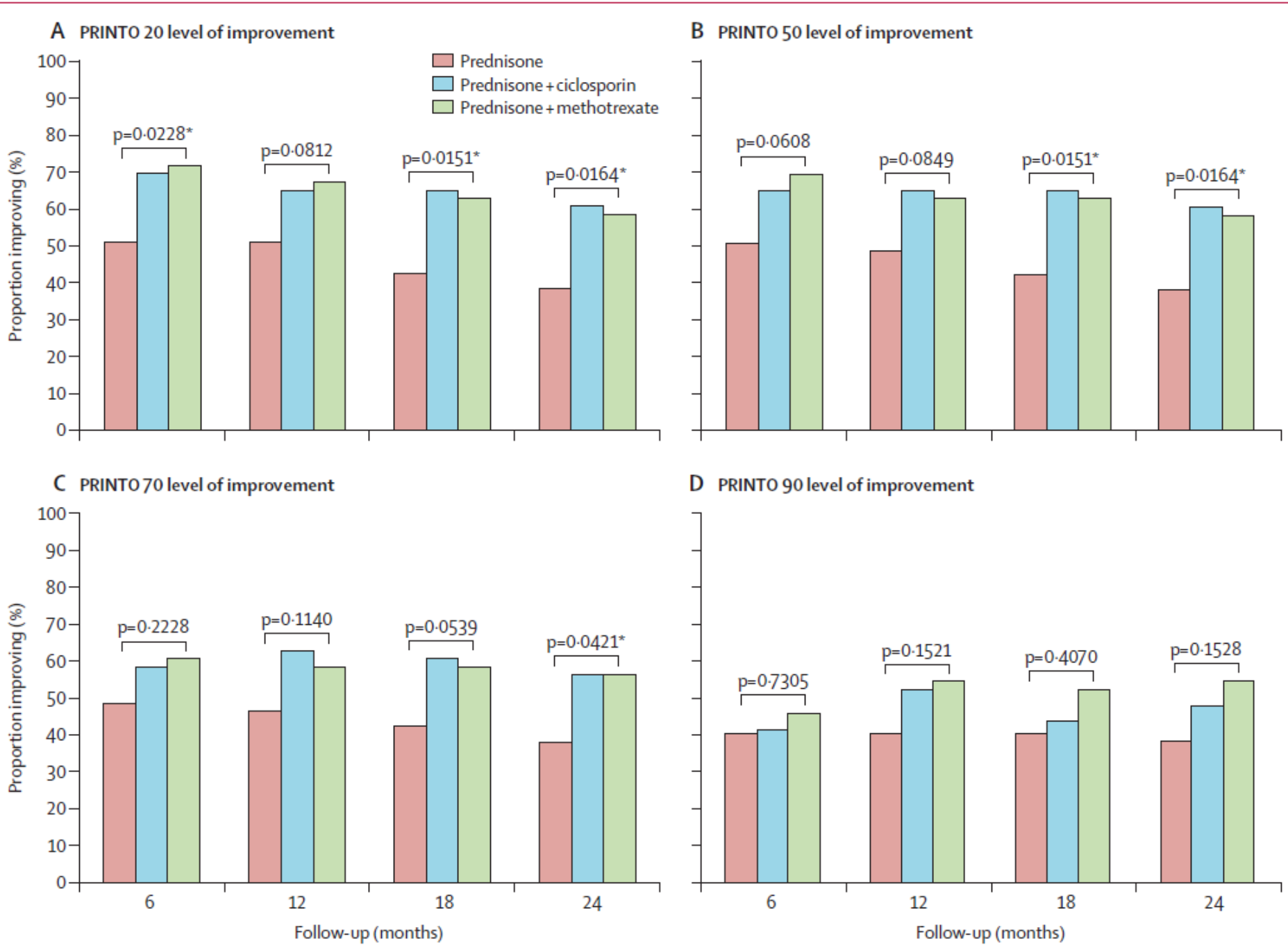
	Prednisone (n=47)	Prednisone plus ciclosporin (n=46)	Prednisone plus methotrexate (n=46)
Women	26 (55%)	26 (57%)	30 (65%)
Men	21 (45%)	20 (43%)	16 (35%)
Ethnic origin			
White European	32 (68%)	32 (70%)	29 (63%)
Hispanic	8 (17%)	5 (11%)	6 (13%)
Other	2 (4%)	5 (11%)	6 (13%)
Unknown	5 (11%)	4 (9%)	5 (11%)
Age at onset (years)	6·7 (4·6–10·0)	8·8 (5·0–11·3)	6·7 (3·9–10·1)
Age at first observation (years)	7·2 (5·1–10·1)	8·9 (5·1–12·4)	7·1 (4·3–10·4)
Disease duration (months)	2·6 (1·2–5·1)	2·7 (1·2–6·2)	2·8 (1·9–5·0)
Bodyweight (kg)	23·2 (17·5–31·3)	31·0 (18·0–41·7)	24·3 (17·0–38·0)
Body surface area (m^2)	0·9 (0·7–1·1)	1·1 (0·8–1·3)	0·9 (0·7–1·2)
Previous use of prednisone, or equivalent	3 (6%)	2 (4%)	3 (7%)

Data are median (IQR) or number of patients (%). No patients had previously received ciclosporin, methotrexate, or other drugs.

Table 1: Baseline demographic and disease characteristics

139 patients
54 centres
22 countries

2 years of tt


A PRINTO 20 level of improvement
B PRINTO 50 level of improvement
C PRINTO 70 level of improvement
D PRINTO 90 level of improvement
Prednisone
Prednisone + ciclosporin
Prednisone + methotrexate
Proportion improving (%)
Follow-up (months)
p=0·0228*
p=0·0812
p=0·0151*
p=0·0164*
p=0·0608
p=0·0849
p=0·0151*
p=0·0164*
p=0·2228
p=0·1140
p=0·0539
p=0·0421*
p=0·7305
p=0·1521
p=0·4070
p=0·1528
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80
90
100
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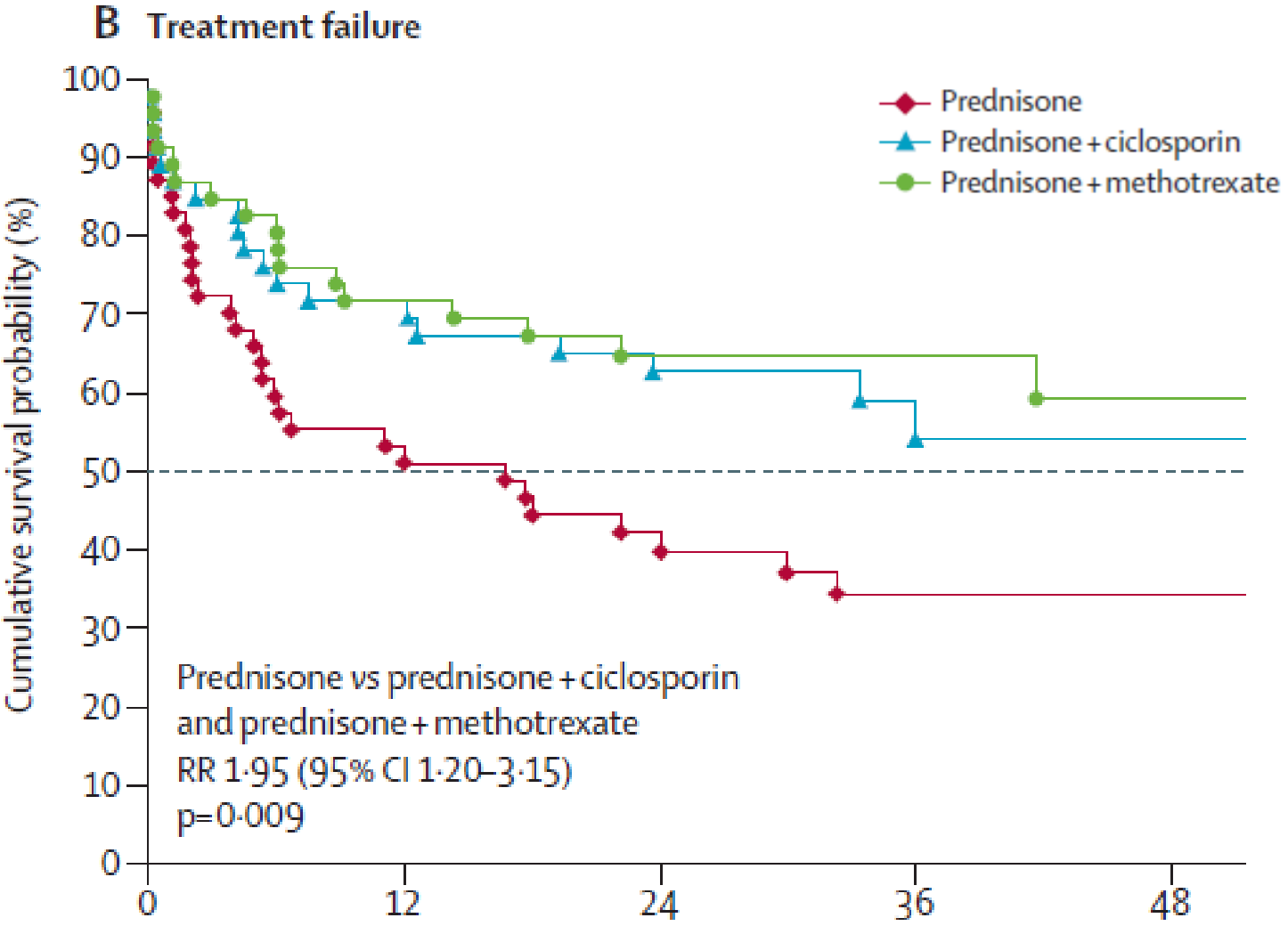
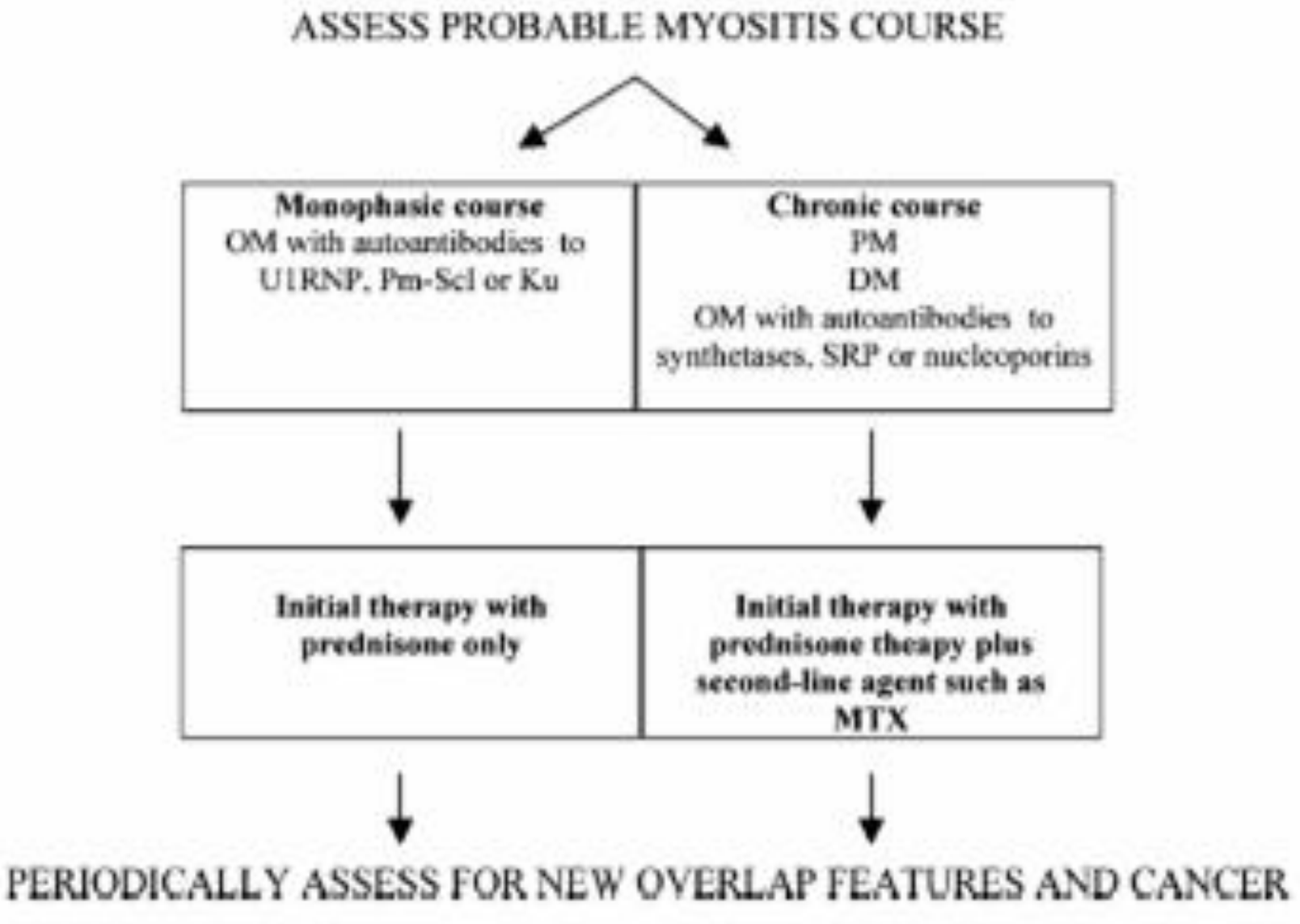
12
18
24



Interpretation Combined treatment with prednisone and either ciclosporin or methotrexate was more effective than prednisone alone. The safety profile and steroid-sparing effect favoured the combination of prednisone plus methotrexate.

Recommandation



Troyanov et al. Medicine 2005; 84(4): 231-49

Intravenous Immune Globulin for Statin-Triggered Autoimmune Myopathy

N ENGL J MED 373;17 NEJM.ORG OCTOBER 22, 2015

Table 1. **Clinical Characteristics of Patients with Statin-Triggered Autoimmune Myopathy Who Received Intravenous Immune Globulin Monotherapy.***

Characteristic	Patient 1	Patient 2	Patient 3†
Age (yr)			
At start of statin	57	53	63
At onset of muscle-related symptoms	57	53	67
At discontinuation of statin	57	65	68
At first IVIG treatment	63	65	69
Evaluation immediately before IVIG			
Creatine kinase (IU/liter)	8916	2323	3517
Strength			
Arm abductors			
Contraction against resistance			
Right	4	4+	4
Left	4	4+	4
Weight resisted (kg)			
Right	2.7	5.0	2.7
Left	2.7	5.0	3.2
Hip flexors			
Contraction against resistance			
Right	2	4	4
Left	2	4	4
Weight resisted (kg)			
Right	NA	13.6	6.4
Left	NA	12.2	6.4
Anti–HMG-CoA reductase antibody titer (NAU)	0.845	0.566	1.650

Table 1. **(Continued.)**

Characteristic	Patient 1	Patient 2	Patient 3†
Most recent evaluation			
Time since first IVIG (mo)	9	19	15
Creatine kinase (IU/liter)	1755	64	877
Strength			
Arm abductors			
Contraction against resistance			
Right	5	5	5
Left	5	5	5
Weight resisted (kg)			
Right	6.8	NA	5.9
Left	6.4	NA	8.2
Hip flexors			
Contraction against resistance			
Right	4+	5	5
Left	4+	5	5
Weight resisted (kg)			
Right	13.6	NA	NA
Left	12.7	NA	NA
Anti–HMG-CoA reductase antibody titer (NAU)	0.764	0.471	1.179

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Eleni Tiniakou, M.D.
Johns Hopkins University School of Medicine
Baltimore, MD

Consensus for the treatment of IMNM

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) 87–99

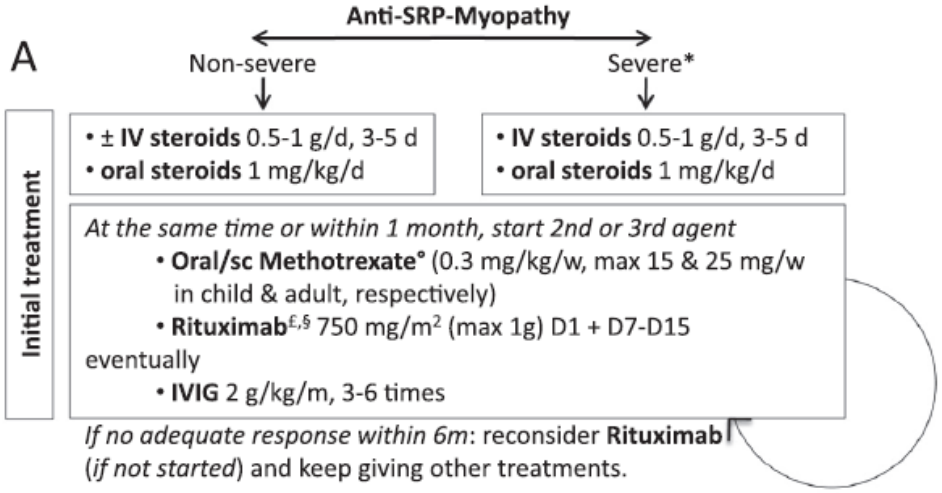
www.elsevier.com/locate/nmd

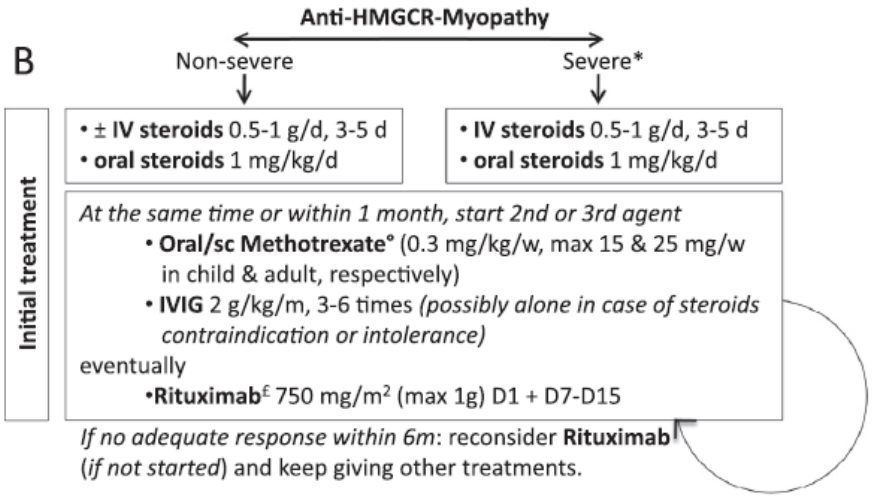
Workshop report

224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016

Yves Allenbach [a,1], Andrew L. Mammen [b,1], Olivier Benveniste [a,2], Werner Stenzel [c,2,*] on behalf of the Immune-Mediated Necrotizing Myopathies Working Group [3]

Treatment of IMNM





Anti-SRP & anti-HMGCR-Myopathy

Maintenance treatment

- Taper **oral steroids** to the lowest dose as tolareted or as soon as possible (regarding the maximum benefit)
- Continue **Methotrexate** at least 2 years of well-controlled disease (slowly tapered later: 2.5 mg/w each month)
- Continue **Rituximab** every 6 months, at least 2 years of well-controlled disease
- If started **IVIG** are stopped or tapered, as tolerated.Nota bene: many HMGCR+patients may required IVIG

The Myositis Association in France: GIMI

AFMTÉLÉTHON
INNOVER POUR GUERIR

Acknowledgements

- Werner Stenzel, Berlin, D
- David Hilton-Jones, Oxford, UK
- Andrew L Mammen, Bethesda, USA
- Olivier Boyer, Rouen, F

and my colleagues from:

- Bruno Eymard
- Pascal Laforêt
- Baptiste Hervier
- Yves Allenbach