Myopathies inflammatoires : leurs nouveaux visages à la lumière des nouveaux biomarqueurs

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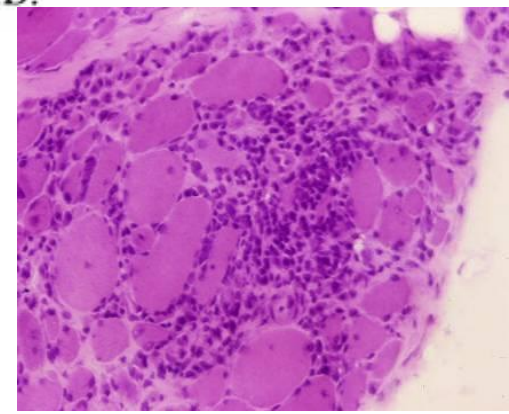
344 THE NEW ENGLAND JOURNAL OF MEDICINE February 13, 1975

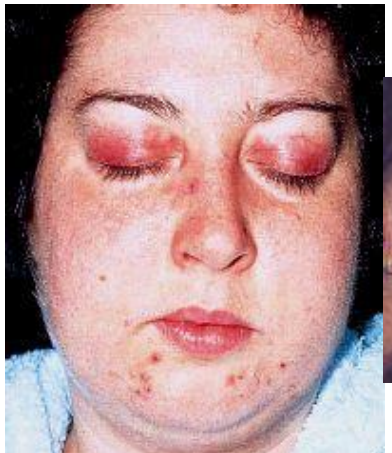
MEDICAL PROGRESS

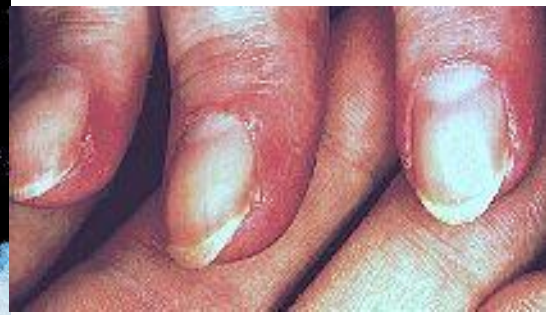
POLYMYOSITIS AND DERMATOMYOSITIS (First of Two Parts)

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

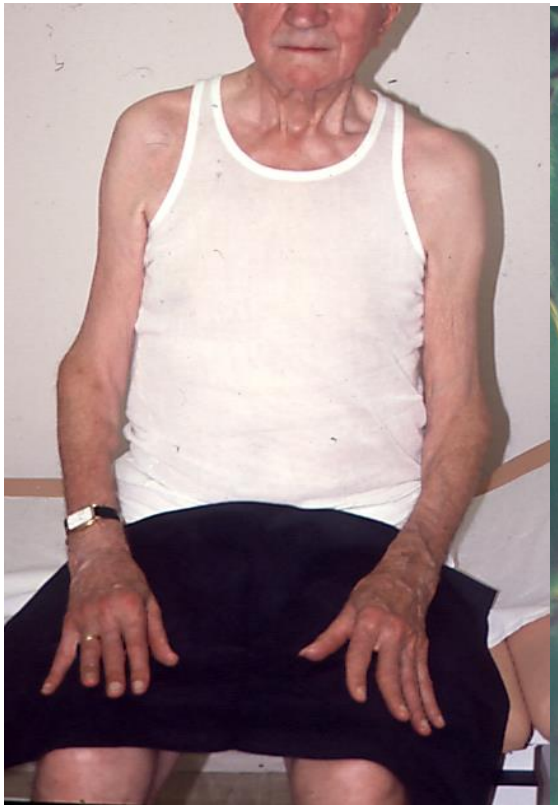


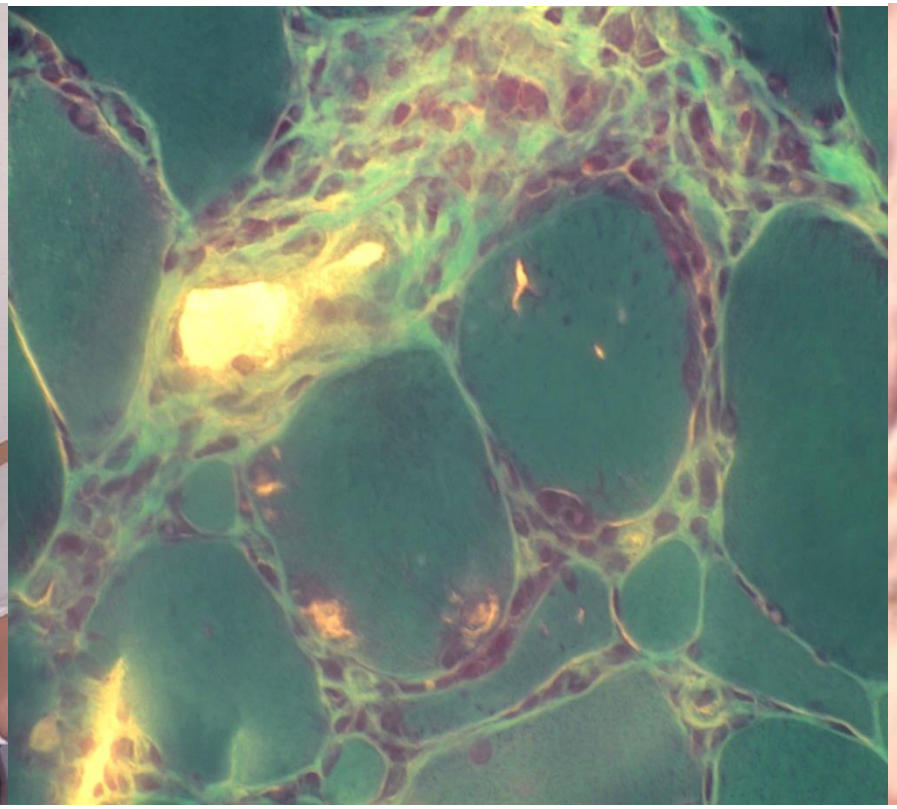
1. Déficit proximal bilatéral et symétrique;
2. Anomalies à la biopsie musculaire :
    1. Nécrose de fibres musculaires;
    2. Régénération;
    3. Infiltrats inflammatoires périvasculaires et interstitels avec destructions des fibres.
3. Elévation des CPK, Transaminases, LDH ou aldolases;
4. EMG : Sd myogène
5. Rash cutanés typiques.

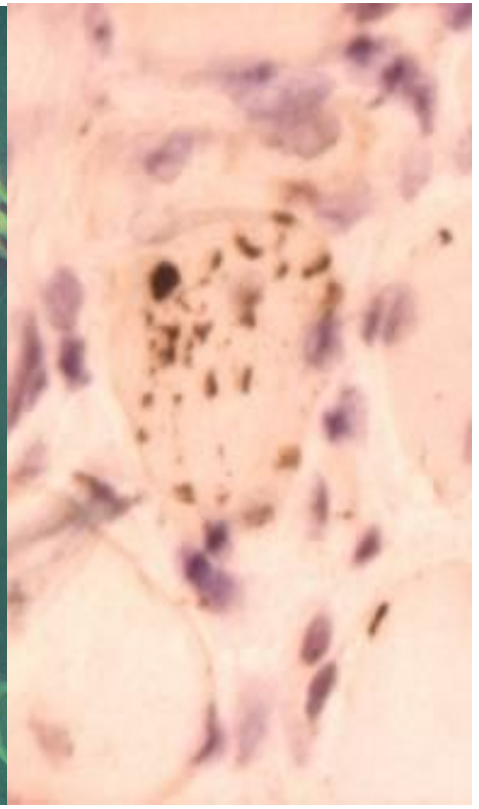




- DEFINITIF : 4 des 5 critères
- PROBABLE : 3 des 5 critères







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

Myopathies Nécrosantes AI

PERGAMON

Neuromuscular Disorders 14 (2004) 337–345

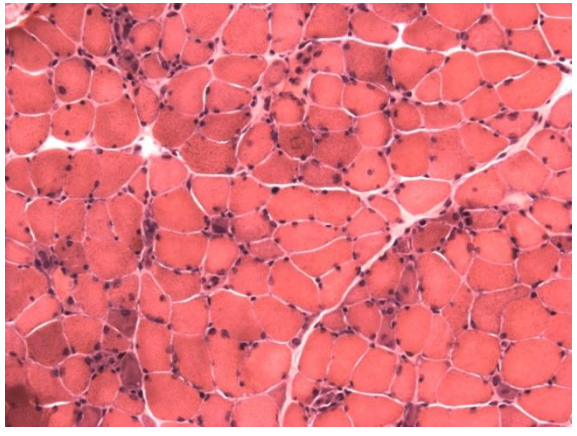
www.elsevier.com/locate/nmd

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

Nécrose + régénération sans inflammation

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

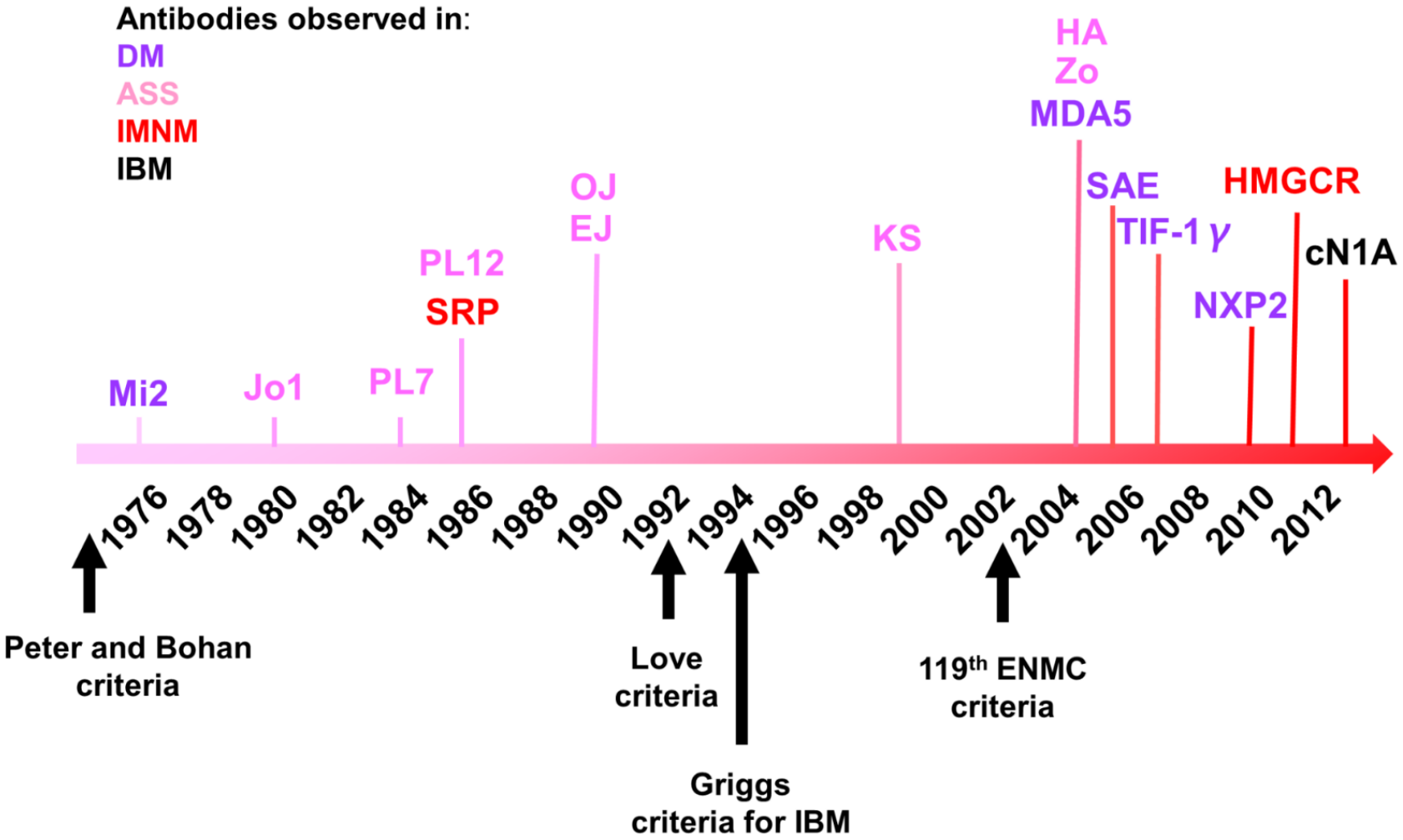
CME

Polymyositis

An overdiagnosed entity

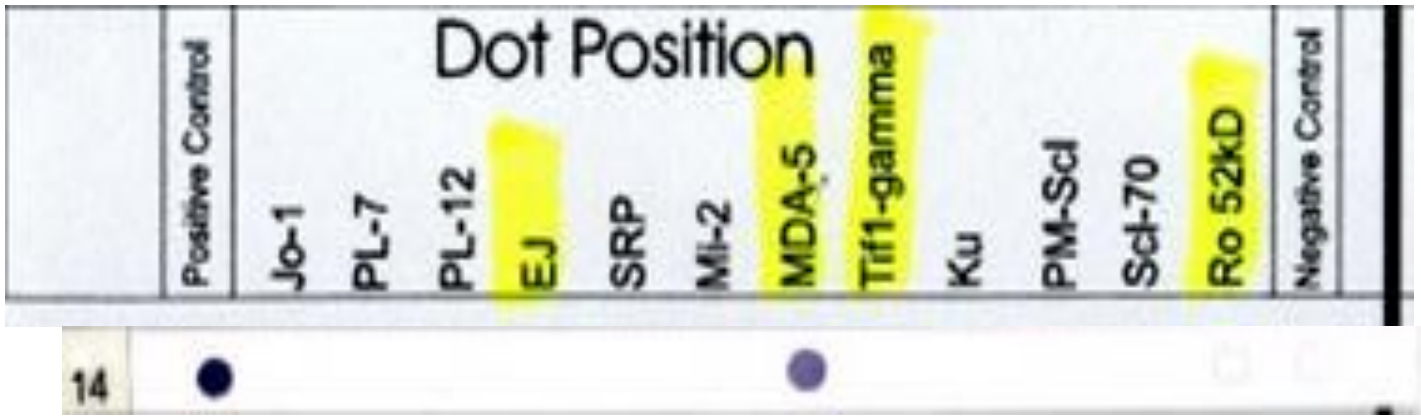
M.F.G. van der Meulen, MD; I.M. Bronner, MD; J.E. Hoogendijk, MD, PhD; H. Burger, MD, PhD; W.J. van Venrooij, PhD; A.E. Voskuyl, MD, PhD; H.J. Dinant, MD, PhD; W.H.J.P. Linssen, MD, PhD; J.H.J. Wokke, MD, PhD; and M. de Visser, MD, PhD

Myositis specific auto-antibodies



Benveniste, Curr Opin Neurol, 2016

Utilisation des tests commerciaux



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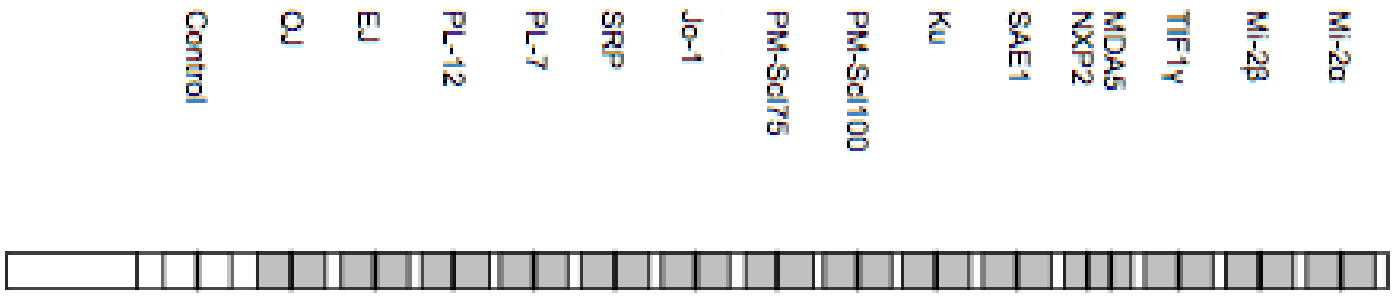


15 Ac

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]

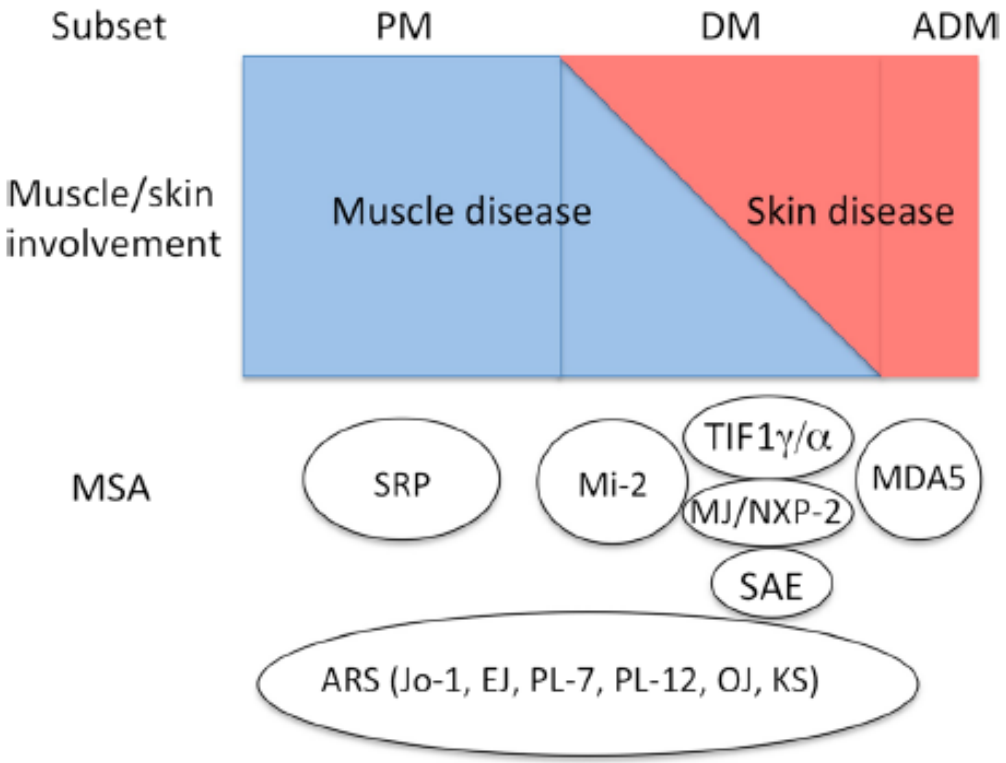
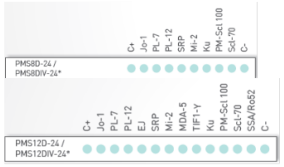


Fig. 1 A summary of the association of myositis-specific autoantibodies with the spectrum of muscle and skin involvements in different subsets of PM/DM



*DM, PM defined in 1975 by Bohan and Peter,
*IBM under the criteria of Griggs & al, 1995 reviewed by Lloyd & all, in 2014
*IMNM by Hoogendijk & al, in 2004

Registry of Myositis in Neuro-Muscular Diseases Reference Center (GHPS)
N= 1150

→ Dot myositis not done (n= 643)

Dot myositis performed (GHPS)
period 2003-2014
N=507

→ Myositis not defined (n=62)

Myositis defined according to historical classifications
N= 445

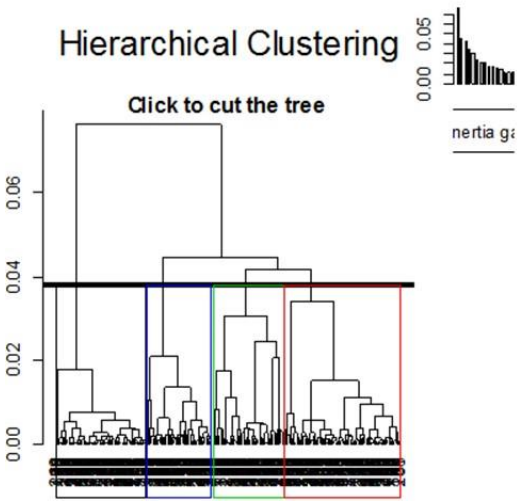
→ Files not available or uncompleted (n=84)

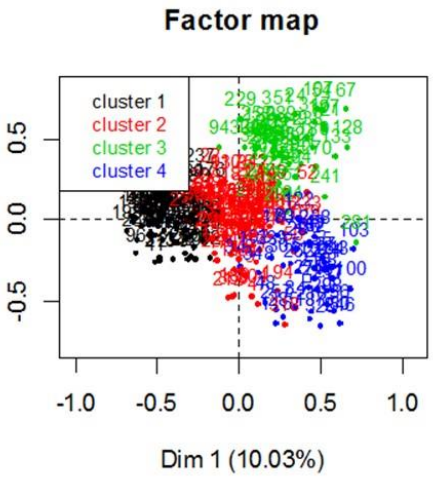
Patient's files completed for analysis
N= 361

Unsupervised classification methods (MCA, HCA) then prediction (CART)

Biobank, n=400

Multiple Correspondence Analysis (MCA) and Hierarchical Cluster Analysis (HCA)





Cluster 1 = IBM, anti-cN1A
Cluster 2 = IMNM, anti-SRP&HMGCR
Cluster 3 = DM, anti-Mi2, TIF1g, MDA5..
Cluster 4 = OM, anti-Jo1, PL7, PL12…

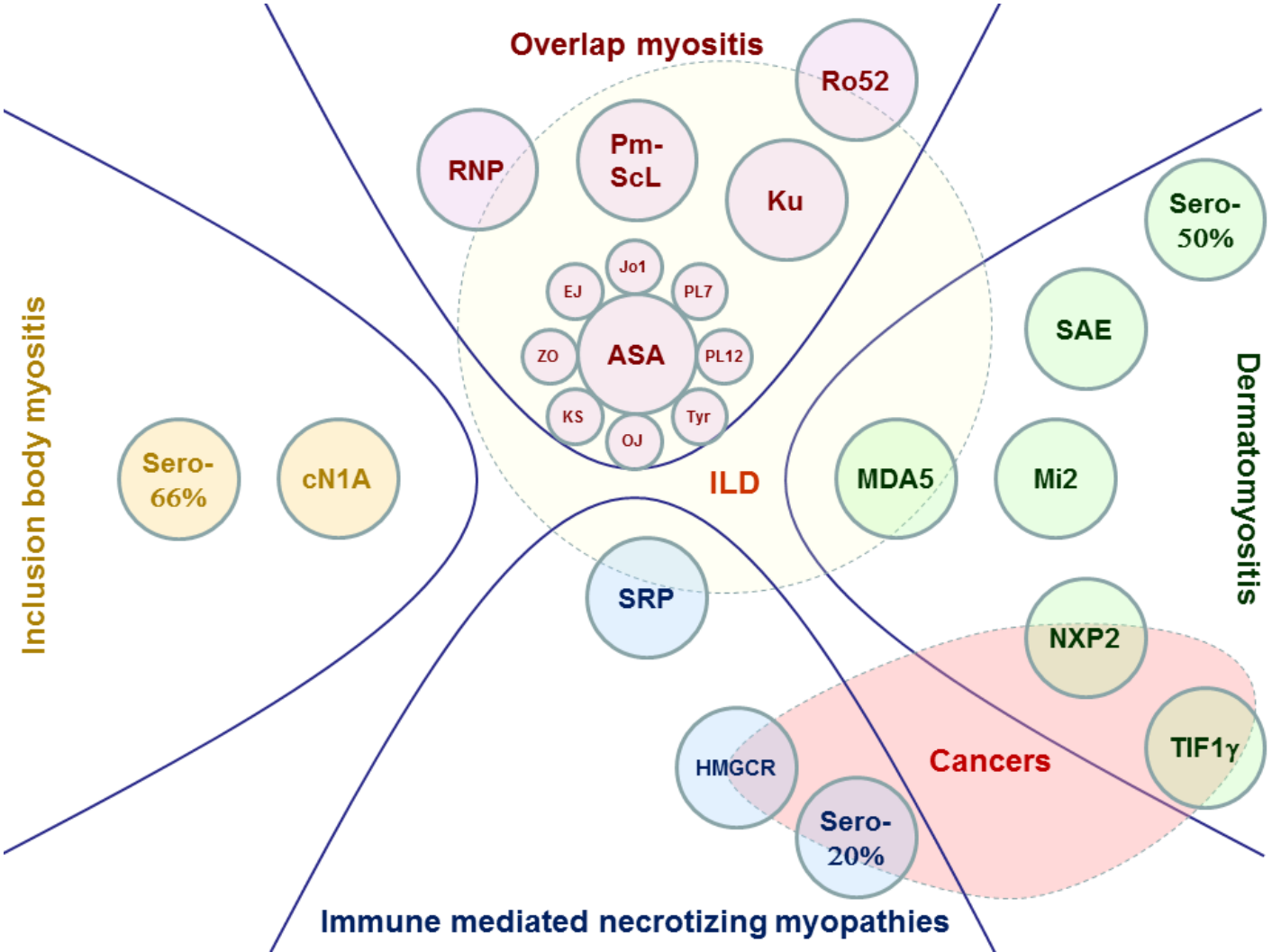
Kuberaka Mariampillai, submitted

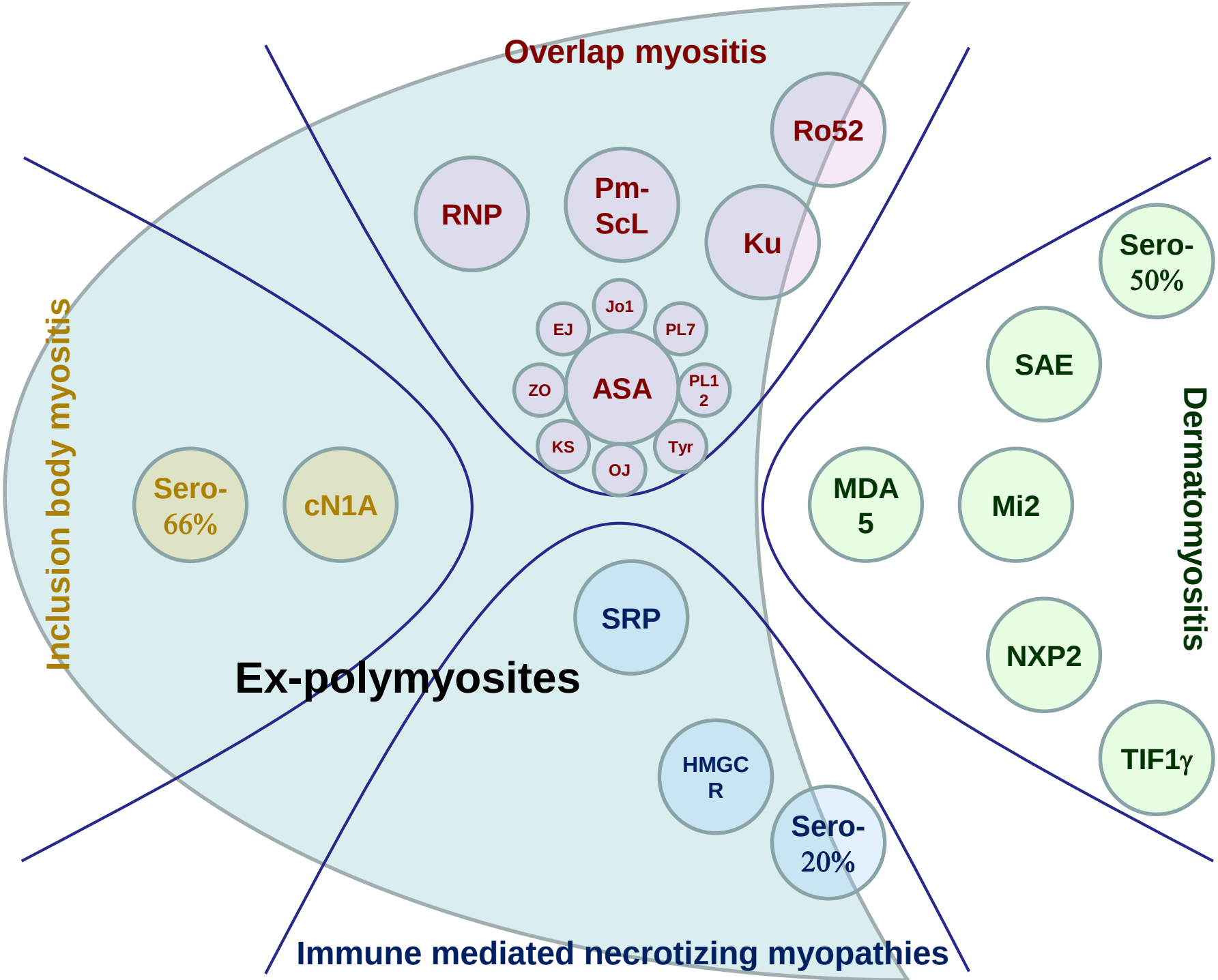
CURRENT OPINION

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]




Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
EJ
PL7
ZO
ASA
PL12
KS
Tyr
OJ
Sero-50%
SAE
Dermatomyositis
Inclusion body myositis
Sero-66%
cN1A
MDA5
Mi2
SRP
Ex-polymyosites
NXP2
TIF1γ
HMGCR
Sero-20%
Immune mediated necrotizing myopathies

Pronostic des myosites

Ikeda *et al. SpringerPlus* (2015) 4:240
DOI 10.1186/s40064-015-1013-8

SpringerPlus
a SpringerOpen Journal

RESEARCH Open Access

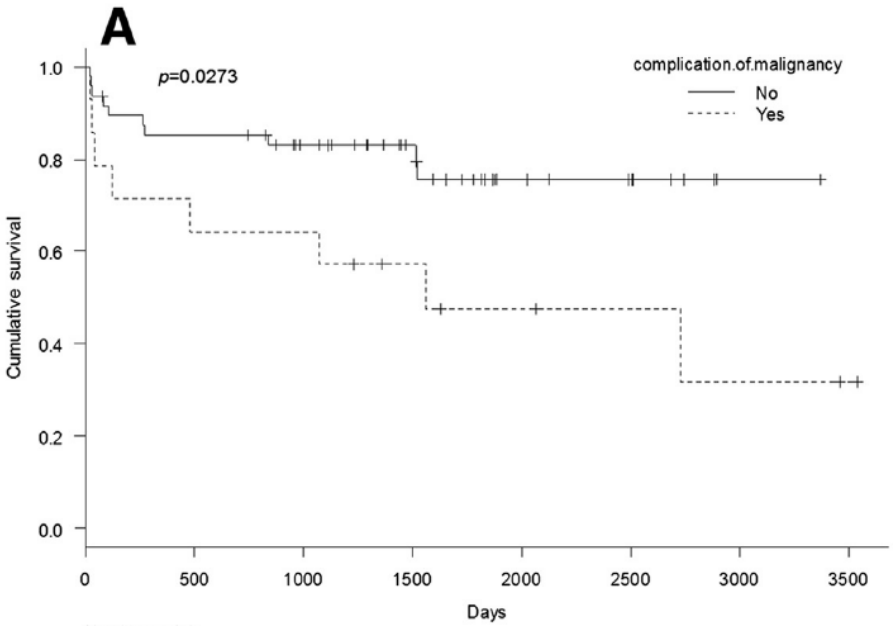
Incidence and impact of interstitial lung disease and malignancy in patients with polymyositis, dermatomyositis, and clinically amyopathic dermatomyositis: a retrospective cohort study

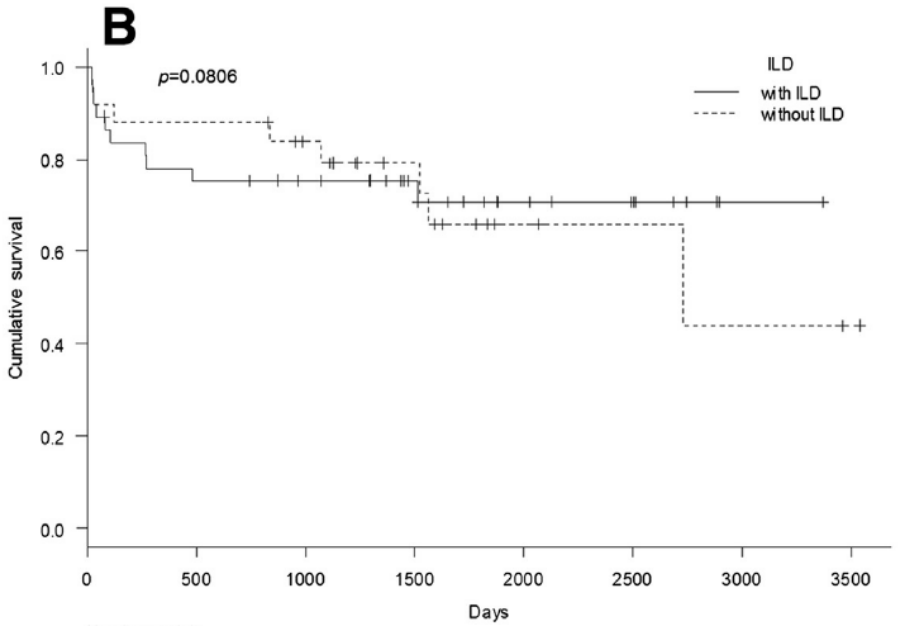
Satoshi Ikeda[1*], Machiko Arita[1], Kenta Misaki[2], Shohei Mishima[1], Takuya Takaiwa[1], Akihiro Nishiyama[1], Akihiro Ito[1], Kenjiro Furuta[1], Toshihide Yokoyama[1], Fumiaki Tokioka[1], Maki Noyama[1], Hiroshige Yoshioka[1] and Tadashi Ishida[1]

N=62

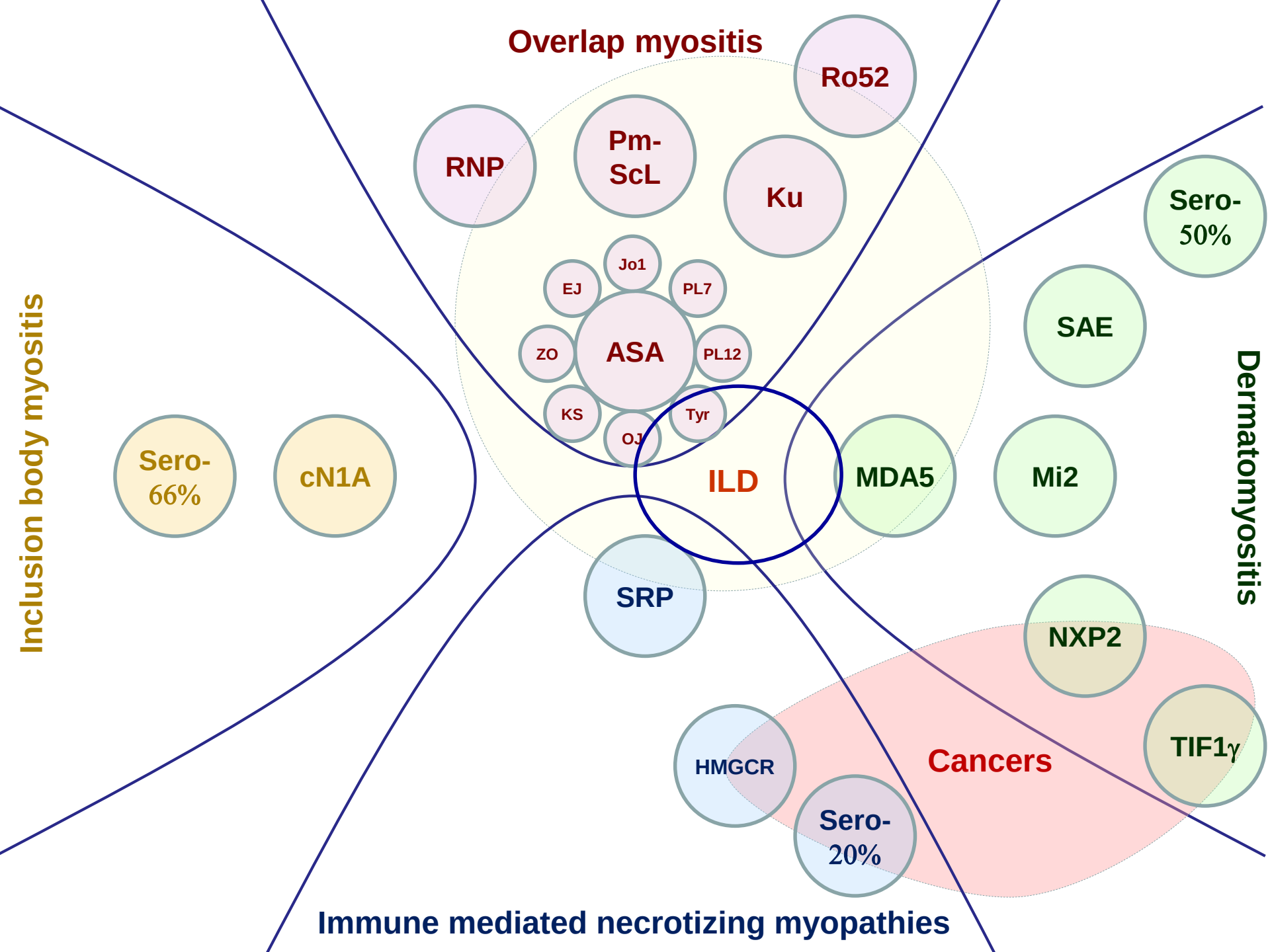
Table 1 Summary of the clinical characteristics and laboratory data

	PM		DM		CADM
	ILD (*N* = 11)	No ILD (*N* = 12)	ILD (*N* = 11)	No ILD (*N* = 13)	ILD (*N* = 15)
Sex (male/female)	2/9	5/7	2/9	4/9	5/10
Age (%)	66.0 (58.0–72.5)	68.5 (62.3–71.3)	65.0 (53.5–68.0)	68.0 (51.0–78.0)	63.0 (60.5–69.0)





Long term fonctional prognosis: muscle damages


Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
EJ
PL7
ZO
ASA
PL12
KS
Tyr
OJ
Sero-50%
SAE
Dermatomyositis
Inclusion body myositis
Sero-66%
cN1A
ILD
MDA5
Mi2
SRP
NXP2
HMGCR
Cancers
TIF1γ
Sero-20%
Immune mediated necrotizing myopathies

Fréquence des PID

Prévalence de la pneumopathie interstitielle au cours des polymyosites/dermatomyosites

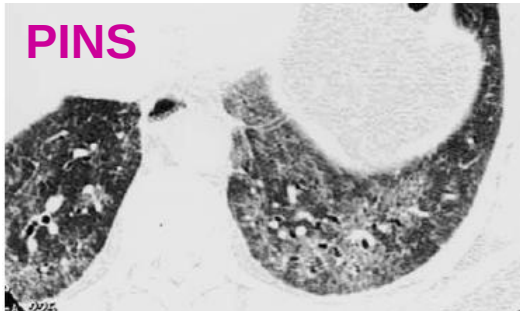
	Prévalence (%)	Nombre de patients
Dickey *et al.* [2]	10	42
Danko *et al.* [10]	22,2	162
Fahti *et al.* [23]	65	17
Frazier *et al.* [11]	5	213
Grau *et al.* [17]	13	104
Marie *et al.* [4]	23,1	156
Marie *et al.* [5]	18,2	77
Marie *et al.* [7]	16	55
Takizawa *et al.* [42]	64	14
	26 %	840

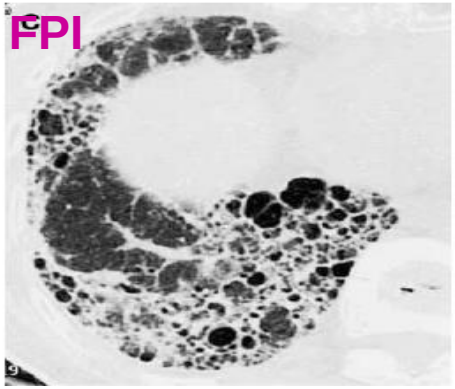
Marie I., Presse Med 2006; 35: 683-95

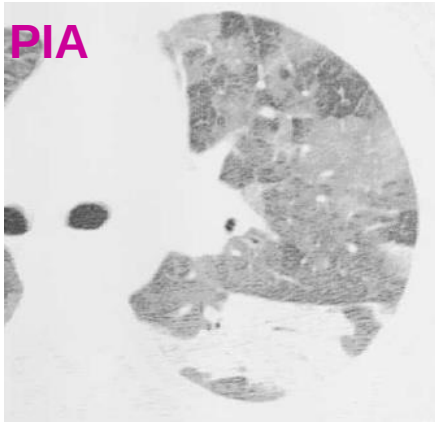
Présentation PID: TDM / Histologie

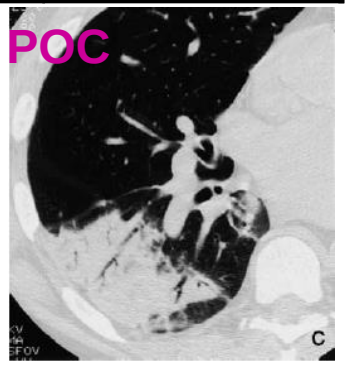
TDM			HISTOLOGIE	
Nom	**Lésions**	**Topographie**	**Nom**	**Lésions**
PINS +++	**Verre dépoli** Réticulations Bronchectasies	**Bases** **Sous pleural** Bilatéral	**NSIP**	**Inflammation** **Fibrose** Architecture préservée
FPI	**Rayon de miel** Réticulations Bronchectasies	**Bases** Sous pleural	**UIP**	**Fibrose dense** Architecture remodelée
PIA (SDRA)	**Verre dépoli** Condensations bronchectasies	**Diffus**	**DAD**	**Inflammation** **Œdème** **Mb Hyalines** +/- fibrose
POC	**Condensations** Nodules	Sous pleural Péribronchique	**Pneumonie Organisée**	**Condensation alvéolaire** Inflammation

PINS: Pneumopathie Interstitielle Non Spécifique
FPI: Fibrose Pulmonaire Idiopathique
PIA: Pneumopathie Interstitielle Aiguë
POC: Pneumopathie Organisée Cryptogénique (BOOP)
UIP: Pneumopathie Interstitielle Commune
DAD: Dommages Alvéolaires Diffus



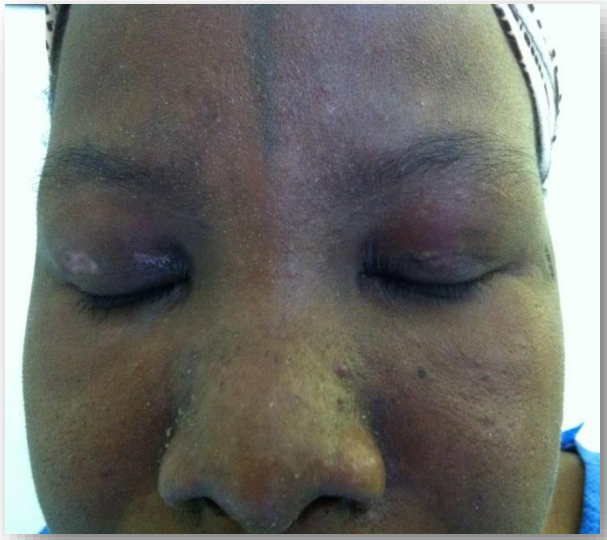




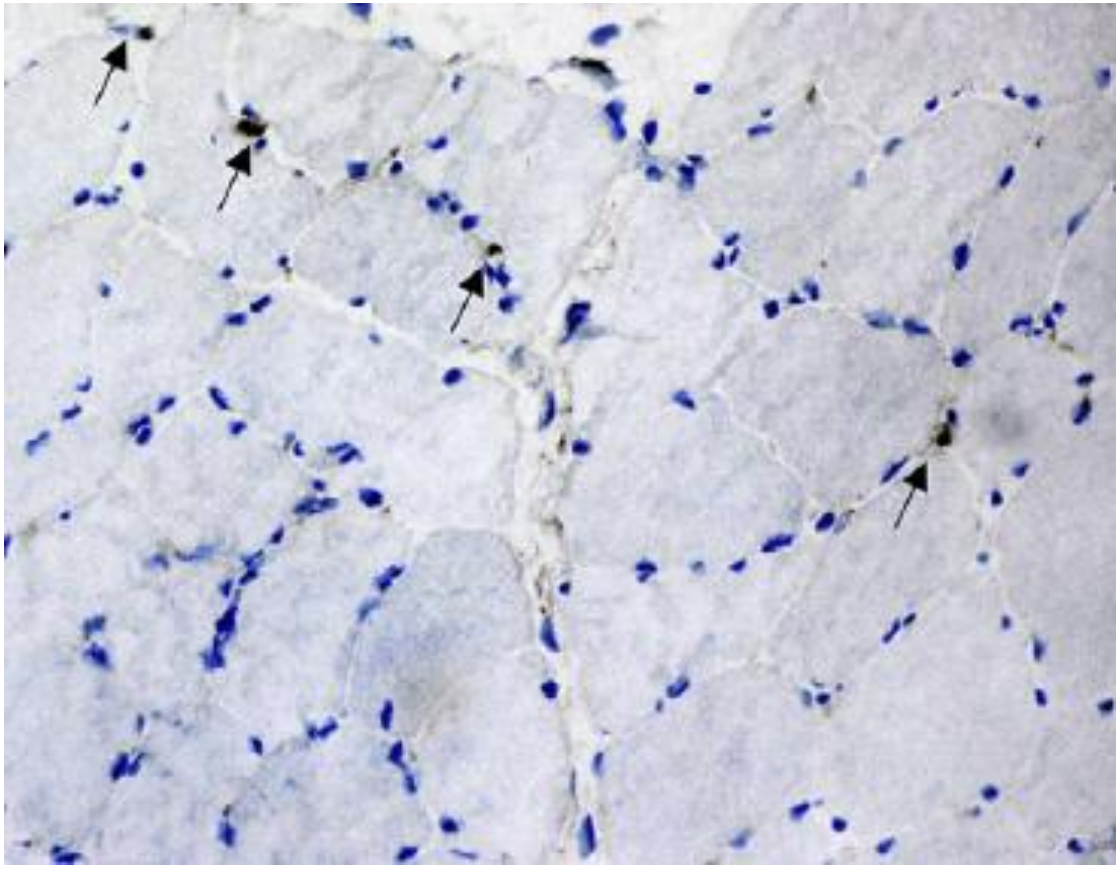


Patiente de 37 ans, hospitalisée via le SAU

- AEG (-10 kg en 2 mois)
- Apyrétique
- Arthralgies mains
  - Petites et grosses articulations
  - Synovites des fléchisseurs des doigts
- Dermatologiques
  - mains de mécaniciens
  - oedème du visage et palpébral
  - signe de la manucure nécroses cutanées (mains, coude, visage)
- Dyspnée NYHAII, toux +++
- Myalgies



- Biopsie musculaire :
- CPK : 300 U/L
- FAN : 1/320

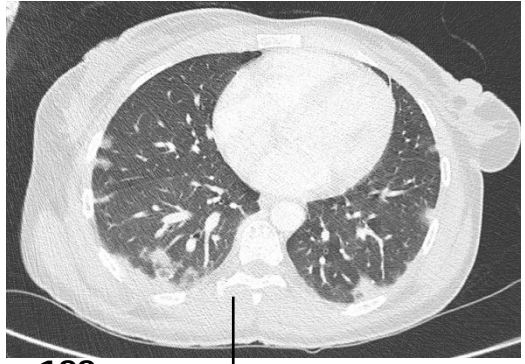


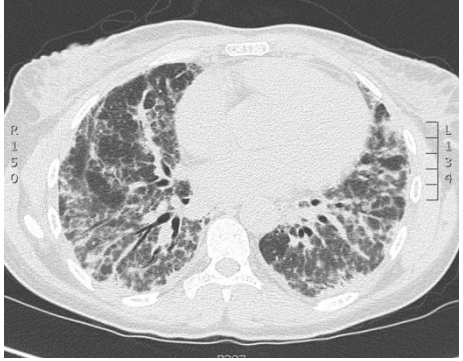
C5b9

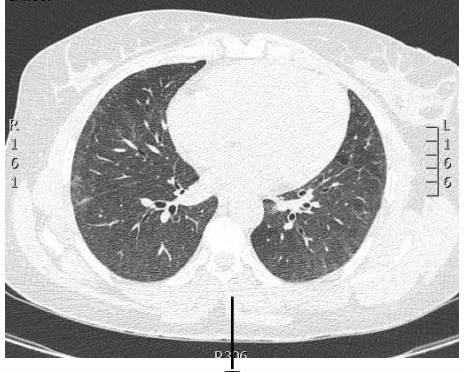
Dermatomyosite ou **Lupus**?

- Œdème des paupières
- Ulcérations (buccales et nasopharyngées)
- Rash malaire
- Arthralgies
- AAN ⟶ **anti-MDA5 +++**

- Dépôt complément sur les capillaires
- CPK







100
90
80
70
60
50
40
30
20

CVF
CPT
DLCO/VA
Test Marche
PaO2

mai-11 | Aout 2011 | oct-11 | janv-12 | mars-12 | mai-12 | aout 2012 | janv-13 | juil-13

CT 60 | CT 60 | CT 60 | CT 50 | 15 | 10 | 8

MTX | MTX | EDX 5X

EP 5X

CICLOSPORINE

Autoantibodies to a 140-kd Polypeptide, CADM-140, in Japanese Patients With Clinically Amyopathic Dermatomyositis

Arthritis 2005

Shinji Sato,[1] Michito Hirakata,[1] Masataka Kuwana,[1] Akira Suwa,[1] Shinichi Inada,[2] Tsuneyo Mimori,[3] Takeji Nishikawa,[1] Chester V. Oddis,[4] and Yasuo Ikeda[1]

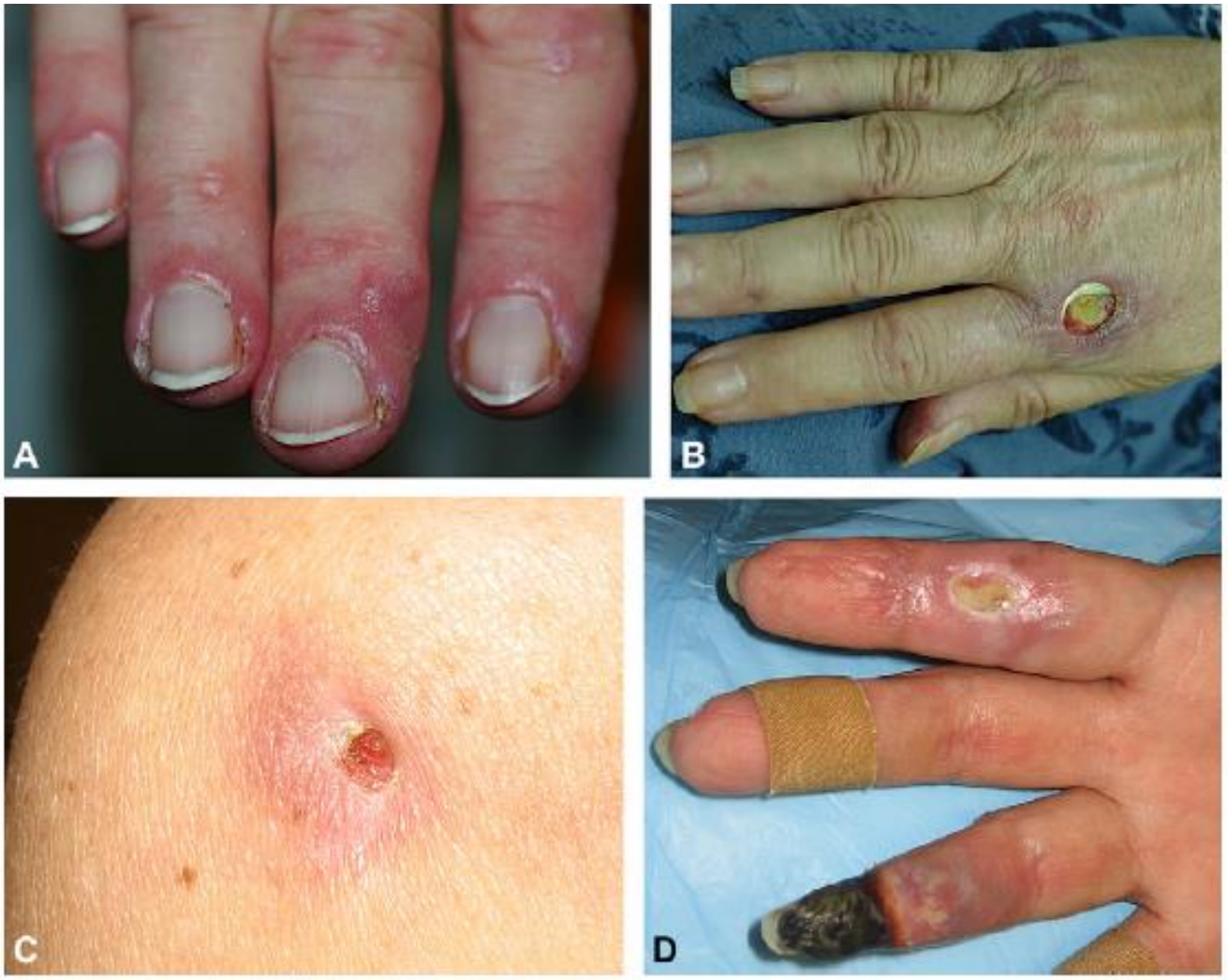
Table 2. Comparison of clinical features in anti–CADM-140–positive versus anti–CADM-140–negative patients with dermatomyositis

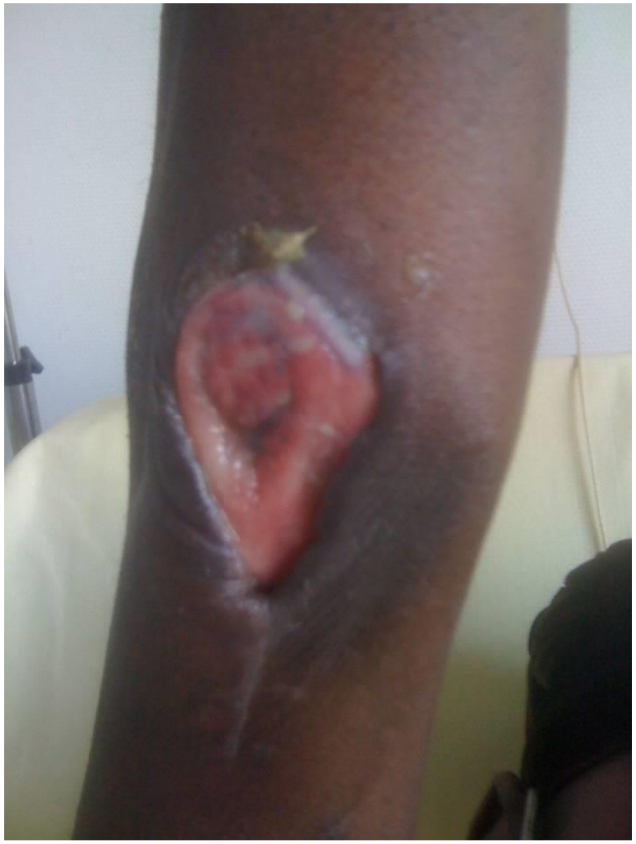
Feature	Anti–CADM-140–positive (n = 8)	Anti–CADM-140–negative (n = 34)	*P*
Age at onset, mean ± SD years	44.5 ± 12.7	46.5 ± 15.7	NS
No. male/no. female	2/6	8/26	NS
Gottron's sign or papules	75	88	NS
Heliotrope rash	50	53	NS
Muscle weakness	0	76	0.02
Elevation of CK	25	74	0.03
Fever	25	50	NS
Raynaud's phenomenon	13	24	NS
Arthritis	50	71	NS
Rapidly progressive ILD	50	6	0.008
Malignancy	0	18	NS
MSAs	0	29	NS
MAAs	13	18	NS

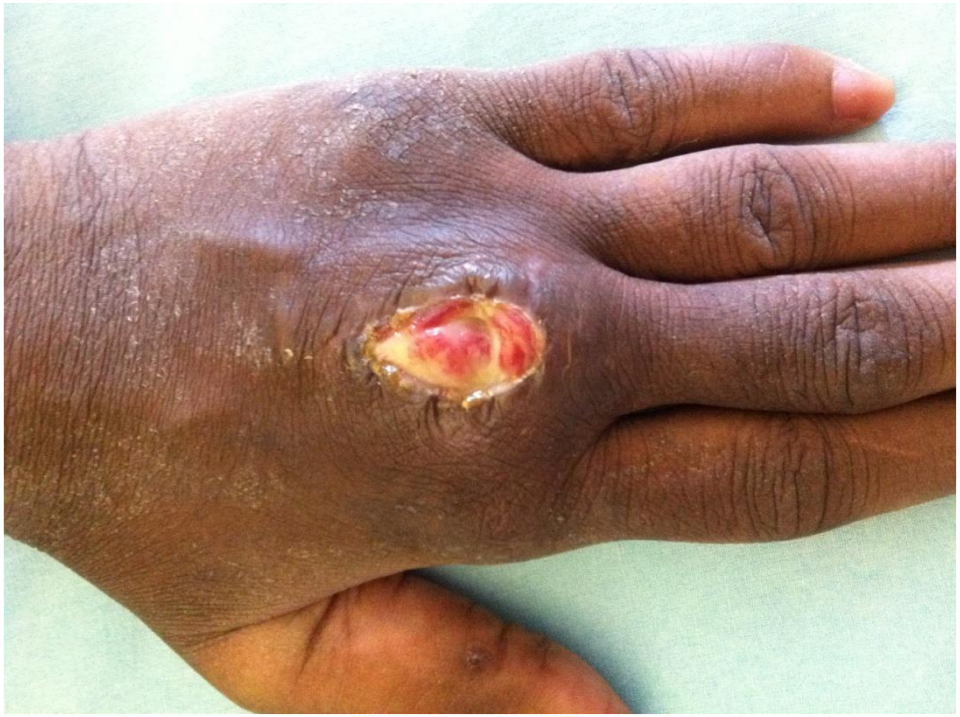
The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): A retrospective study

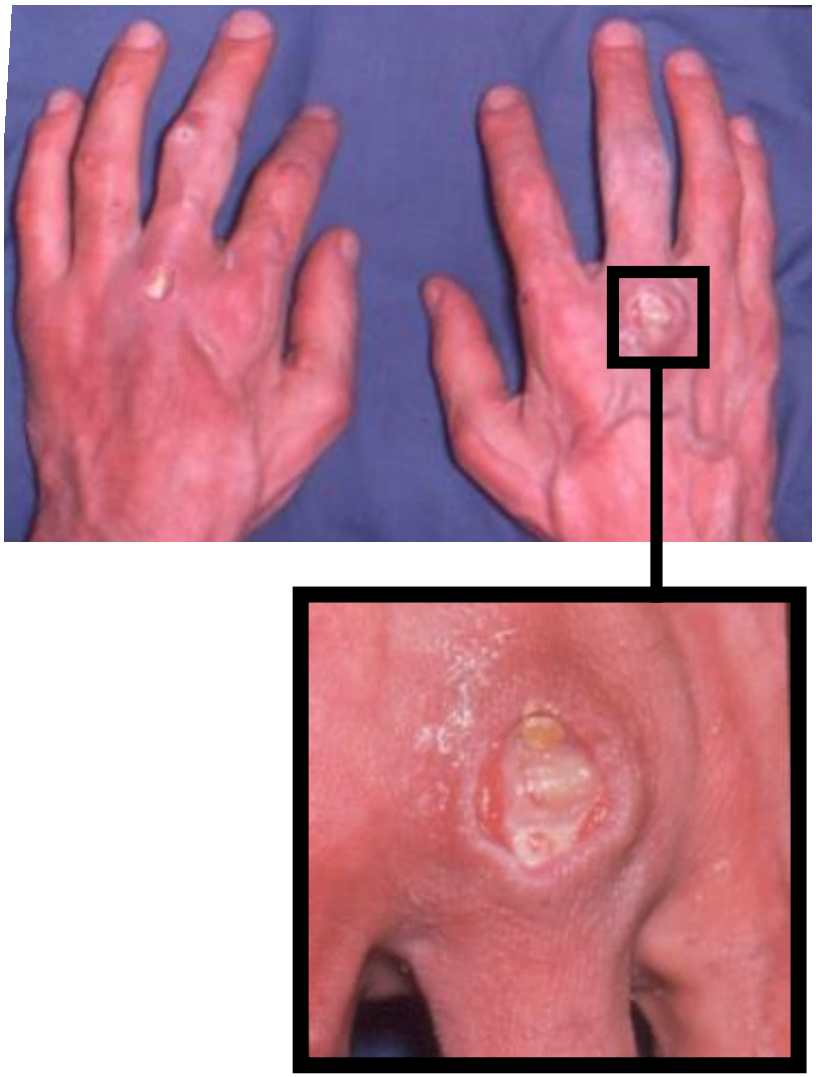
J AM Acad Dermatol, 2011

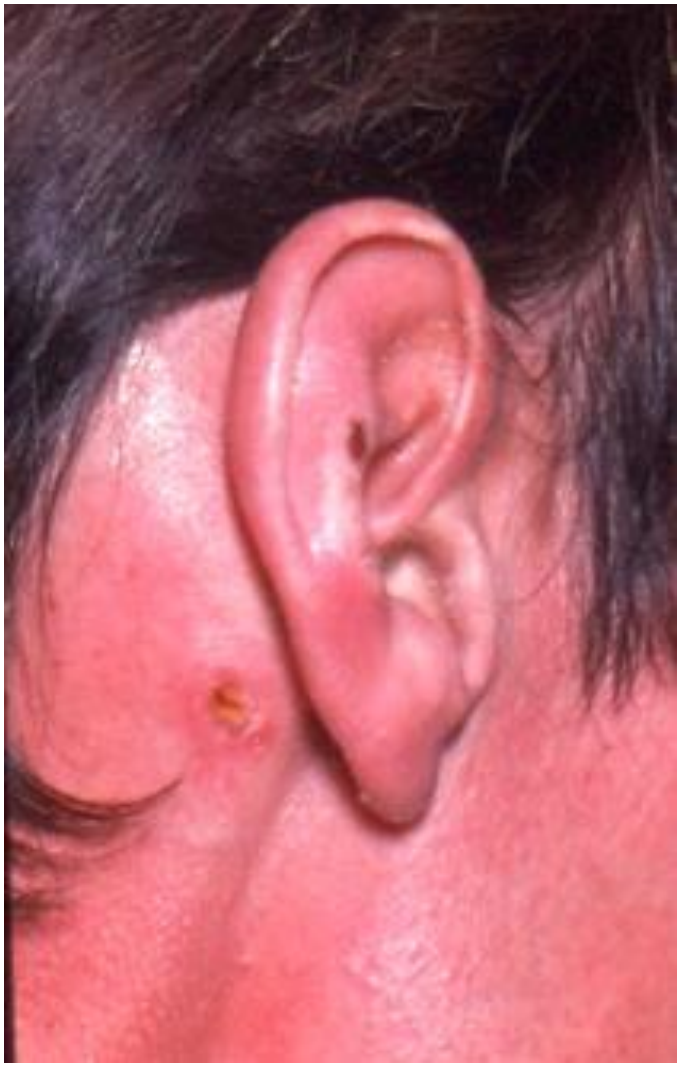
David Fiorentino, MD, PhD,[a] Lorinda Chung, MD, MS,[b] Jeff Zwerner, MD, PhD,[c] Antony Rosen, MD,[d] and Livia Casciola-Rosen, PhD[d]



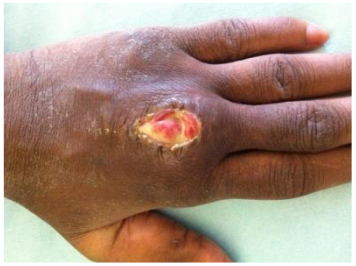




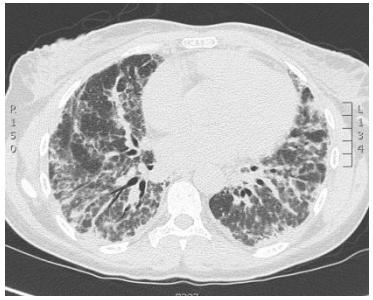




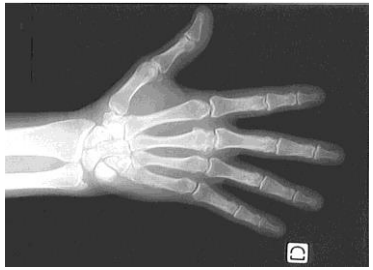
5 séries de patients anti-MDA5+



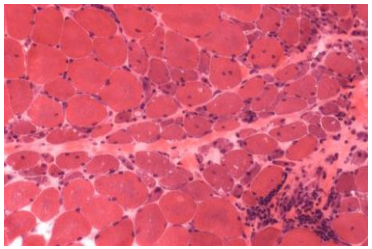
93-100%



65-100%

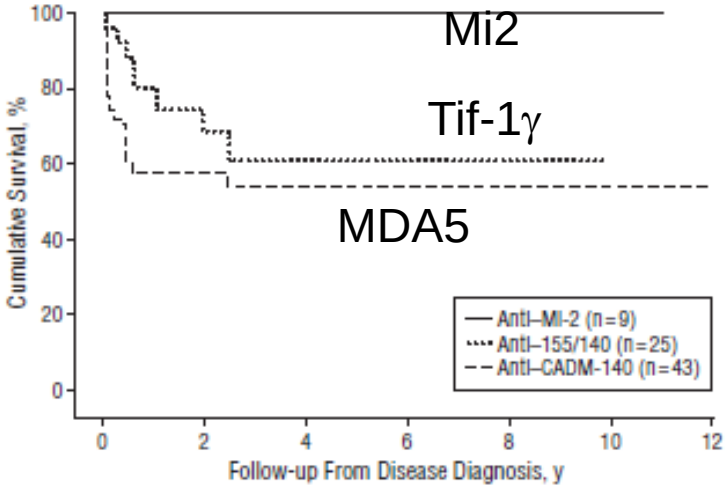


40-85%



20-50%

Hamaguchi al. 2012



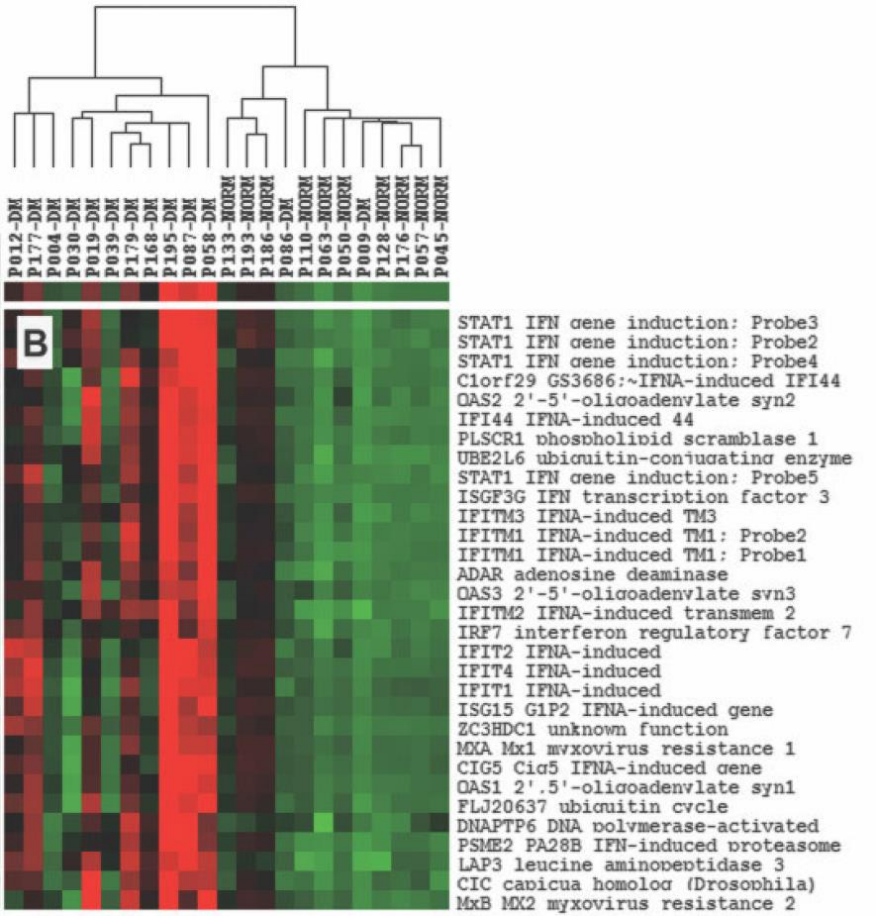
Décès: 12-37%

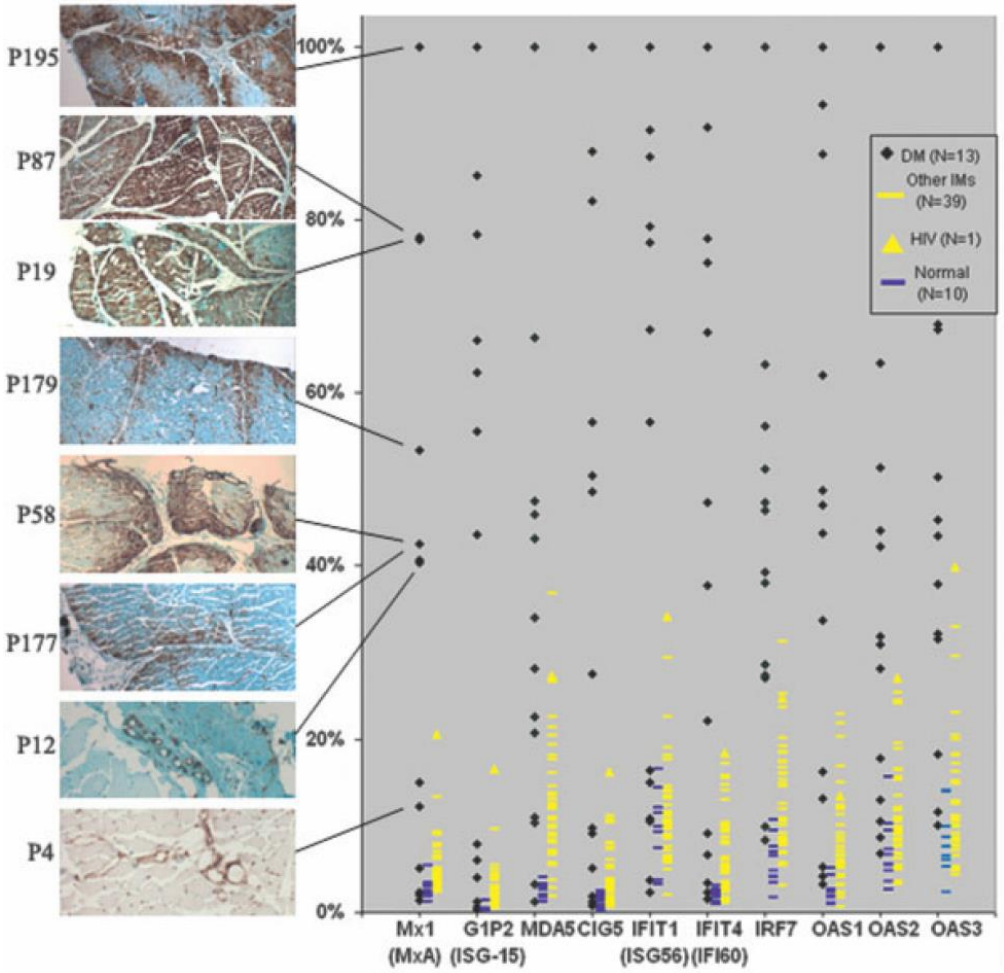
En France: 18/60 (30%)

Gono T, Rheumatol. 2010
Hoshino K, Rheumatol. 2010
Hamaguchi Y, Arch Dermatol. 2011
Hall JC, Arthritis Care Res. 2013

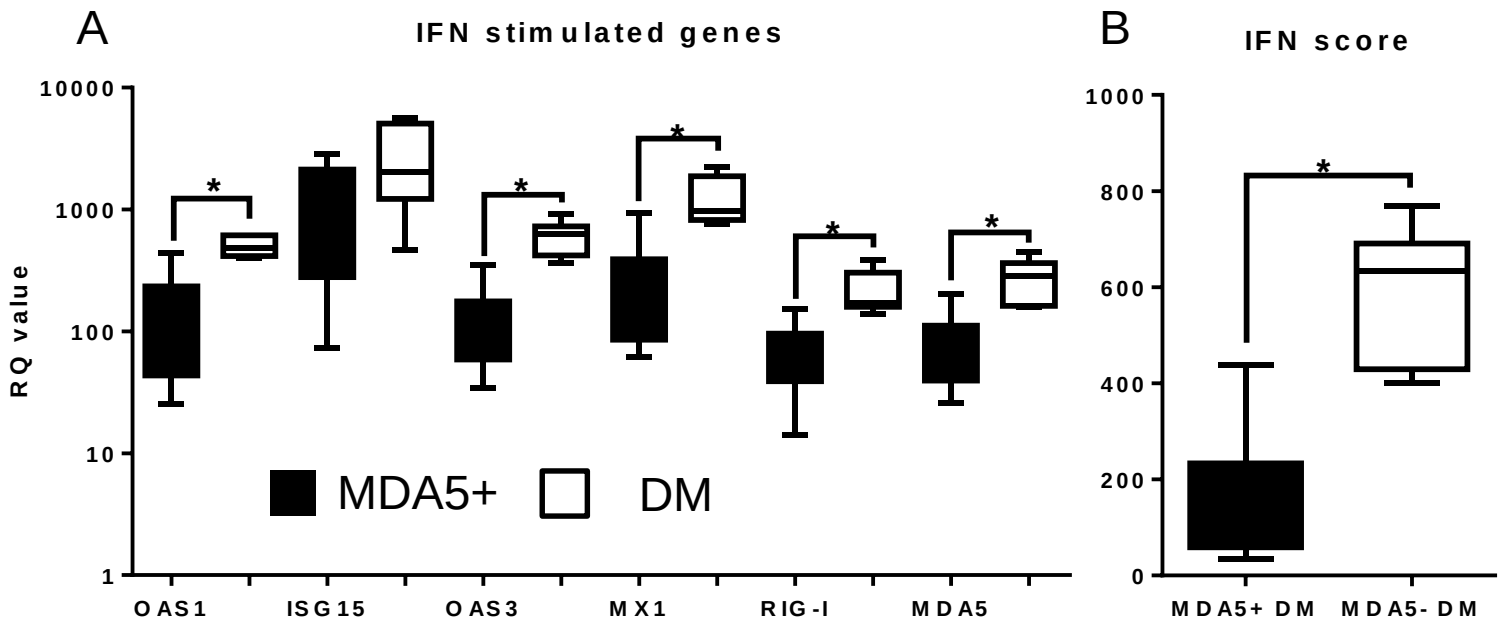
Interferon-α/β–Mediated Innate Immune Mechanisms in Dermatomyositis

Greenberg et al 2005. Ann Neurol.



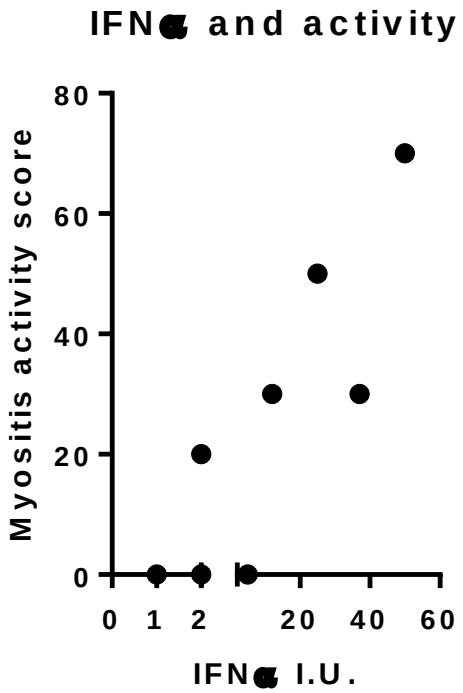


Comparison DM classique et anti-MDA5+



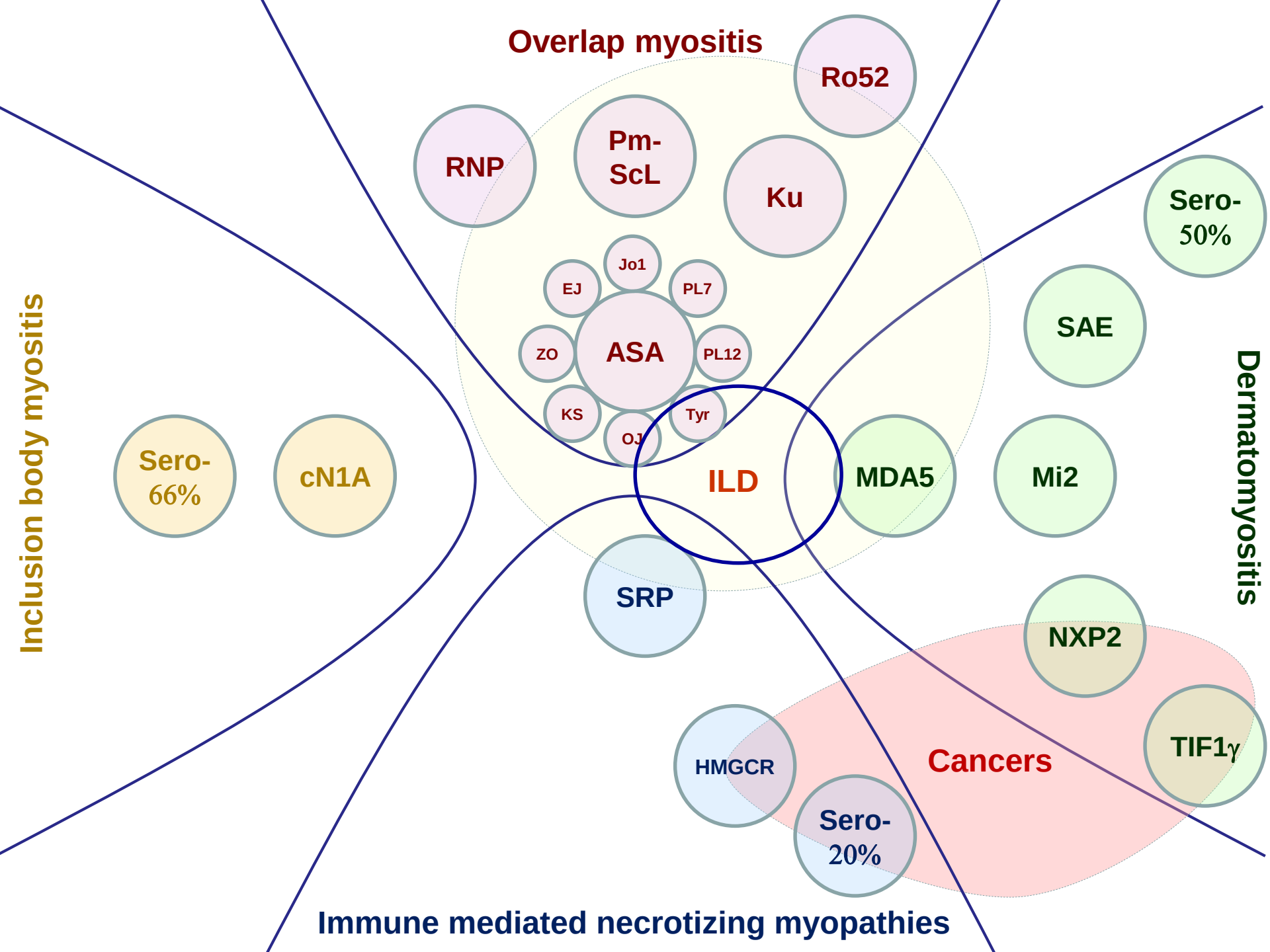
Y Allenbach et al, Am J Path, 2016

Patients MDA5+



r=0.8
p<0.0001

Y Allenbach et al, Am J Path, 2016


Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
EJ
PL7
ZO
ASA
PL12
KS
Tyr
OJ
Sero-50%
SAE
Dermatomyositis
Inclusion body myositis
Sero-66%
cN1A
ILD
MDA5
Mi2
SRP
NXP2
HMGCR
Cancers
TIF1γ
Sero-20%
Immune mediated necrotizing myopathies

Première description des anti-Jo-1

ARTHRITIS
&
RHEUMATISM

1980

OFFICIAL JOURNAL OF THE AMERICAN RHEUMATISM ASSOCIATION
SECTION OF THE ARTHRITIS FOUNDATION

HETEROGENEITY OF PRECIPITATING ANTIBODIES IN POLYMYOSITIS AND DERMATOMYOSITIS

Characterization of the Jo-1 Antibody System

MASAHIKO NISHIKAI and MORRIS REICHLIN

Table 5. Incidence of Jo-1 antibody

	No. of patients	No. positive	% positive
Polymyositis	26	8	30.8
Dermatomyositis	22	1	4.5
Overlap syndromes*			4.5
PM–PSS	11	1	
PM–SLE	4	0	
PM–RA	2	0	
PM–Sjögren's	5	0	
Systemic lupus erythematosus	22	0	0
Progressive systemic sclerosis	11	0	0
Rheumatoid arthritis	9	0	0
Myasthenia gravis	14	0	0
Progressive muscular dystrophy	12	0	0
Normal subjects	12	0	0

31%

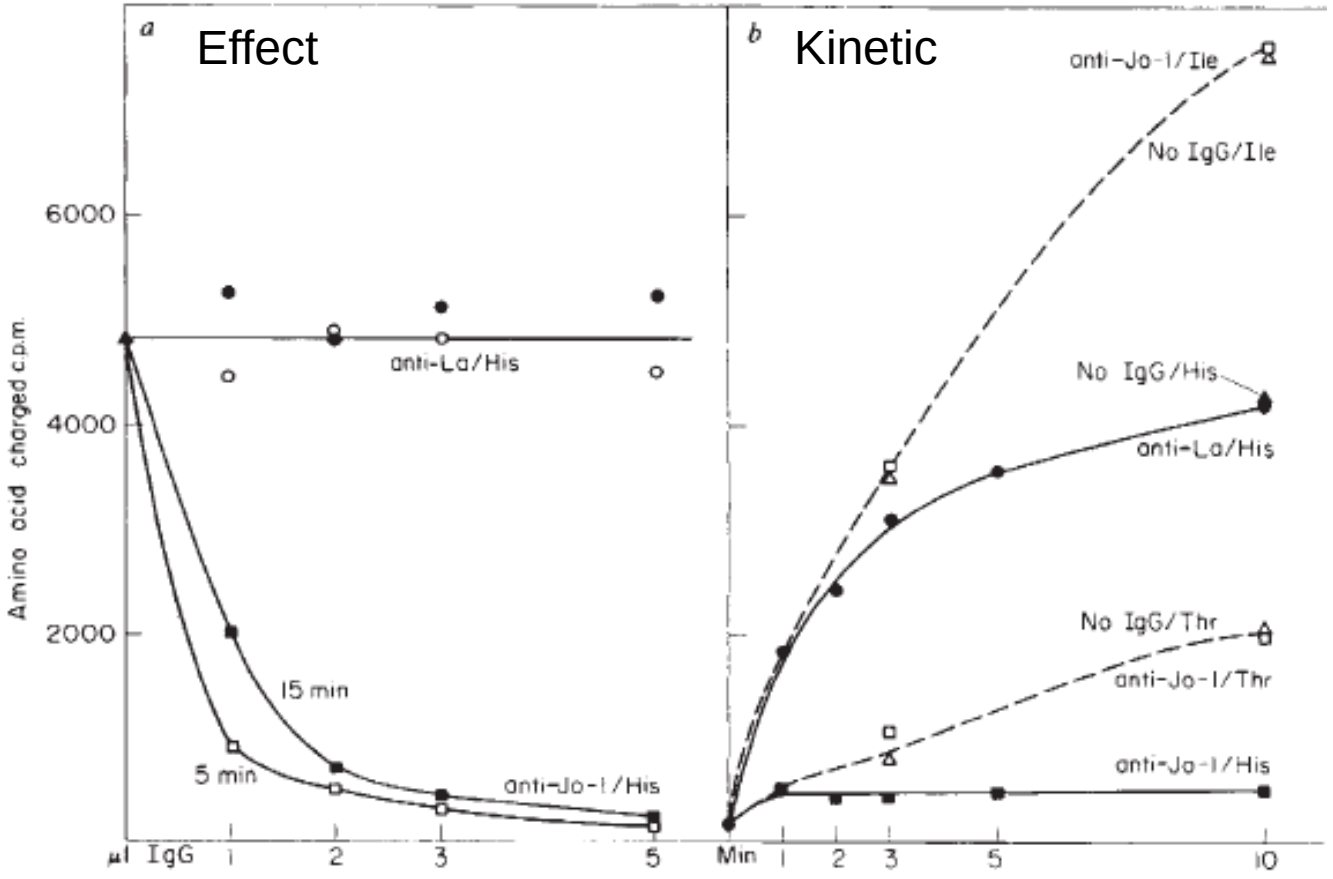
Cible des Ac anti-Jo-1

Myositis autoantibody inhibits histidyl-tRNA synthetase: a model for autoimmunity

NATURE VOL. 304 14 JULY 1983

Michael B. Mathews* & Robert M. Bernstein†

Inhibition de la synthèse des histidyl-tRNA



Première série de cas

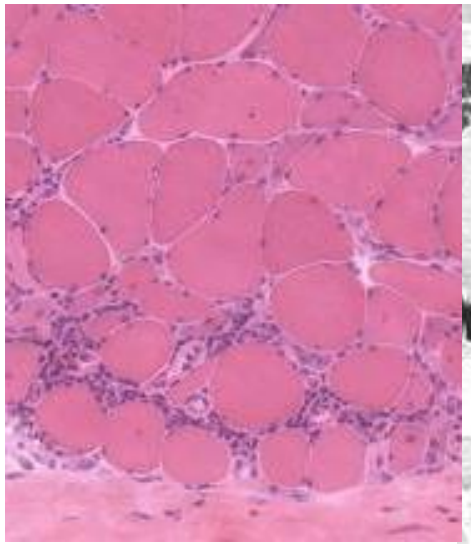
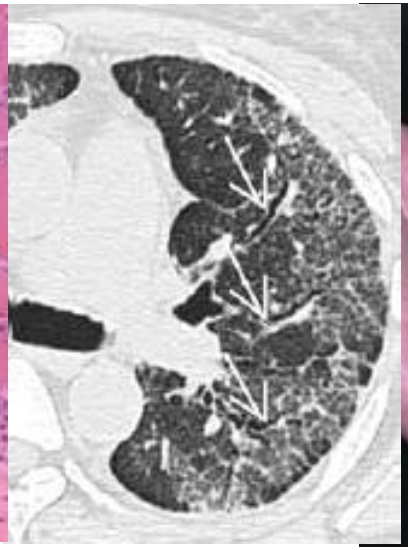
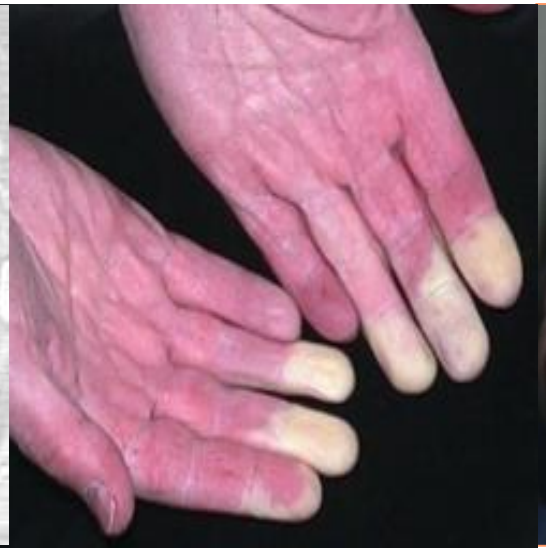
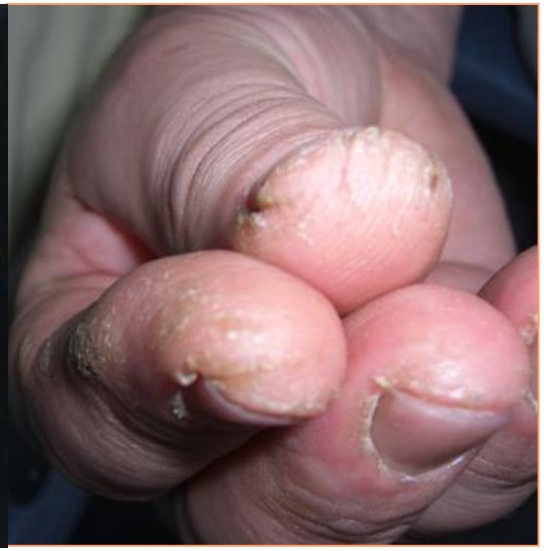
Quarterly Journal of Medicine, New Series 77, No. 282, pp. 1019–1038, October 1990

Polymyositis, Pulmonary Fibrosis and Autoantibodies to Aminoacyl-tRNA Synthetase Enzymes

C. MARGUERIE, C. C. BUNN, H. L. C. BEYNON, R. M. BERNSTEIN*, J. M. B. HUGHES†, A. K. SO, and M. J. WALPORT

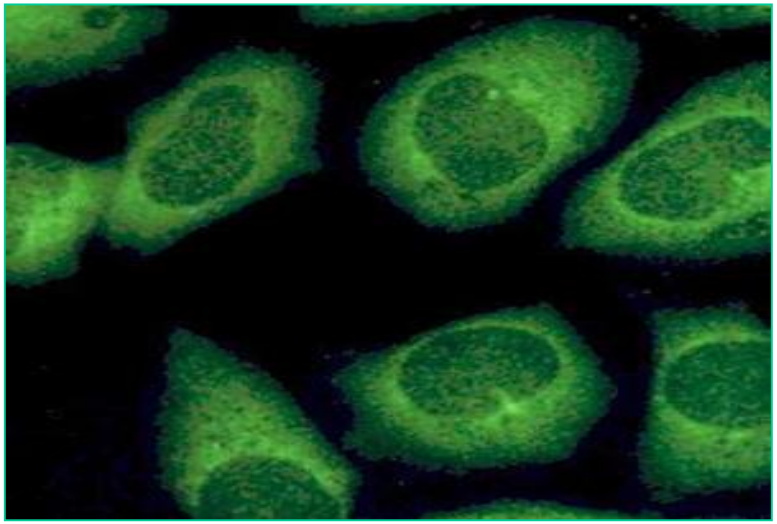
n=29
- 19 anti-Jo-1
- 4 anti-PL7
- 6 anti-PL12

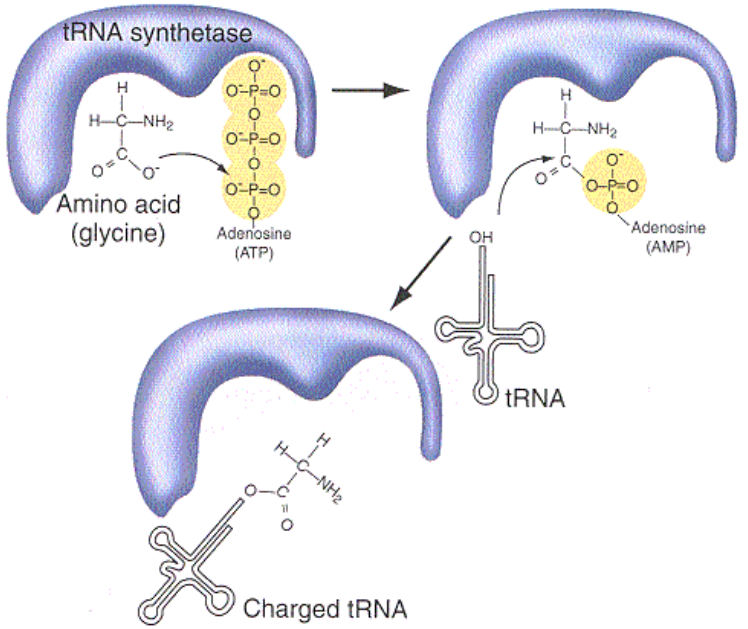
PM + PID + Raynaud + mains de mécanicien + arthrites = **syndrome des anti-synthetases**

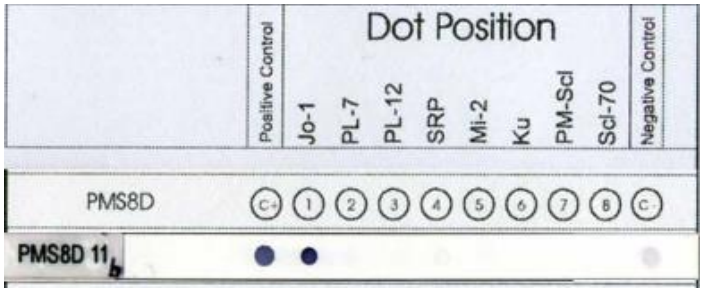
Anticorps anti-synthetases

- Ac anti-aminoacyl-t-RNA-synthetases :
  - **Anti-JO1** (histidyl t-RNA),
  - PL7 (threonyl t-RNA),
  - PL12 (alanine t-RNA),
  - OJ (isoleucil t-RNA),
  - EJ (glycyl t-RNA) etc…
- AAN





- Dot myosite



Autoimmunity Reviews 12 (2012) 210–217

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

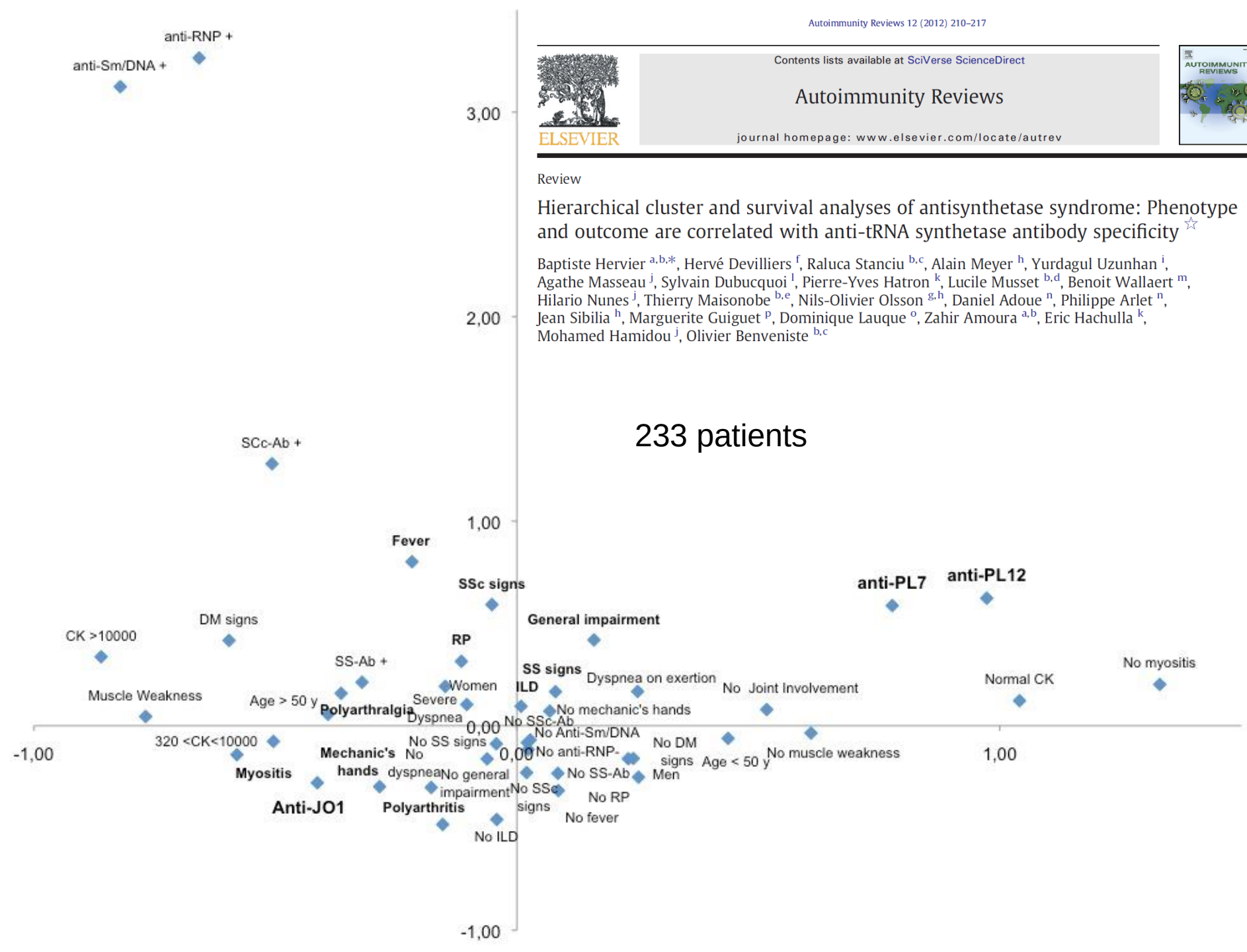
journal homepage: www.elsevier.com/locate/autrev

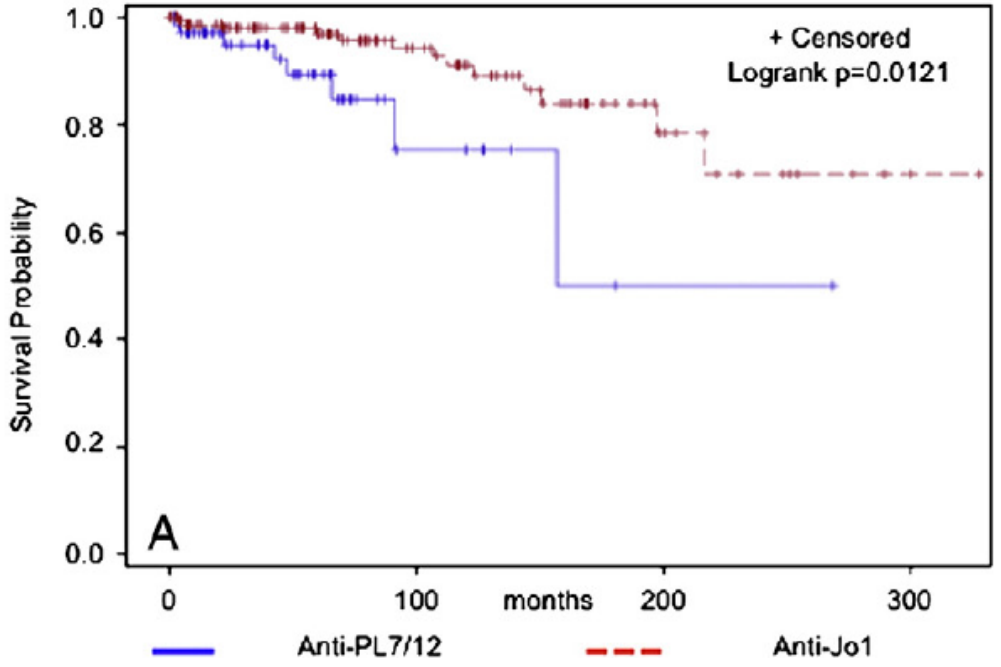
Review

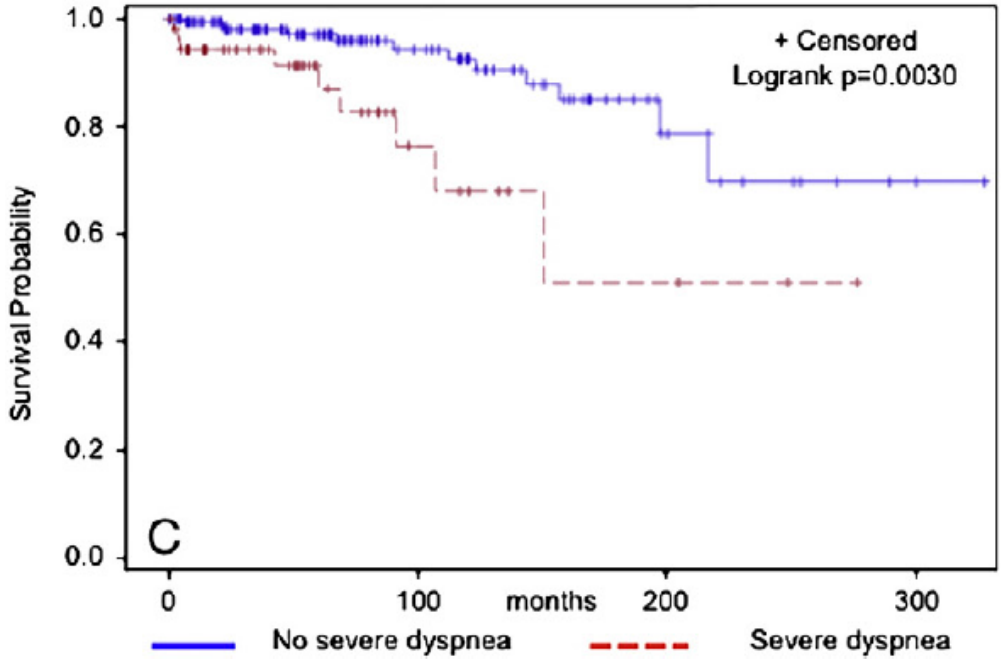
Hierarchical cluster and survival analyses of antisynthetase syndrome: Phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity ☆

Baptiste Hervier [a,b,*], Hervé Devilliers [f], Raluca Stanciu [b,c], Alain Meyer [h], Yurdagul Uzunhan [i], Agathe Masseau [j], Sylvain Dubucquoi [l], Pierre-Yves Hatron [k], Lucile Musset [b,d], Benoit Wallaert [m], Hilario Nunes [j], Thierry Maisonobe [b,e], Nils-Olivier Olsson [g,h], Daniel Adoue [n], Philippe Arlet [n], Jean Sibilia [h], Marguerite Guiguet [p], Dominique Lauque [o], Zahir Amoura [a,b], Eric Hachulla [k], Mohamed Hamidou [j], Olivier Benveniste [b,c]

233 patients




+ Censored
Logrank p=0.0121
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
A
0
100
months
200
300
Anti-PL7/12
Anti-Jo1


+ Censored
Logrank p=0.0030
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
C
0
100
months
200
300
No severe dyspnea
Severe dyspnea

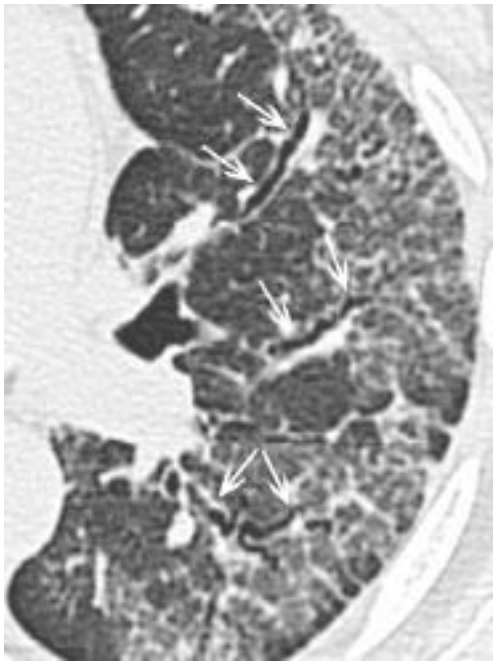
Antisynthetase Syndrome with Anti-Jo1 Antibodies in 48 Patients: Pulmonary Involvement Predicts Disease-modifying Antirheumatic Drug Use

RALUCA STANCIU, MARGUERITE GUIGUET, LUCILE MUSSET, DIANE TOUITOU, CATHERINE BEIGELMAN, AUDE RIGOLET, NATHALIE COSTEDOAT-CHALUMEAU, YVES ALLENBACH, BAPTISTE HERVIER, ODILE DUBOURG, THIERRY MAISONOBE, JEAN-LUC CHARUEL, ANTHONY BEHIN, SERGE HERSON, ZAHIR AMOURA, PHILIPPE GRENIER, and OLIVIER BENVENISTE

J Rheumatol 2012

- Suivi : 4,5 ans
  - Pas besoin de “DMARD”: 14 patients (29%)
  - Besoin de “DMARD”: 34 patients (71%)

- Facteurs prédictifs du besoin de “DMARD” :
  - Mains de mécanicien : p=0.02
  - Haut CPK (6000 vs. 1000): p=0.002
  - Score de PINS (7 vs. 4): p=0.04
  - CPT (57% vs. 70%): p=0.02



Data analysis

- Type and extent of ILD assessed in consensus by two chest radiologists

- Five levels were reviewed:

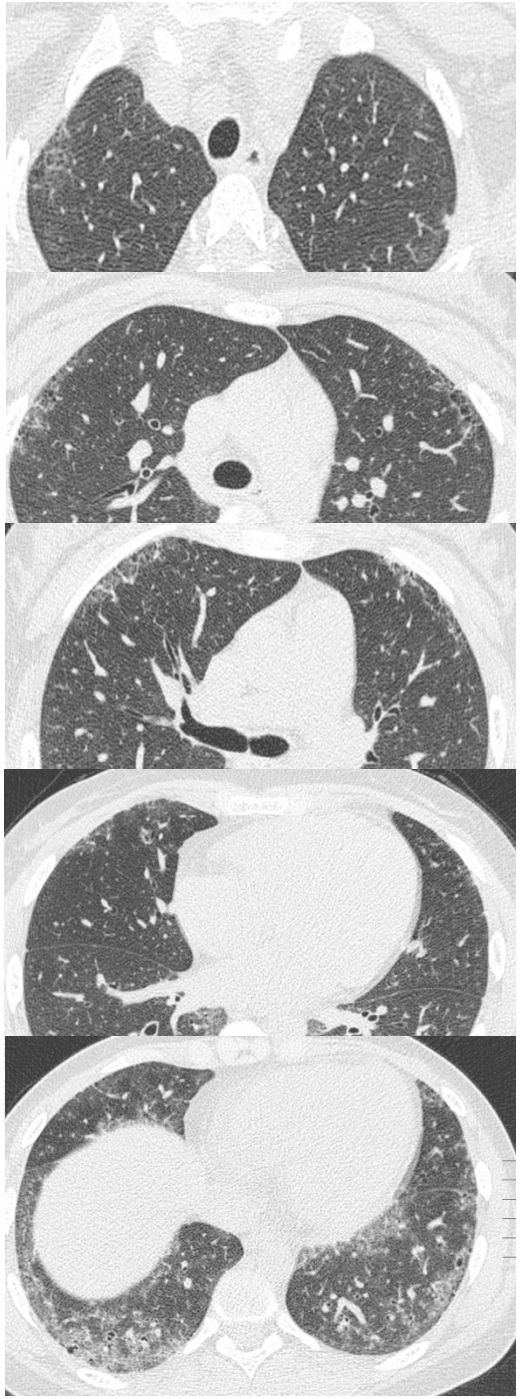
  1- Great vessels

  2- Aortic arch

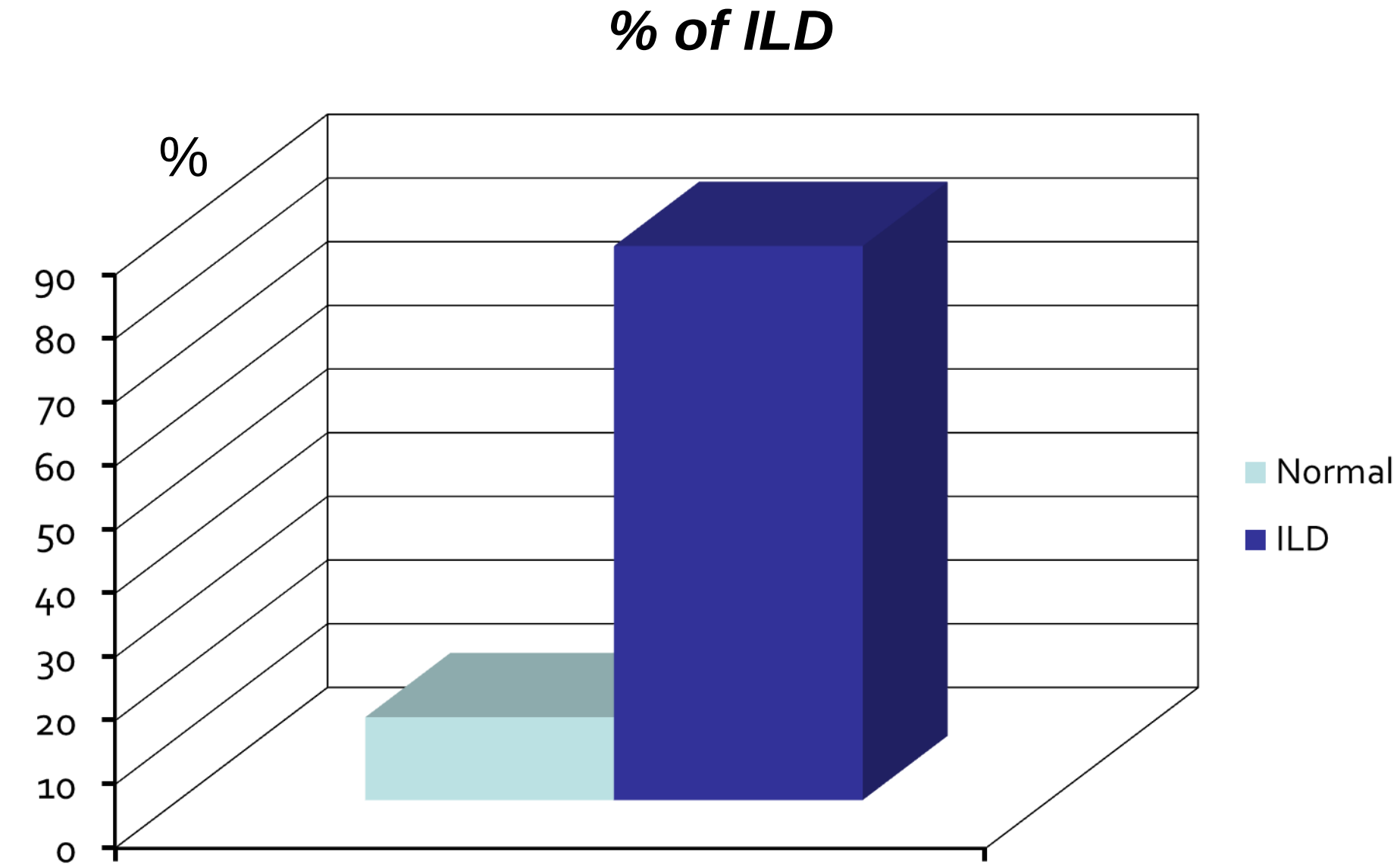
  3- Carina

  4- Left inferior pulmonary vein

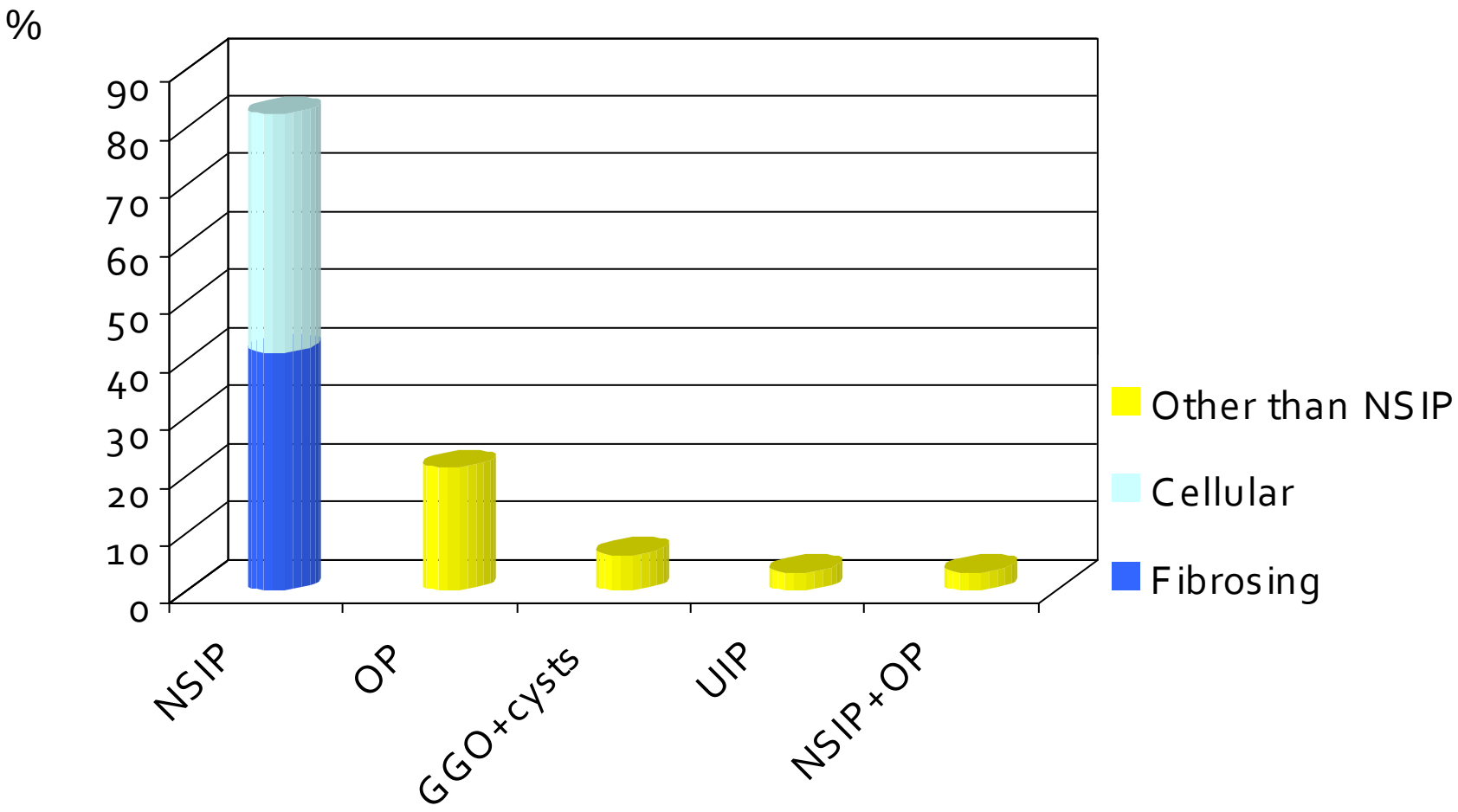
  5- Halfway point between level 4 and extreme left costophrenic angle



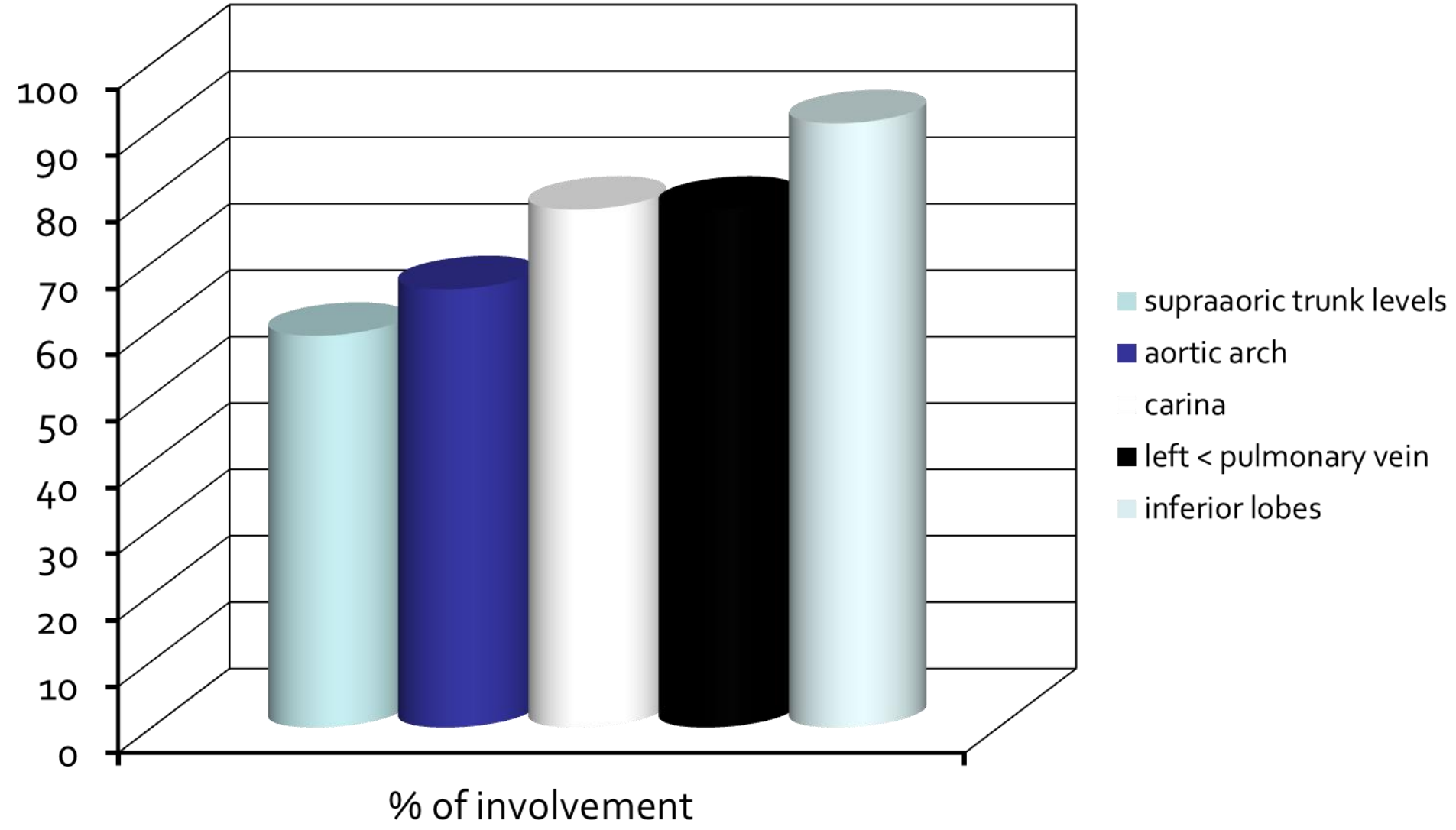
Results: first evaluation



Patterns of ILD at first evaluation

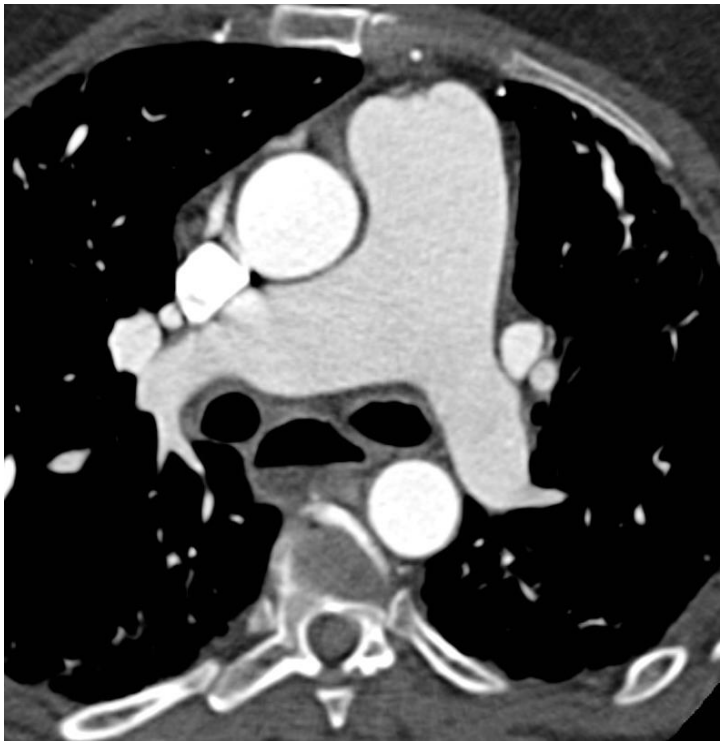


Topography of lesions



Associated findings

- Diaphragmatic dysfonction: **N=9**
- Oesophagal hypotonia: **N=5**
- Pulmonary artery trunk enlargement:
  Diameter > 30 mm **N= 5**



Results: follow-up

- **Follow-up HRCT** **N=26**
- **Mean follow-up time** **29 months**

Results: follow-up

- **Onset of ILD** — **N=2**
- **Change in pattern** — **N=10**
  - **Apparition of OP** — **n=4**
  - **Apparition of cellular NSIP** — **n=4**
  - **Fibrosing evolution** — **n=2**
- **2 cellular NSIP** → **fibrosing NSIP**

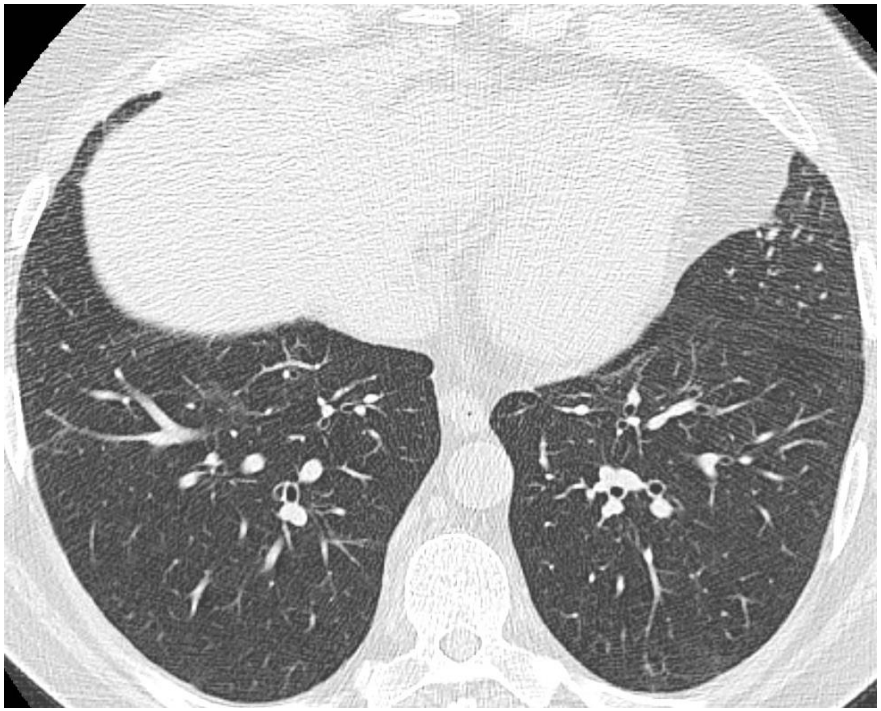
91% ILD at the end of the study

Results: follow-up

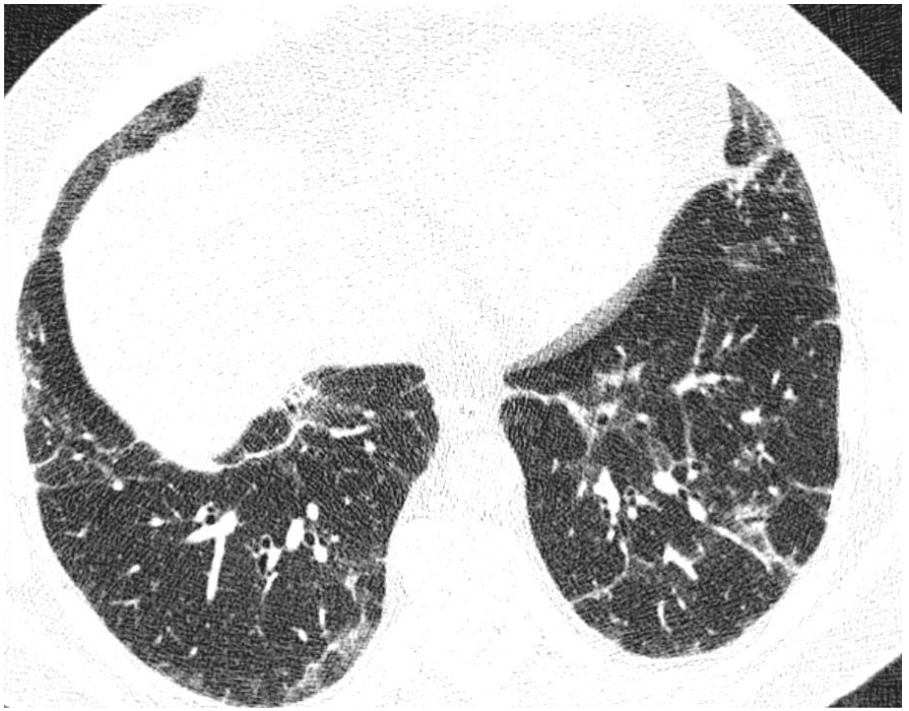
Evolution

- **Stable** **N=11**
- **Worsened** **N=12**
- **Improved under treatment** **N=3**

Example 1

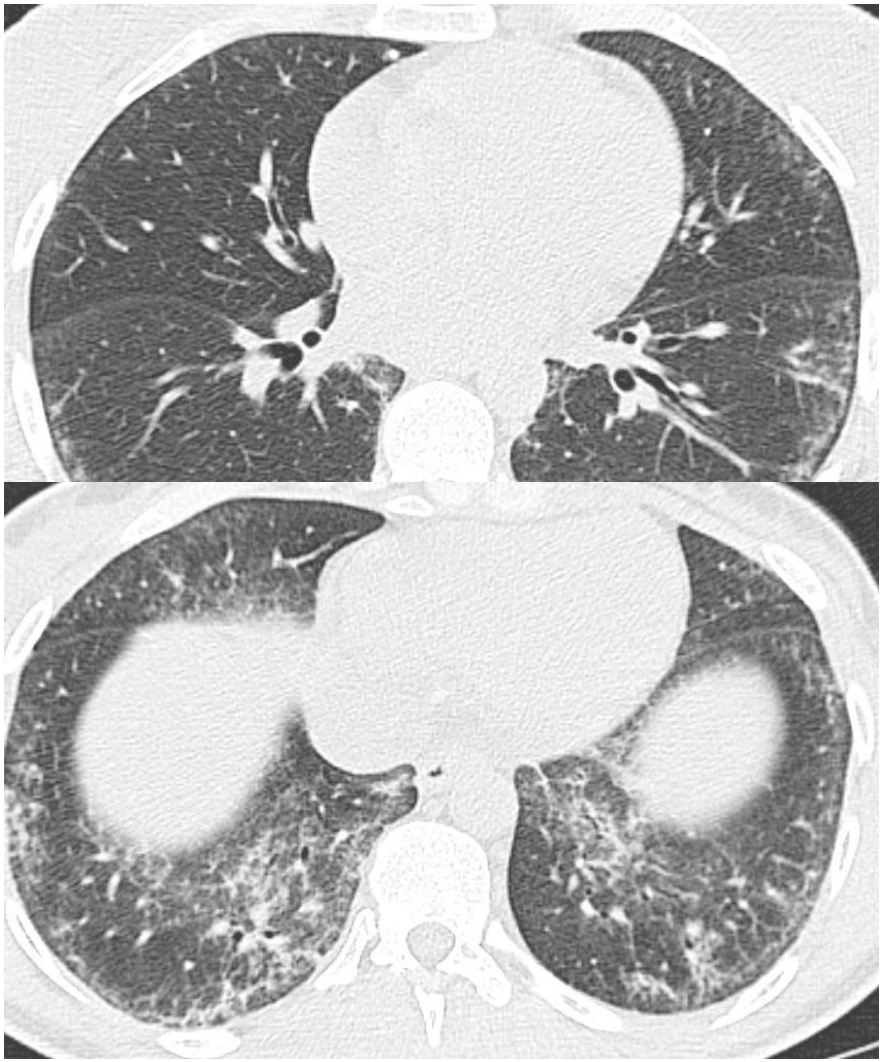


06/2006

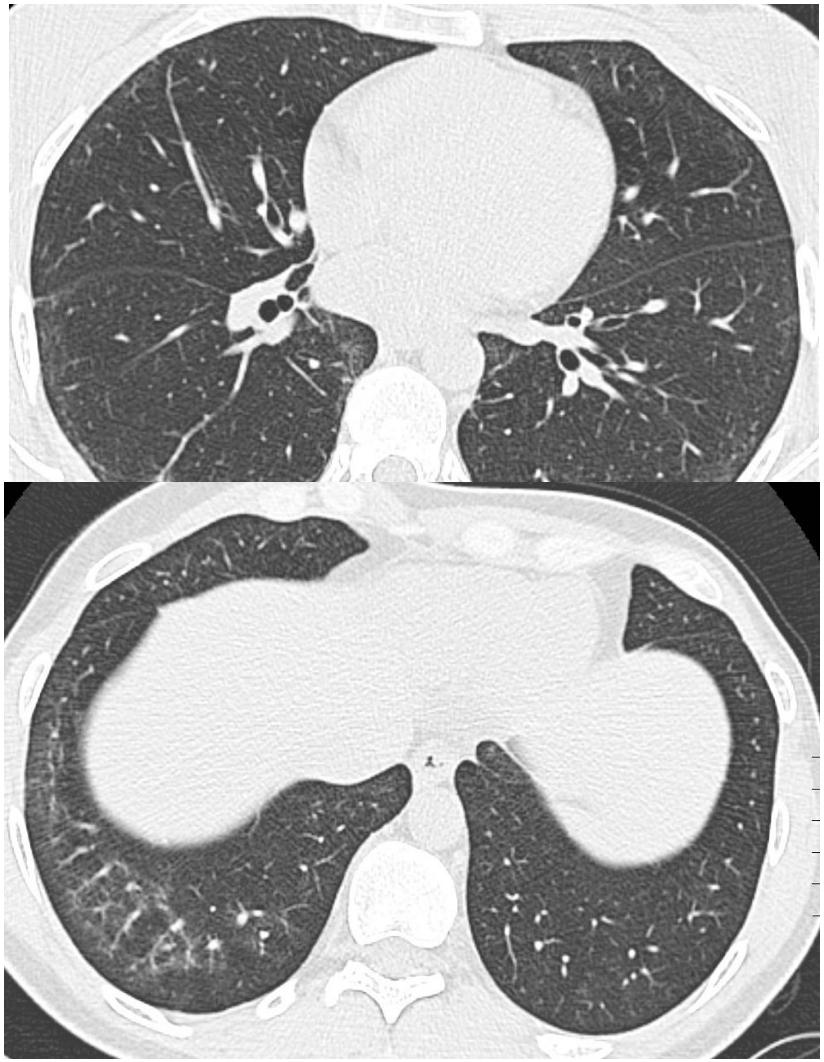


04/2008

Example 2

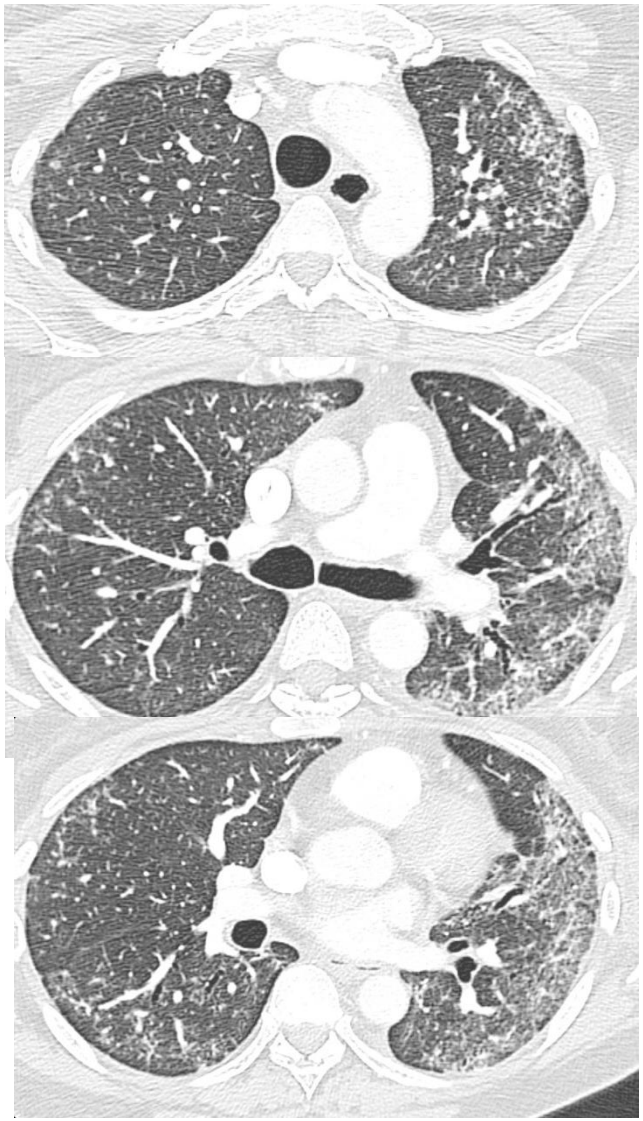


11/2006

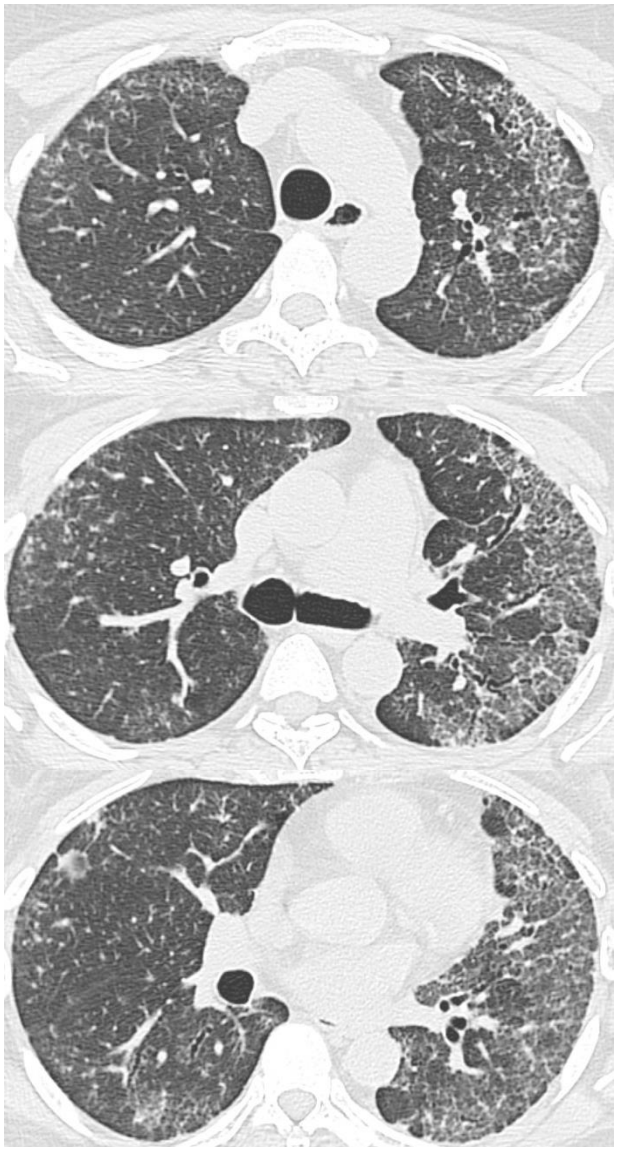


03/2008

Example 3



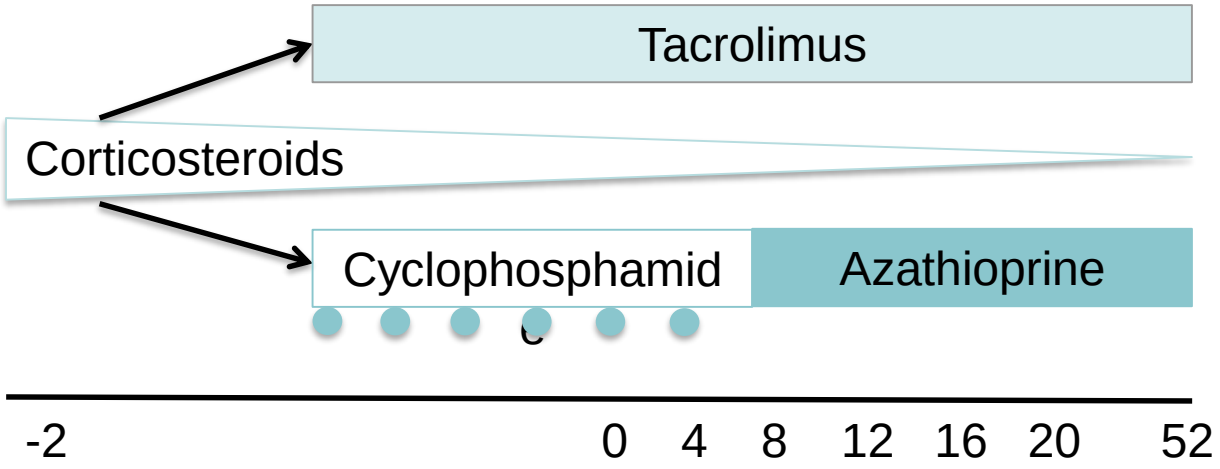
11/2007



11/2008

CATR.PAT Study, PHRC 2014

- Mars 2018
- PID avec un antisynthetase
- 88 patients



doi:10.1093/brain/aww192 BRAIN 2015: 138; 2485–2492 | 2485

BRAIN
A JOURNAL OF NEUROLOGY

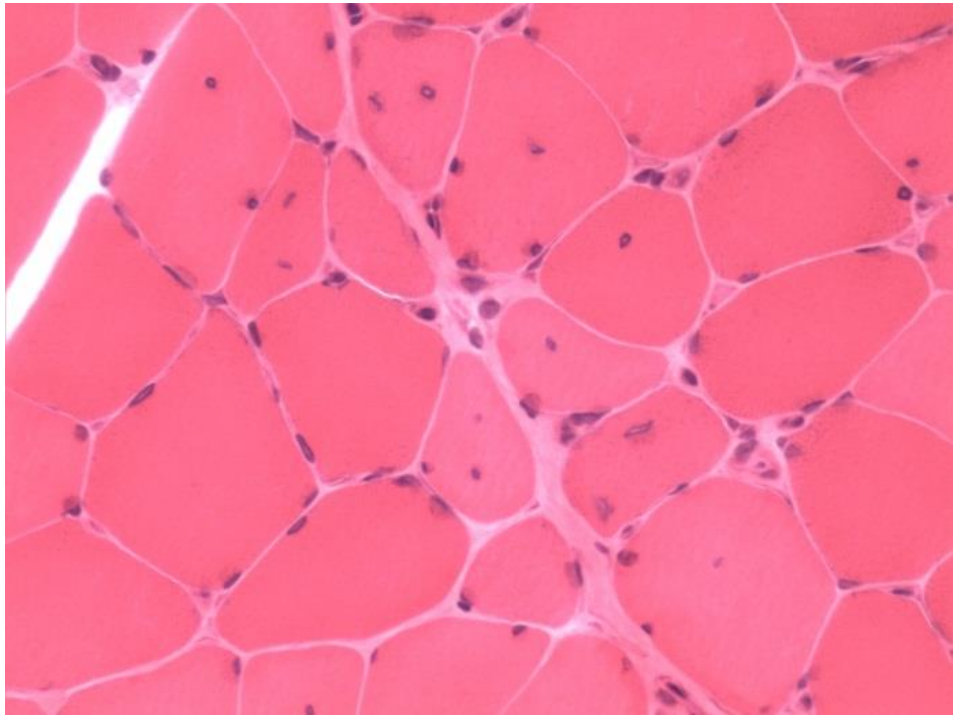
REPORT

Anti-Jo-1 antibody-positive patients show a characteristic necrotizing perifascicular myositis

Lénaig Mescam-Mancini,[1,*] Yves Allenbach,[2,3,*] Baptiste Hervier,[2,4,*] Hervé Devilliers,[5] Kuberaka Mariampillay,[2] Odile Dubourg,[6] Thierry Maisonobe,[6] Romain Gherardi,[7] Paulette Mezin,[1] Corinna Preusse,[3] Werner Stenzel[3] and Olivier Benveniste[2]

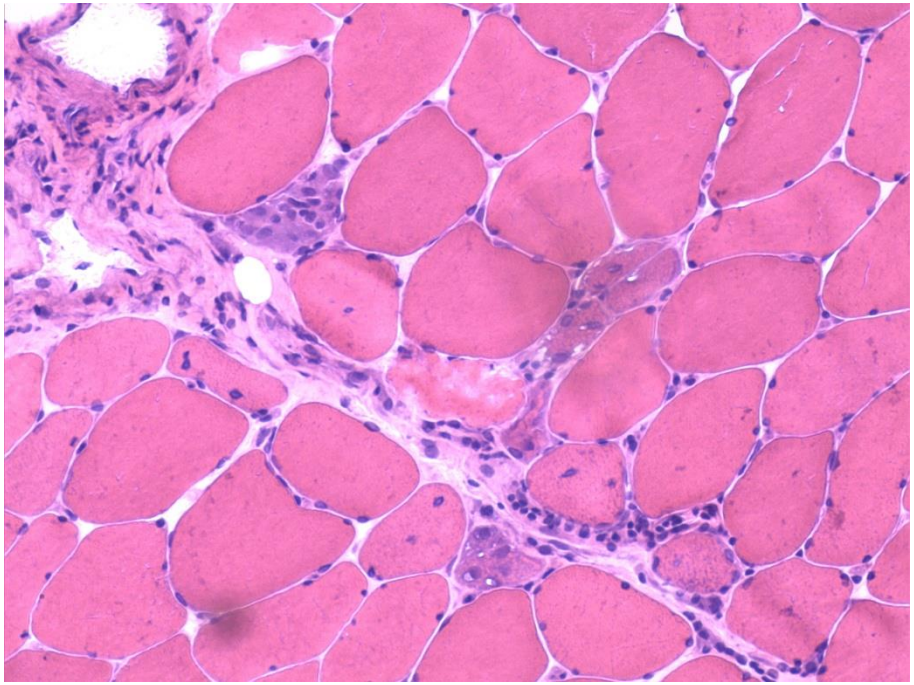
Spécificité et sensibilité des critères histologiques chez les patients anti-Jo-1+

- Série Parisienne de biopsies musculaires : n=53
- Série Berlinoise : n=19
- Cas contrôles
  - DM: n=17
  - MNAI: n=21
  - MI: n=16

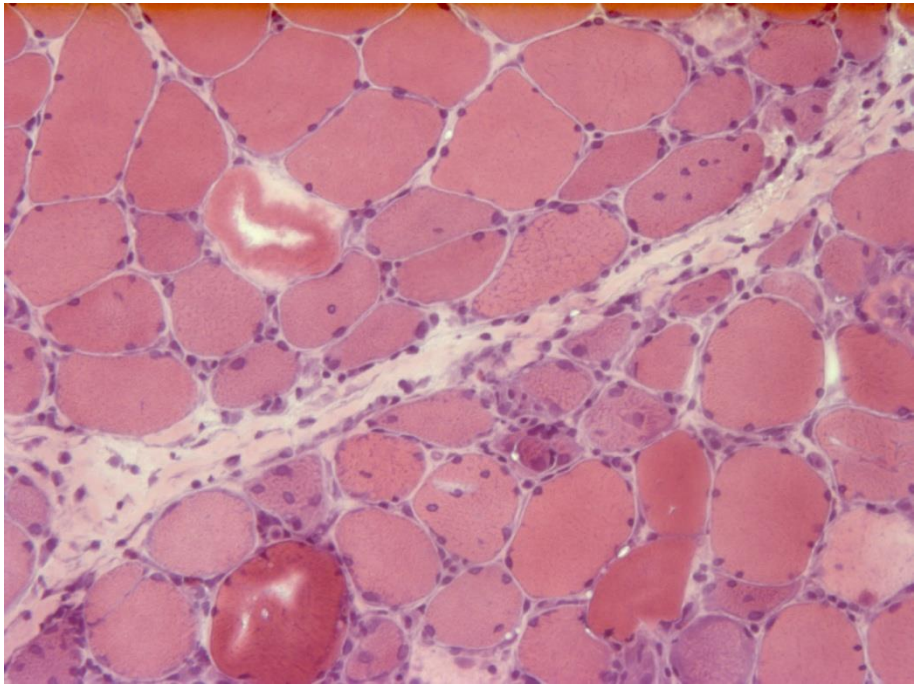


Collaboration avec:
Yves Allenbach, Baptiste Hervier
Werner Stenzel

1

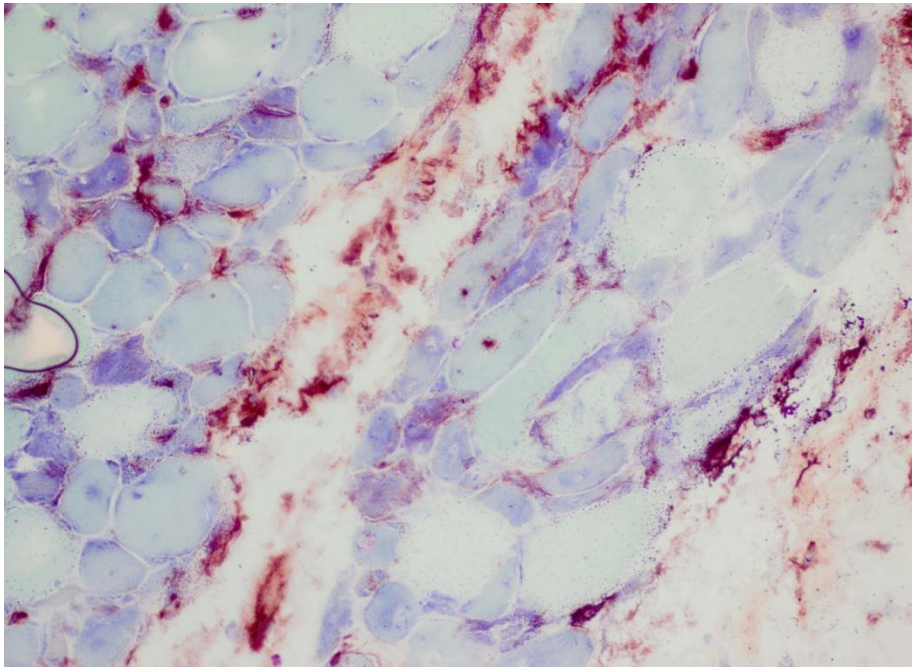


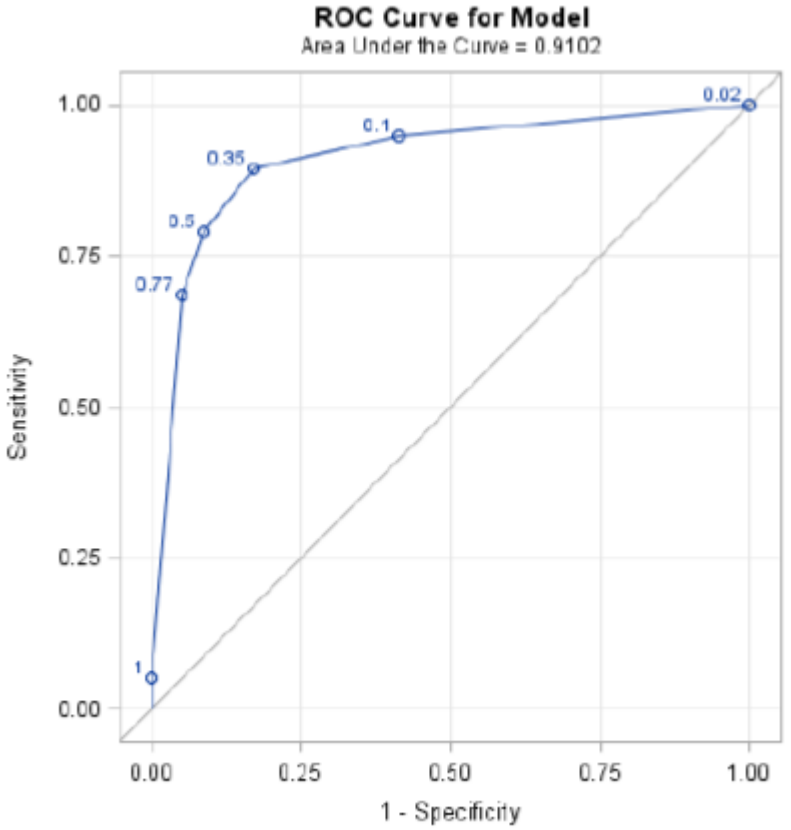
2



1. Nécrose périfasciculaire (non observée au cours DM ou PM)
2. Atrophie périfasciculaire (DM like)

3





3. Fragmentation du périmysium (alcaline phosphatase)

ARTHRITIS & RHEUMATISM
Vol. 56, No. 9, September 2007, pp 3125–3131
DOI 10.1002/art.22865

Anti–Jo-1 Antibody Levels Correlate With Disease Activity in Idiopathic Inflammatory Myopathy

Kerry B. Stone, Chester V. Oddis, Noreen Fertig, Yasuhiro Katsumata, Mary Lucas, Molly Vogt, Robyn Domsic, and Dana P. Ascherman

Table 4. Longitudinal correlations with Jo-1 ELISA results*

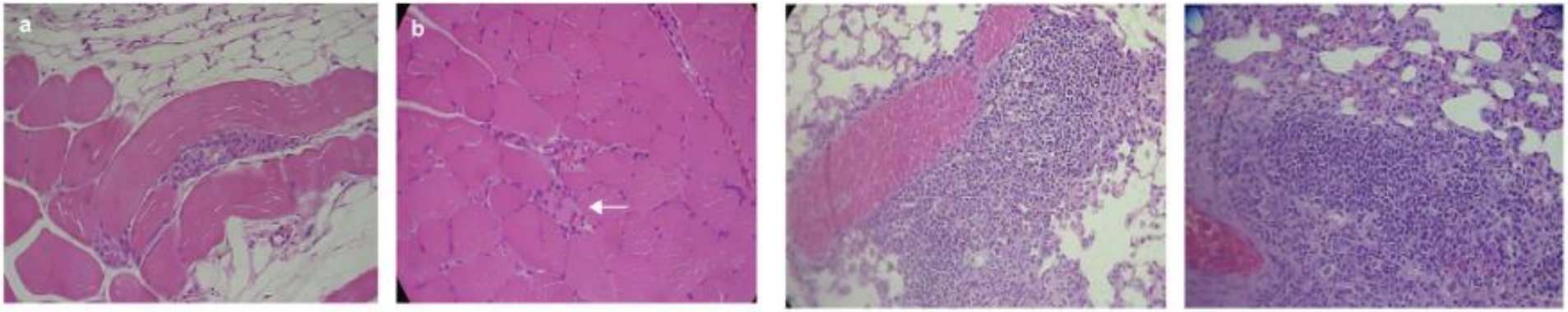
Clinical parameter	Commercial Jo-1 ELISA		Custom rHuJo-1 ELISA	
	Adjusted R^2†	*P*	Adjusted R^2†	*P*
CK (× the ULN)‡	0.65	0.0002	0.78	0.0001
Myositis VAS§	0.53	0.0008	0.69	0.0001
Myositis MITAX‡	0.63	0.06	0.68	0.008
Arthritis VAS§	0.53	0.006	0.73	0.002
Arthritis MITAX‡	0.62	0.04	0.75	0.02
Lung VAS§	0.69	0.005	0.69	0.29
Lung MITAX‡	0.68	0.05	0.75	0.05
Global VAS§	0.63	0.002	0.74	0.005
Global MITAX‡	0.64	0.0003	0.74	0.003

* See Table 3 for definitions.
† Based on a mixed linear regression model.
‡ Determined in 50 serial samples from 11 patients.
§ Determined in 35 serial samples from 9 patients.

J Autoimmun. 2007 ; 29(2-3): 174–186. doi:10.1016/j.jaut.2007.07.005.

Species-specific immune responses generated by histidyl-tRNA synthetase immunization are associated with muscle and lung inflammation

Yasuhiro Katsumata[a], William M. Ridgway[a], Timothy Oriss[b], Xinyan Gu[a], David Chin[a], Yuehong Wu[a], Noreen Fertig[a], Tim Oury[c], Daniel Vandersteen[d], Paula Clemens[e], Carlos J. Camacho[f], Andrew Weinberg[g], and Dana P. Ascherman[a,*]



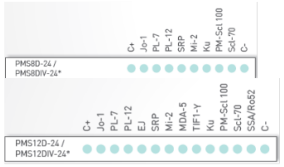
En conclusion

- Ensemble de signes clinico-pathologiques définissant un groupe homogène de patients
- Biomarqueur spécifique = Ac anti-synthetase (par ex. Anti-Jo-1)
- Modèle chez la souris
- Correlation entre le niveau du biomarqueur (titre des Ac) et l'activité de la maladie

→ { Définition d'une maladie indépendante :

La maladie des anti-synthetases!

- Ni un syndrome, ni une PM ou une DM!



*DM, PM defined in 1975 by Bohan and Peter,
*IBM under the criteria of Griggs & al, 1995 reviewed by Lloyd & all, in 2014
*IMNM by Hoogendijk & al, in 2004

Registry of Myositis in Neuro-Muscular Diseases Reference Center (GHPS)
N= 1150

→ Dot myositis not done (n= 643)

Dot myositis performed (GHPS)
period 2003-2014
N=507

→ Myositis not defined (n=62)

Myositis defined according to historical classifications
N= 445

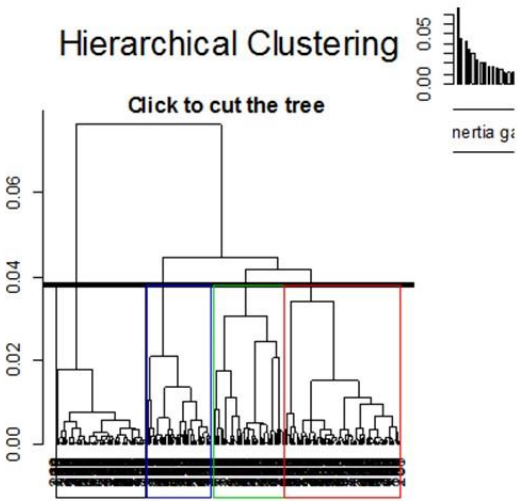
→ Files not available or uncompleted (n=84)

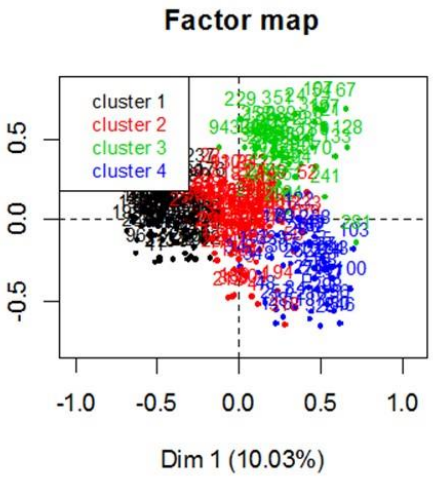
Patient's files completed for analysis
N= 361

Unsupervised classification methods (MCA, HCA) then prediction (CART)

Biobank, n=400

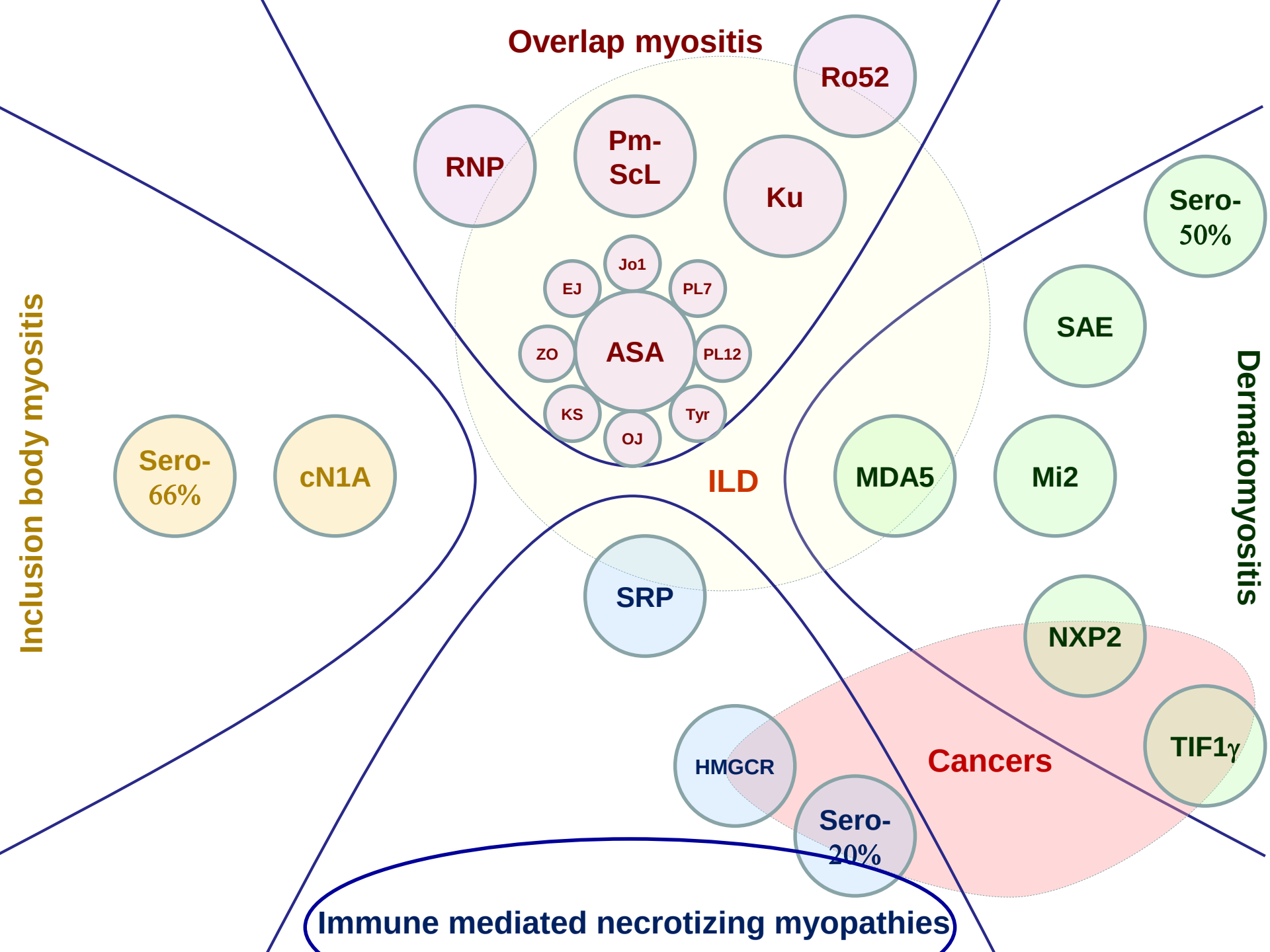
Multiple Correspondence Analysis (MCA) and Hierarchical Cluster Analysis (HCA)





Cluster 1 = IBM, anti-cN1A
Cluster 2 = IMNM, anti-SRP&HMGCR
Cluster 3 = DM, anti-Mi2, TIF1g, MDA5..
Cluster 4 = OM, anti-Jo1, PL7, PL12…

Kuberaka Mariampillai, submitted


Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
EJ
PL7
ZO
ASA
PL12
KS
Tyr
OJ
Sero-50%
SAE
Dermatomyositis
Inclusion body myositis
Sero-66%
cN1A
ILD
MDA5
Mi2
SRP
NXP2
HMGCR
Cancers
TIF1γ
Sero-20%
Immune mediated necrotizing myopathies

Myopathies Nécrosantes AI

PERGAMON

Neuromuscular Disorders 14 (2004) 337–345

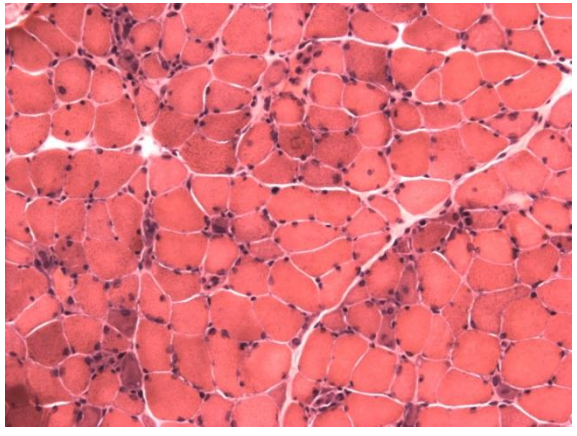
www.elsevier.com/locate/nmd

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]

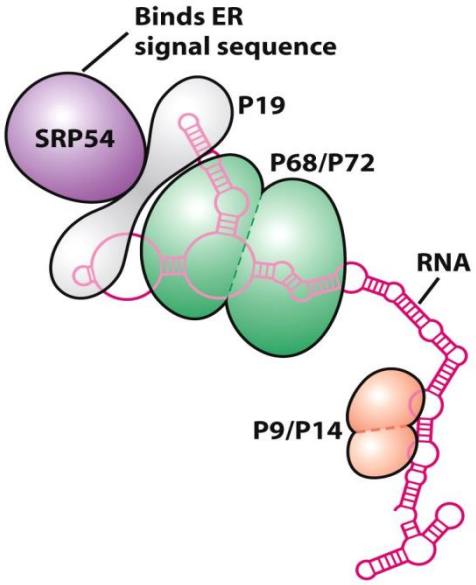
Immune-mediated necrotizing myopathy

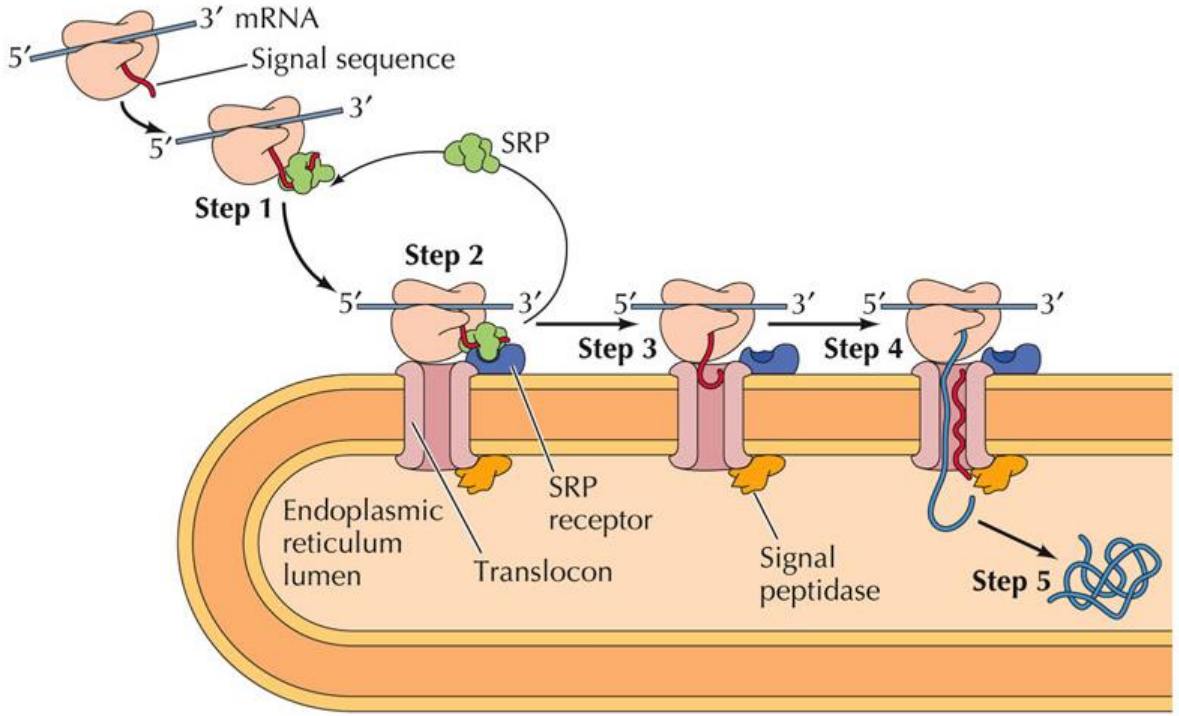


1. All clinical criteria with the exception of rash
2. Elevated serum CK
3. Other laboratory criteria (1 of 3) EMG, MRI, auto-Abs
4. Muscle biopsy criteria include *g*, and exclude all others

Necrosis + regeneration without inflammation

Signal recognition particule (SRP)

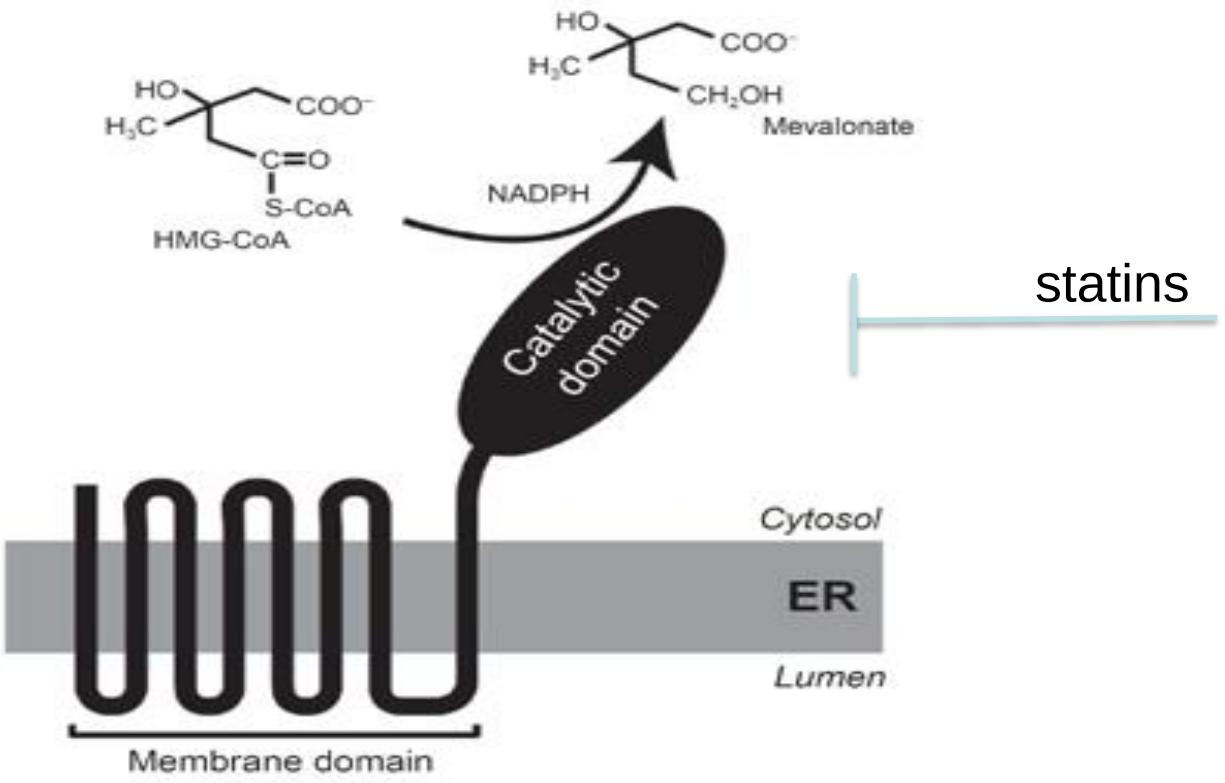




Berg et al. Biochemistry. 2012

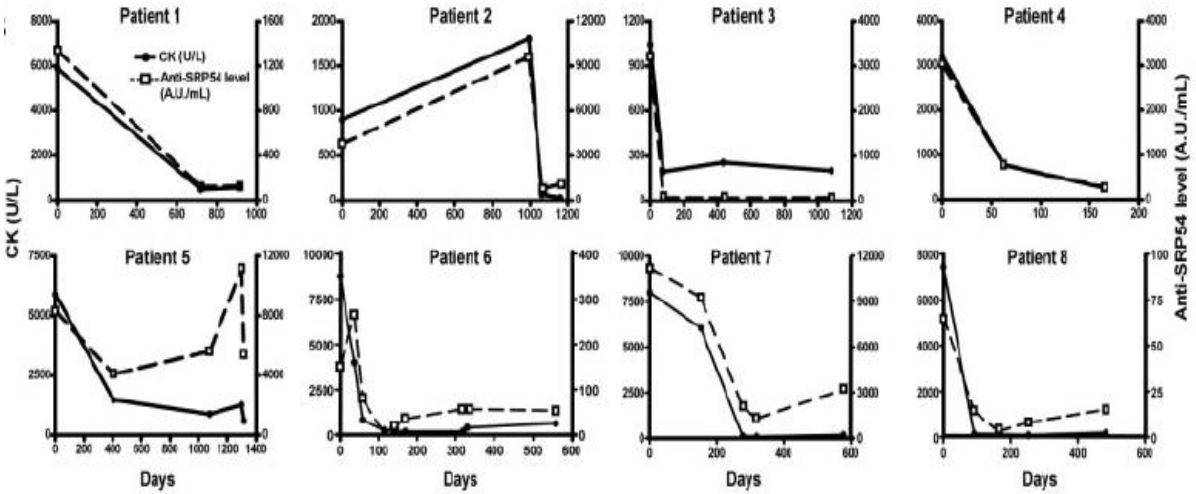
The cell, 4th edition. 2006

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

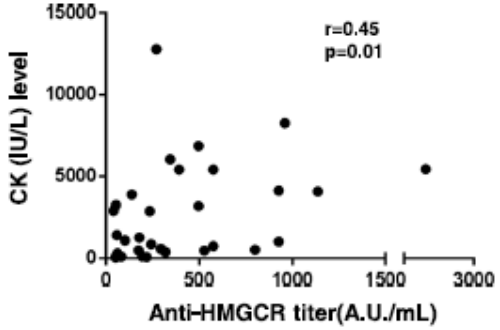


DeBose-Boyd, cell research. 2008

Corrélations entre CPK et titres Acs

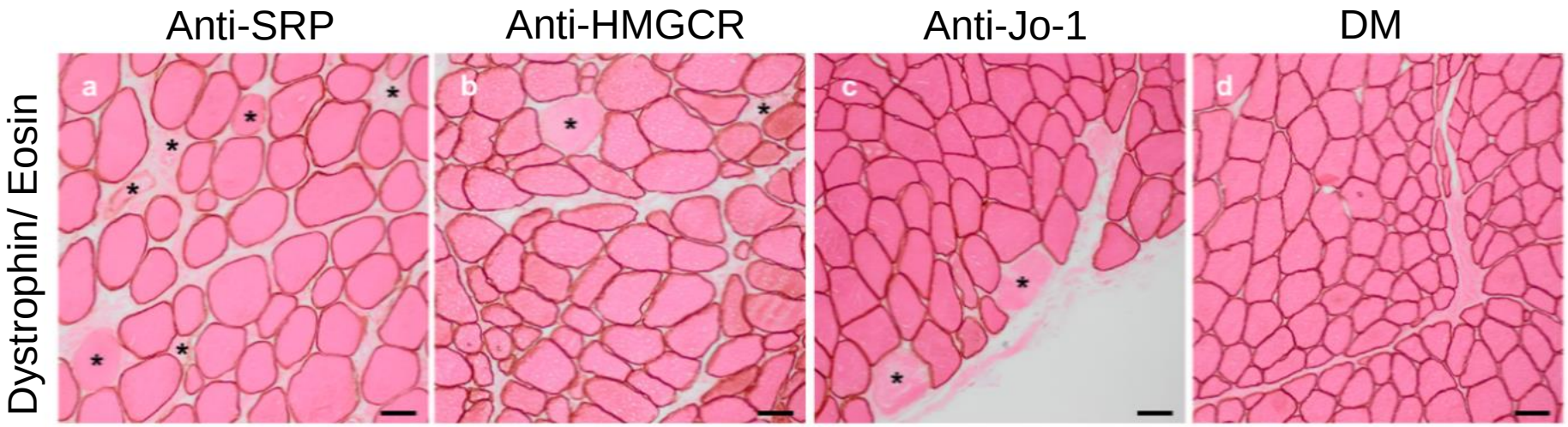


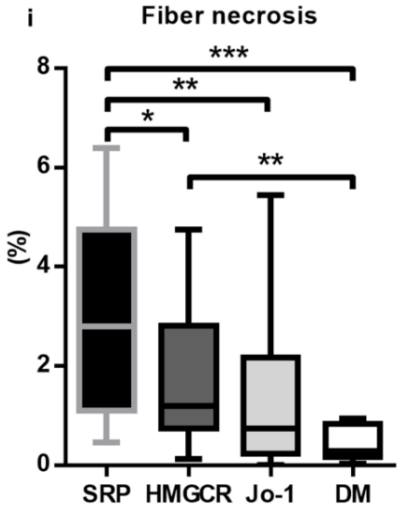
Benveniste et al; Arthritis, 2011

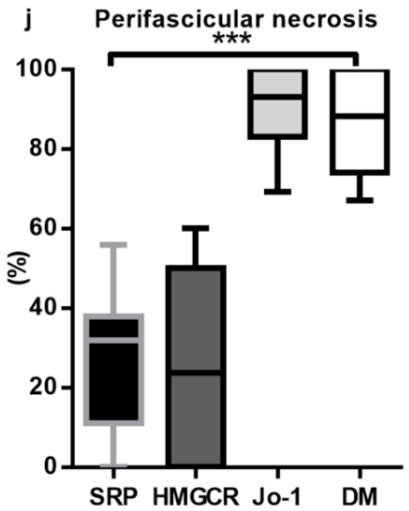


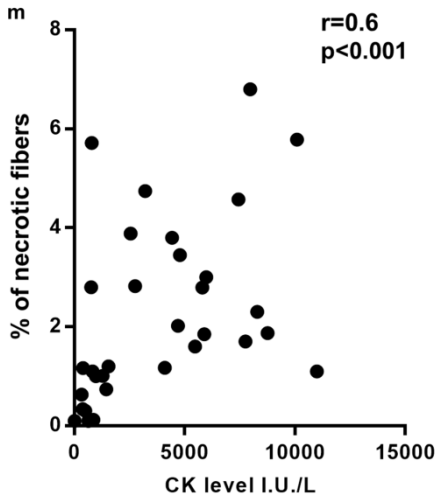
Allenbach et al; Medicine, 2014

Quantification de la nécrose musculaire

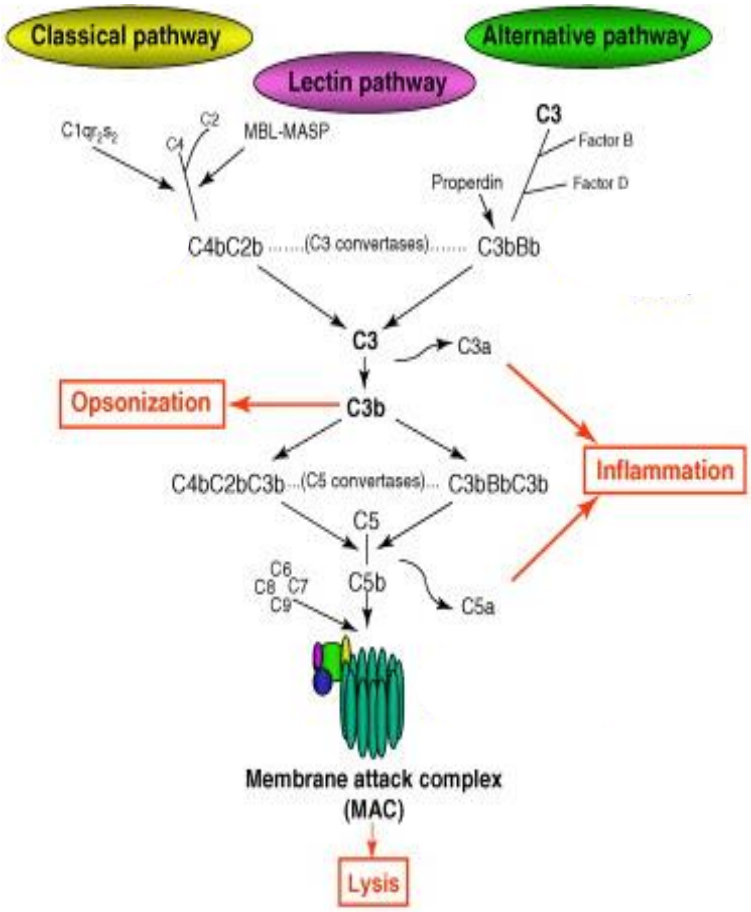




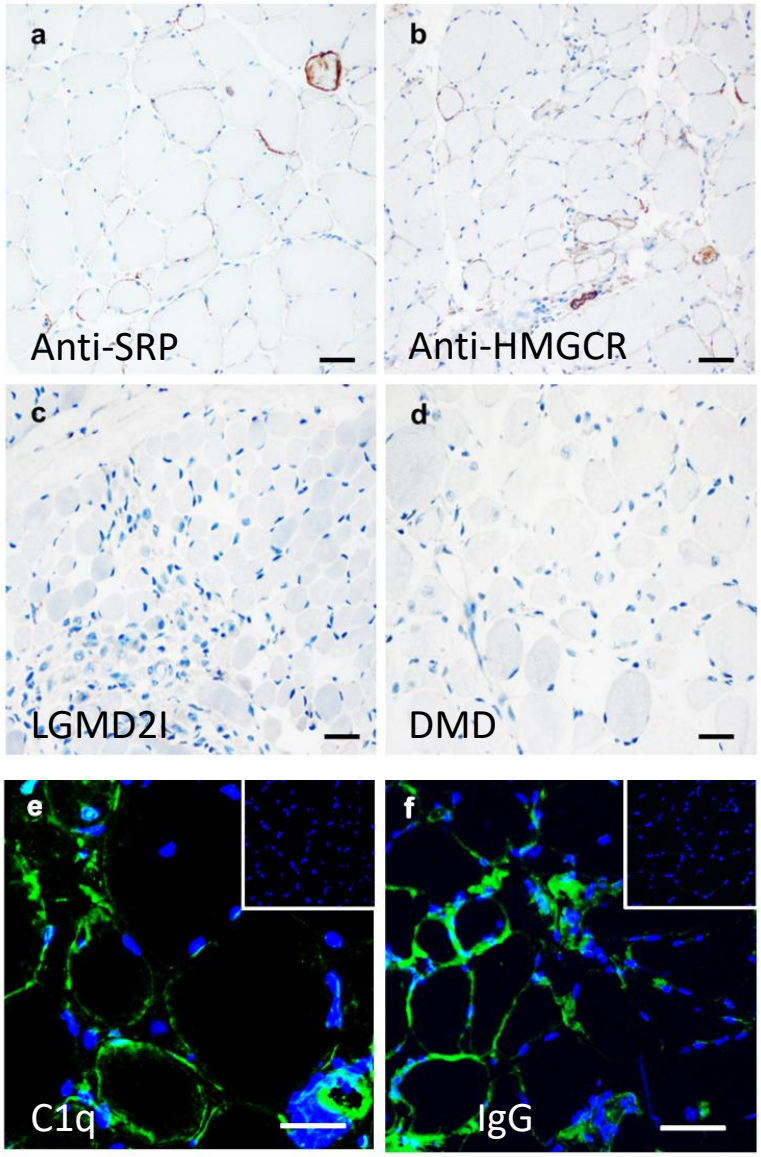




Nécrose : rôle du complément

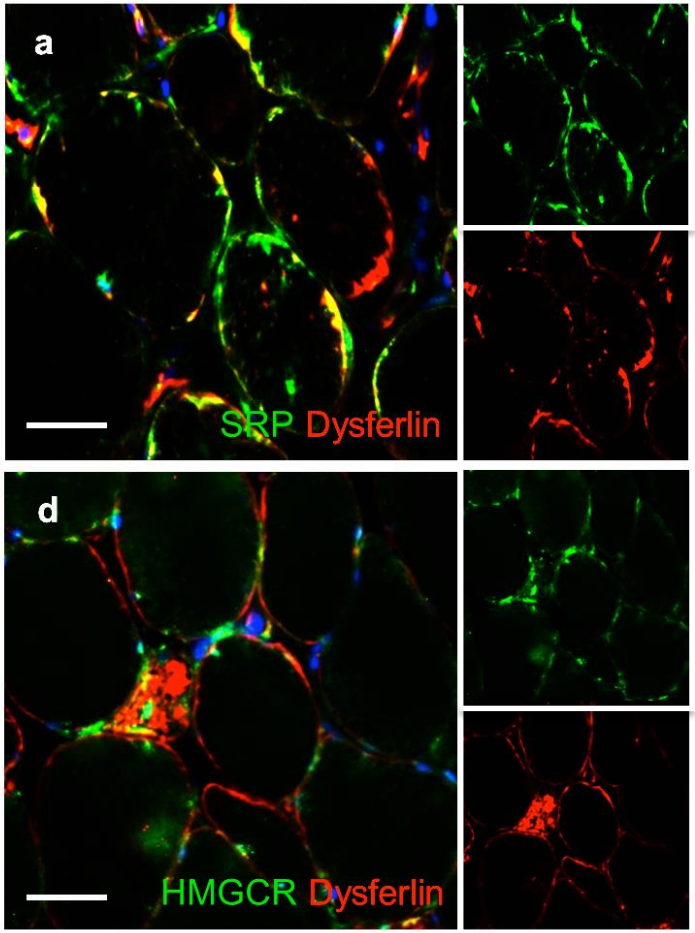


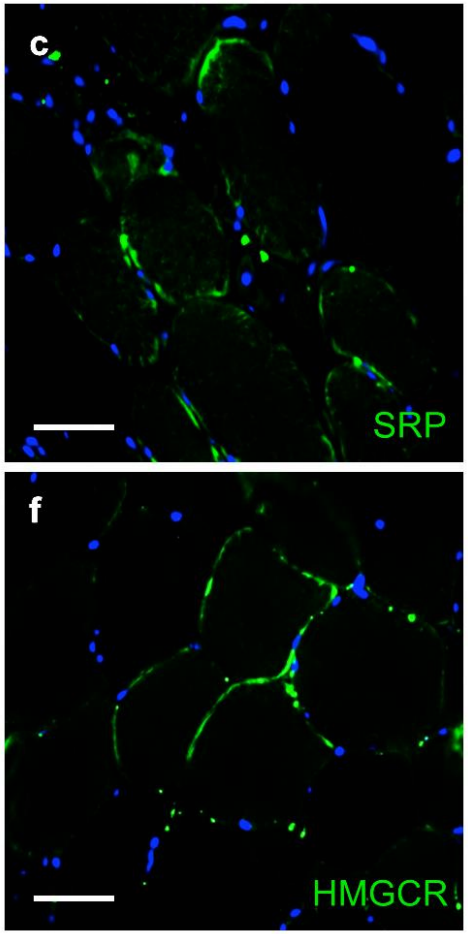
C5b9



Hallstrom T and Riesbeck; Trends in microbiol.,2010

Comment ces Acs atteignent leurs cibles?





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

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

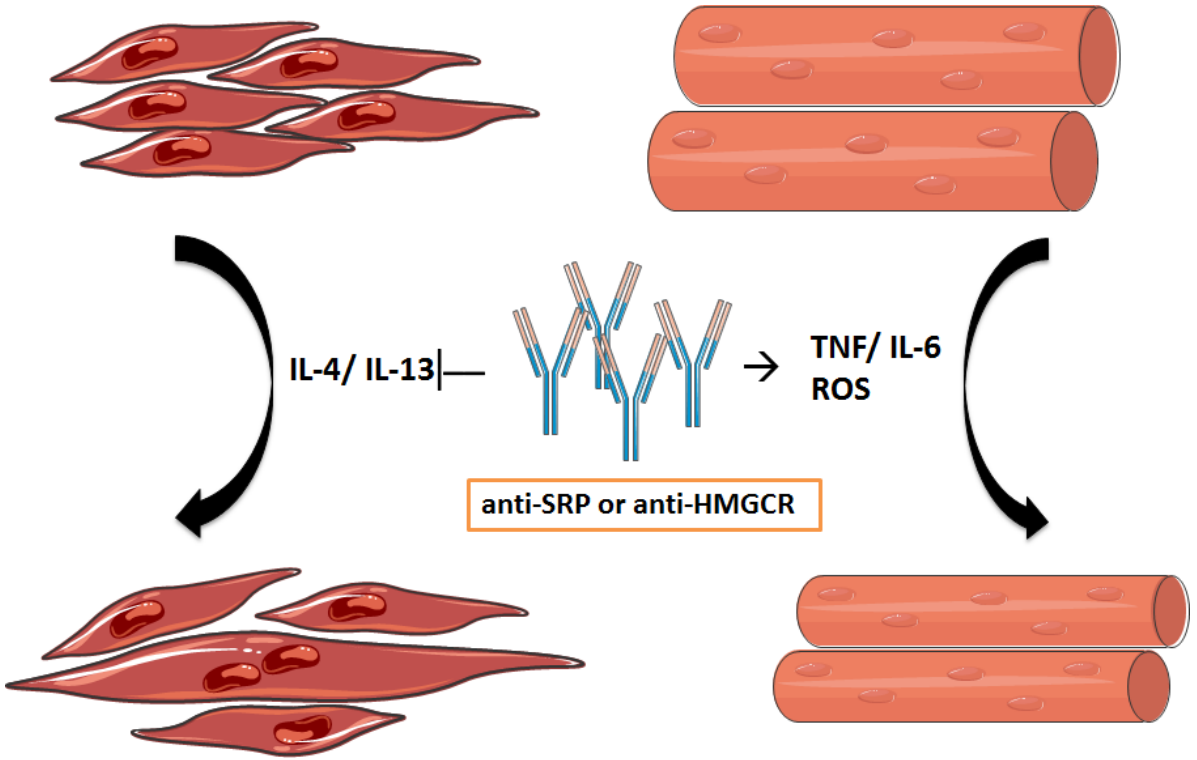
Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

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



IMNM, HMGCR and muscle strength

RHEUMATOLOGY

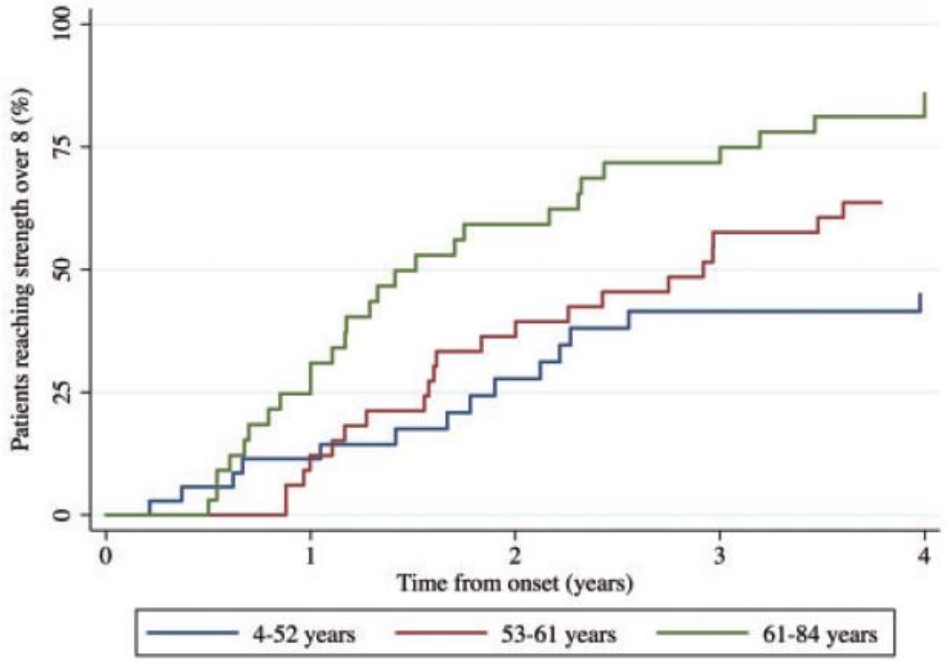
Original article

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]

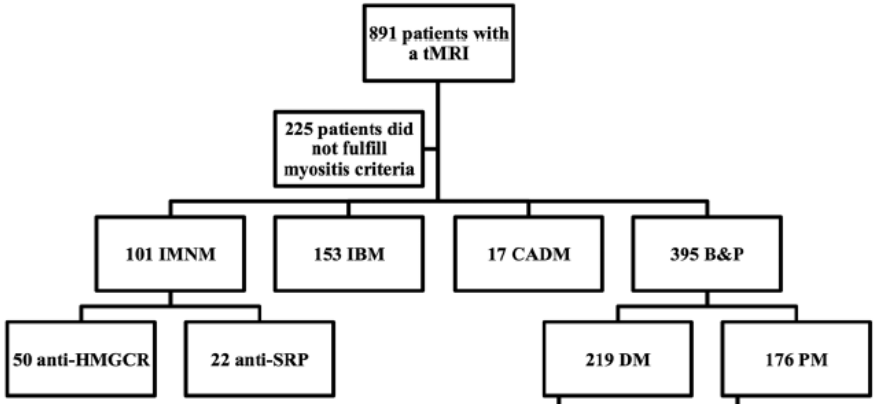
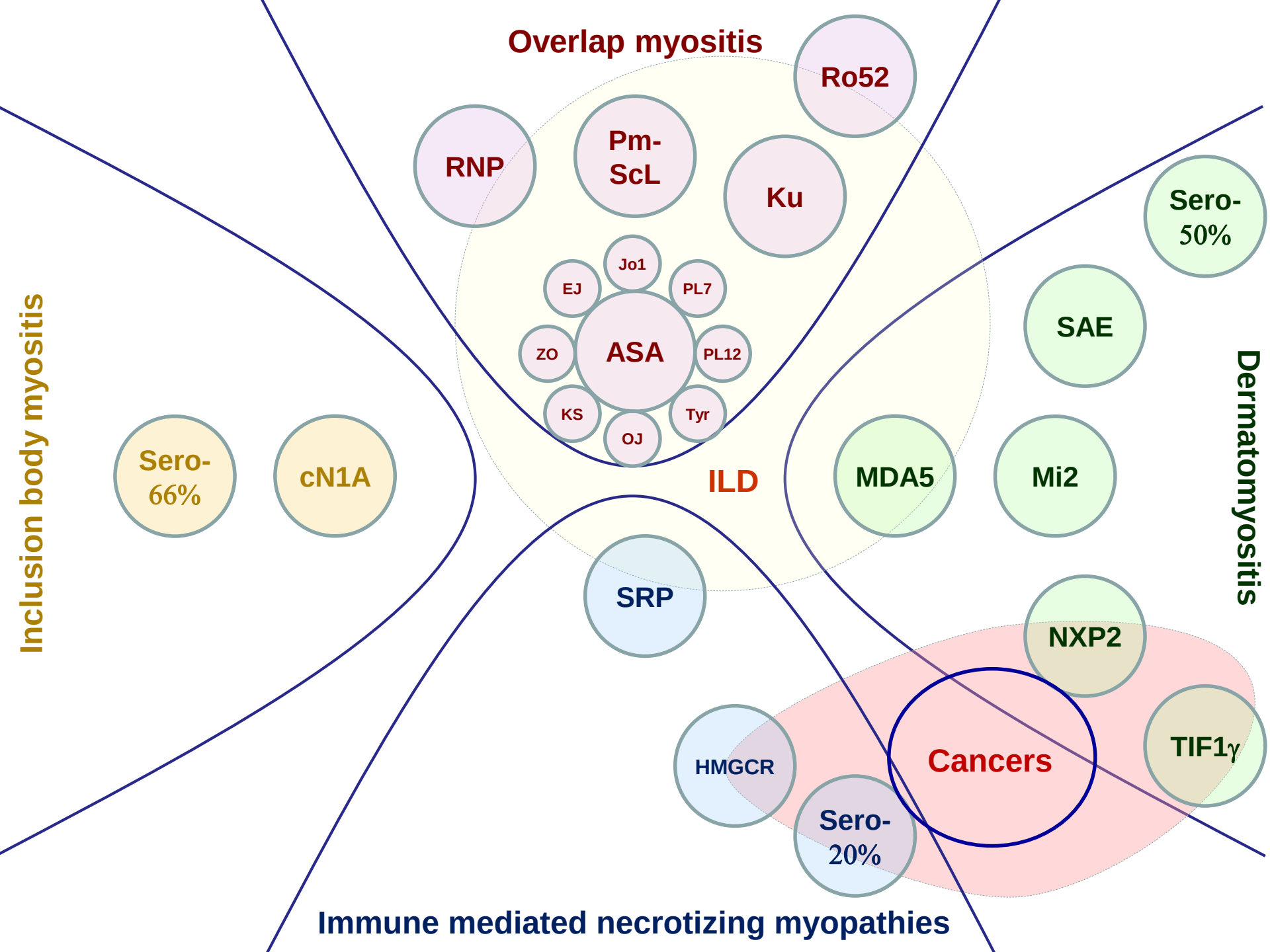


Table 2 Extent of thigh MRI findings among clinical subsets

	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)


Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
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ILD
Sero-50%
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Sero-66%
cN1A
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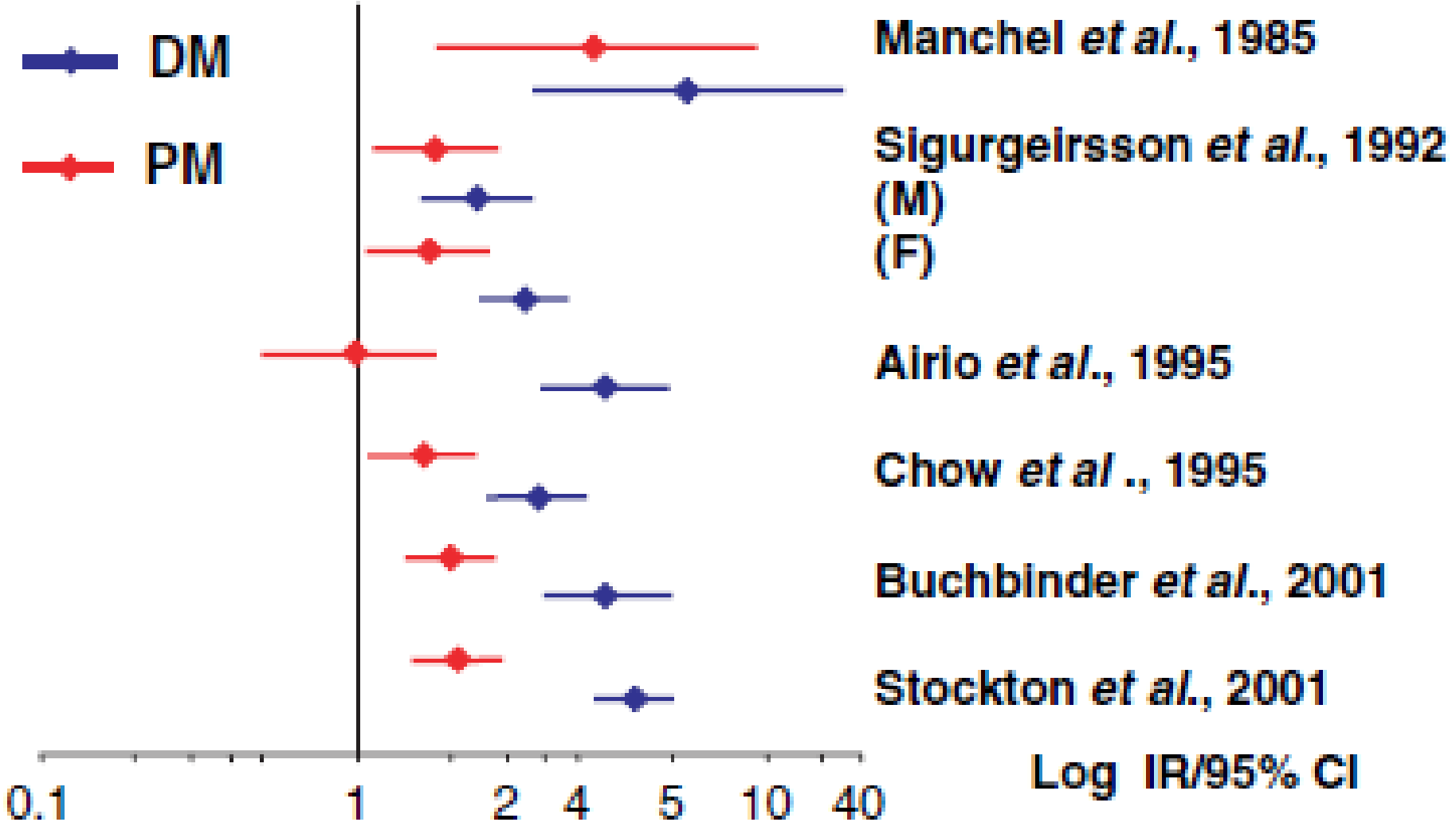
Immune mediated necrotizing myopathies

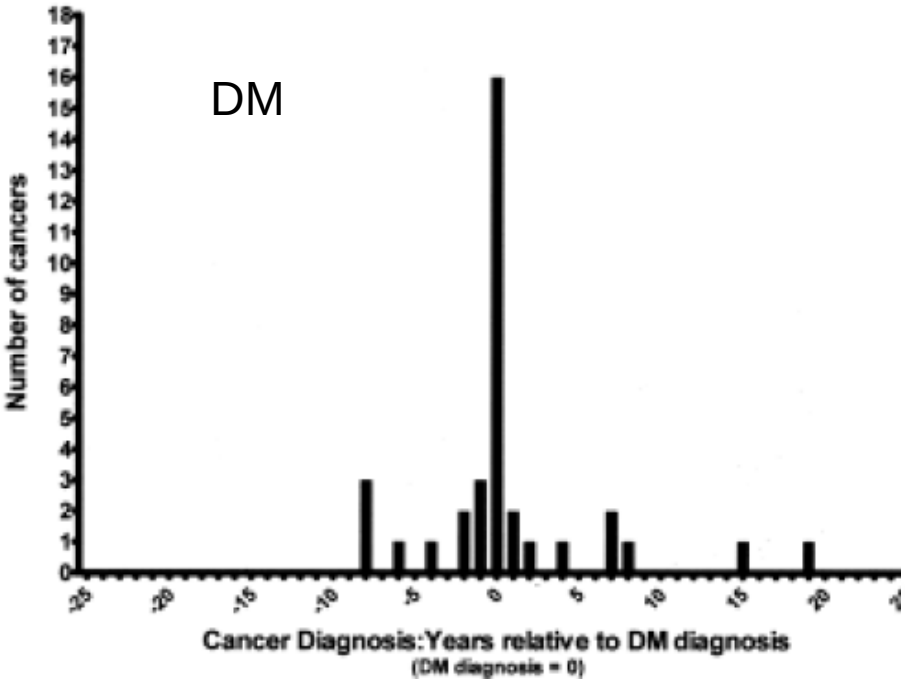


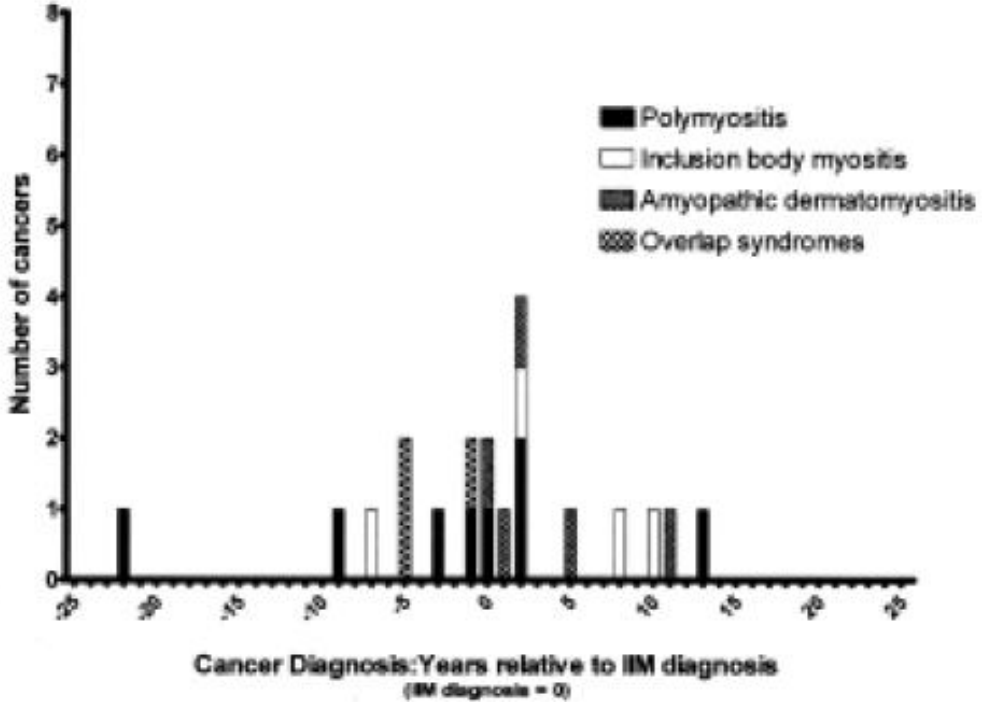
V. Madan, Clin Exp Dermatol, 2009; 34:451-5

Malignancy Is Associated with Dermatomyositis But Not Polymyositis in Northern New England, USA

BRENDAN B. ANTIOCHOS, LIN A. BROWN, ZHONGZE LI, TOR D. TOSTESON, ROBERT L. WORTMANN, and WILLIAM F.C. RIGBY

J Rheumatol, 2009;36:2704-10

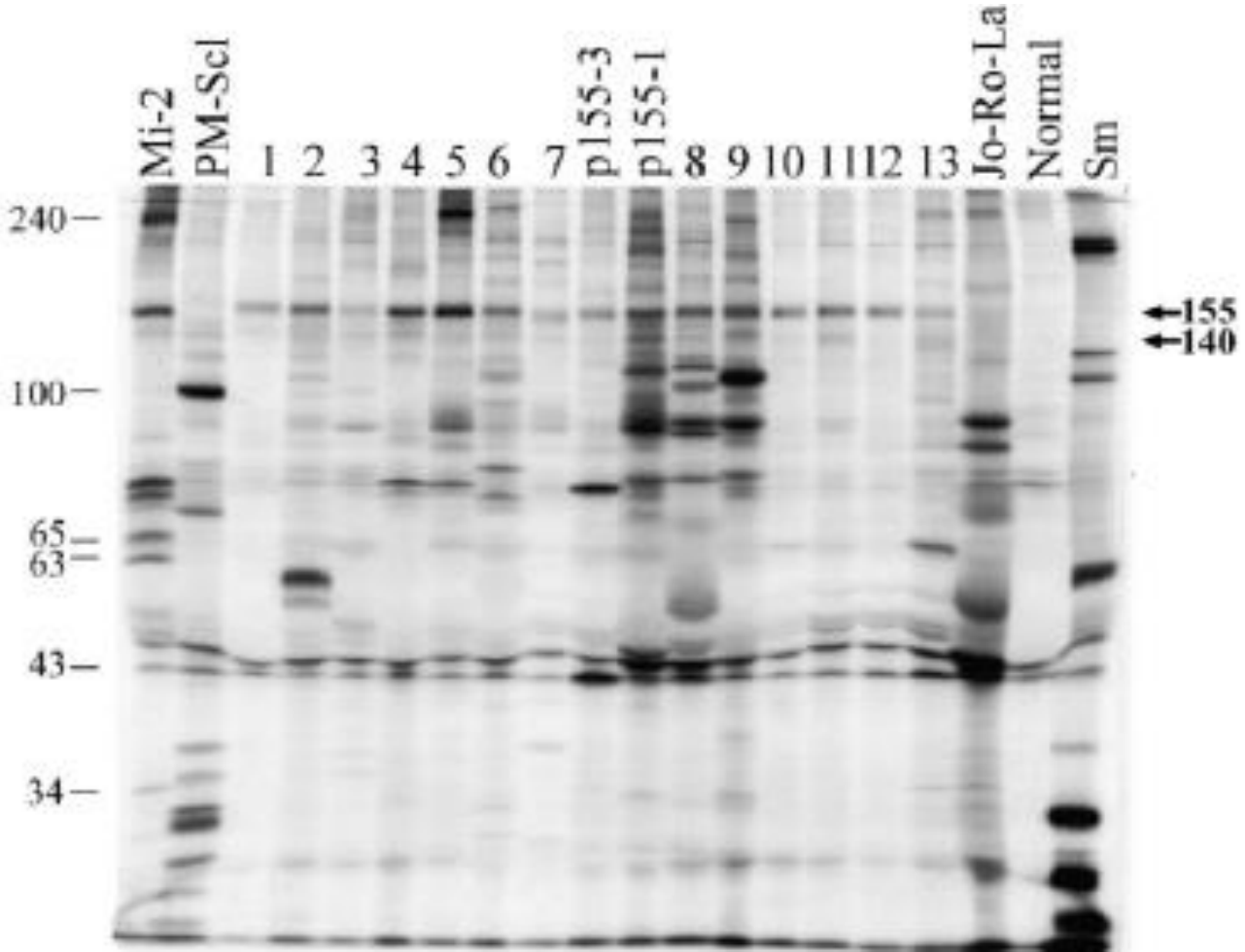




A Novel Autoantibody to a 155-kd Protein Is Associated With Dermatomyositis

Arthritis 2006

Ira N. Targoff,[1] Gulnara Mamyrova,[2] Edward P. Trieu,[3] Osvaldo Perurena,[4] Bhanu Koneru,[2] Terrance P. O'Hanlon,[2] Frederick W. Miller,[2] and Lisa G. Rider,[2] for the Childhood Myositis Heterogeneity and International Myositis Collaborative Study Groups



Anti-MDA5 and anti-TIF1-γ antibodies have clinical significance for patients with dermatomyositis

Kei Hoshino[1], Yoshinao Muro[1], Kazumitsu Sugiura[1], Yasushi Tomita[1], Ran Nakashima[2] and Tsuneyo Mimori[2]

Rheumatology 2010

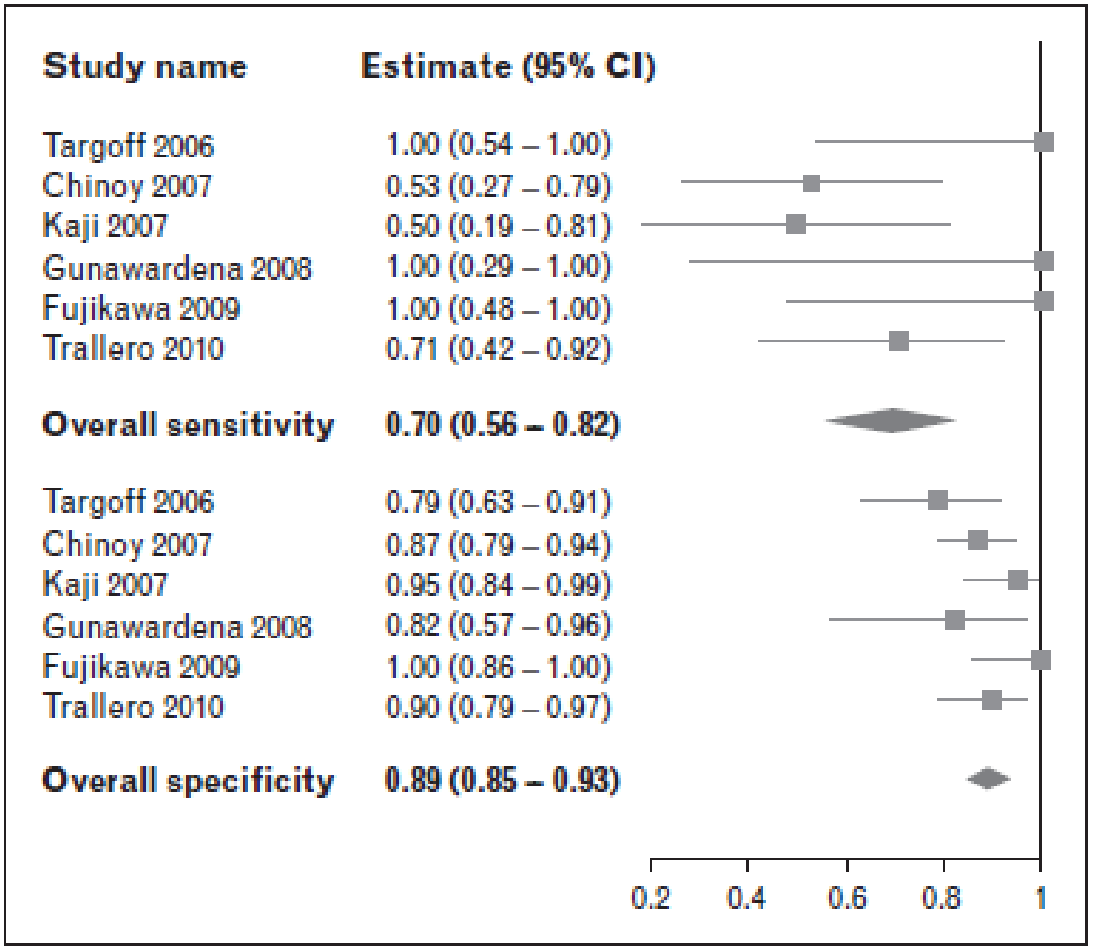
p155/140 = **TIF1-γ** = TRIM33 = Ret-fused gene 7 = PTC 7 = ectodermin
Facteur nucléaire agissant comme une ubiquitin ligase de Smad4

TABLE 5 Clinical feature comparison of anti-TIF1-γ-positive and -negative DM patients

Feature	Anti-TIF1-γ antibody	
	Positive ($n=12$)[a]	Negative ($n=70$)[a]
Age at onset, mean (S.D.), years	47 (26)	46 (18)
Gender, male : female	5 : 7	19 : 51
Heliotrope rash, *n* (%)	6/12 (50)	38/52 (73)
Gottron's papules or sign, *n* (%)	9/12 (75)	35/53 (66)
Elevation of CK, *n* (%)	6/10 (60)	29/57 (51)
ILD, *n* (%)	1/10 (10)*	31/51 (61)
PSL maximum dose, mean (S.D.)[b], mg/day	20 (13)* ($n=10$)	43 (20) ($n=52$)
i.v. mPSL pulse therapy, mean (S.D.), number of times	0.5 (1.1) ($n=10$)	1.0 (1.5) ($n=55$)
Immunosuppressive therapy, *n* (%)	0/10 (0)**	22/56 (39)
Pneumomediastinum, *n* (%)	0/10 (0)	4/51 (8)
Internal malignancy, *n* (%)	7/12 (58)*	5/62 (8)

[a]Not all patients had clinical data available for each feature. [b]The i.v. mPSL pulse therapy was not counted for PSL maximum dose. *$P<0.005$, *vs* anti-TIF1-γ-negative DM patients by a Fisher's exact test or an unpaired Student's *t*-test. **$P<0.05$, *vs* anti-TIF1-γ-negative DM patients by a Fisher's exact test.

Figure 1 Meta-analysis results: pooled sensitivity and specificity of antip155 for predicting occult malignancy in patients diagnosed with dermatomyositis



- Negative predictive value: 93%
- OR = 18 [95% IC 8-40]

Selva-O'Callaghan, Curr Opin Rheumatol, 2010

Dermatomyosites à anti-NXP2

Most Patients With Cancer-Associated Dermatomyositis Have Antibodies to Nuclear Matrix Protein NXP-2 or Transcription Intermediary Factor 1γ

Arthritis & Rheumatology 13

David F. Fiorentino,[1] Lorinda S. Chung,[2] Lisa Christopher-Stine,[3] Lisa Zaba,[1] Shufeng Li,[1] Andrew L. Mammen,[3] Antony Rosen,[3] and Livia Casciola-Rosen[3]

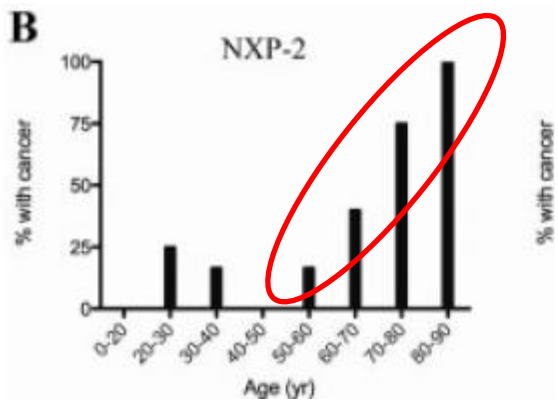
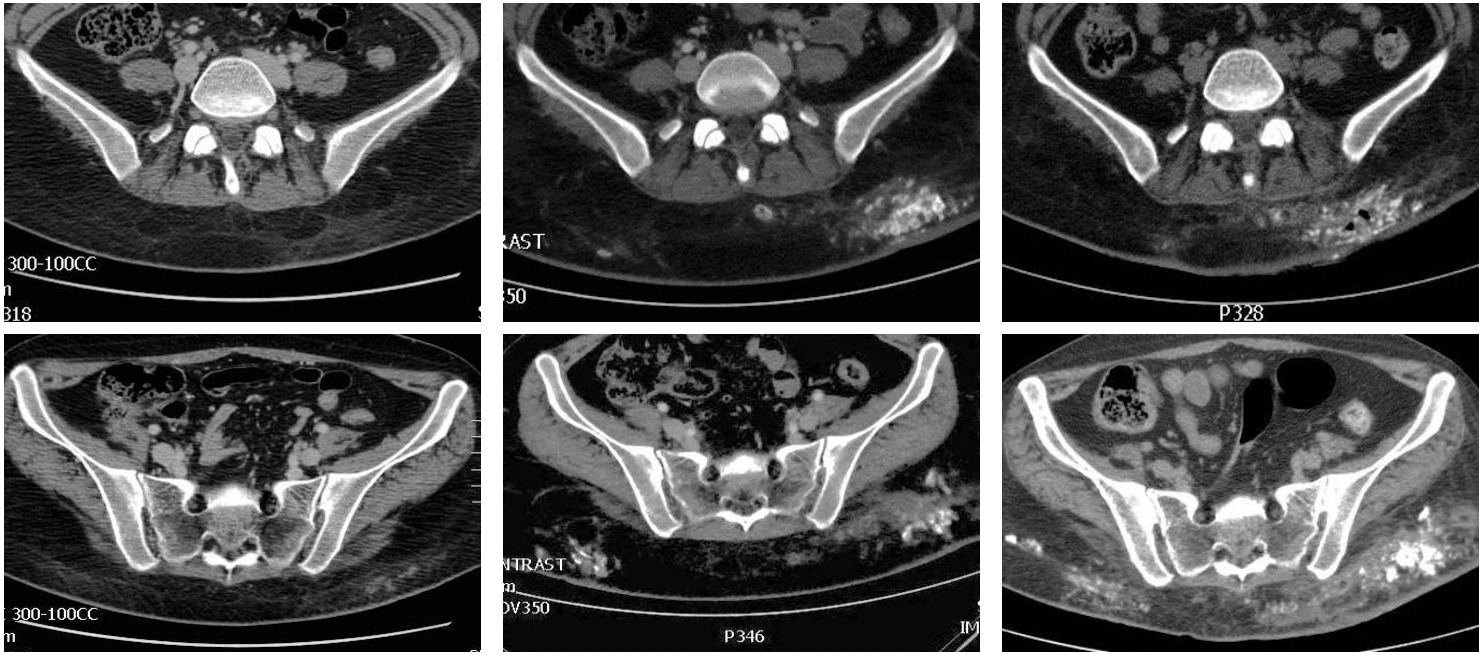
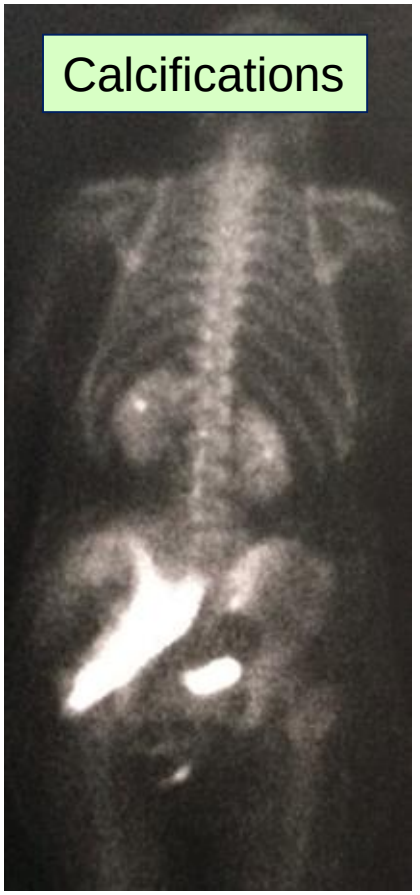


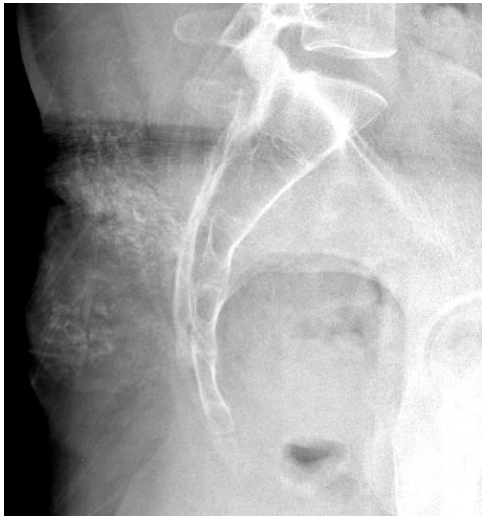
Table 3. Risk factors for cancer (univariate analysis)*

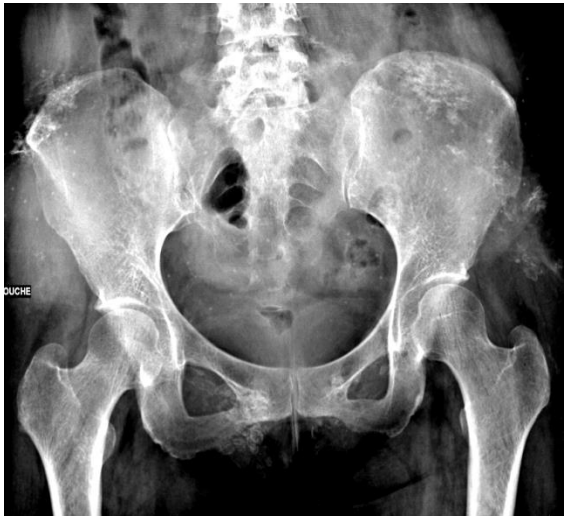
	OR (95% CI)	*P*
Sex		
Female	Referent	
Male	3.3 (1.5–7.4)	0.003
Age at diagnosis, per year	1.06 (1.03–1.1)	<0.0001
Anti–NXP-2		
No	Referent	
Yes	2.5 (1.0–6.1)	0.042
Anti–TIF-1γ		
No	Referent	
Yes	1.9 (0.9–4.1)	0.12

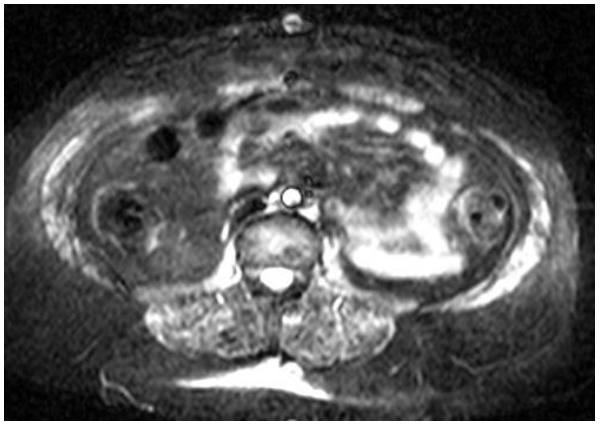
12/2008 **12/2011** **04/2012**

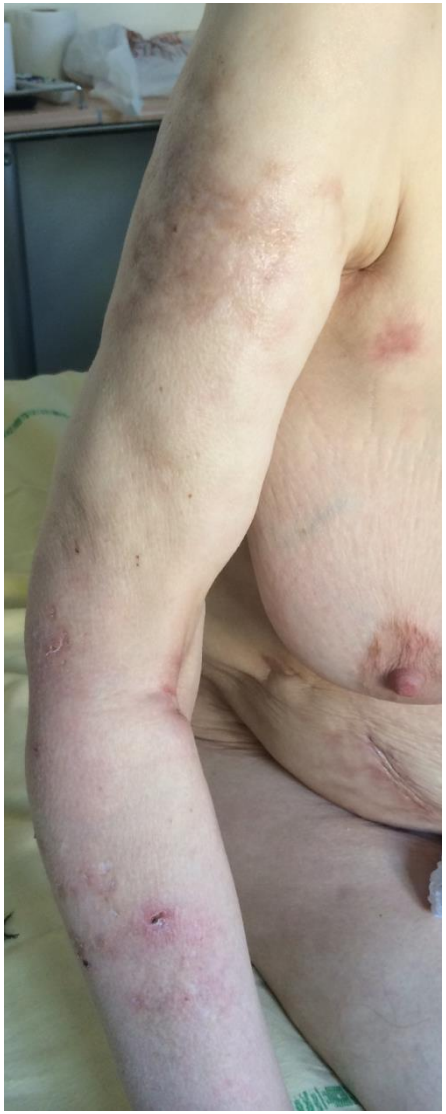


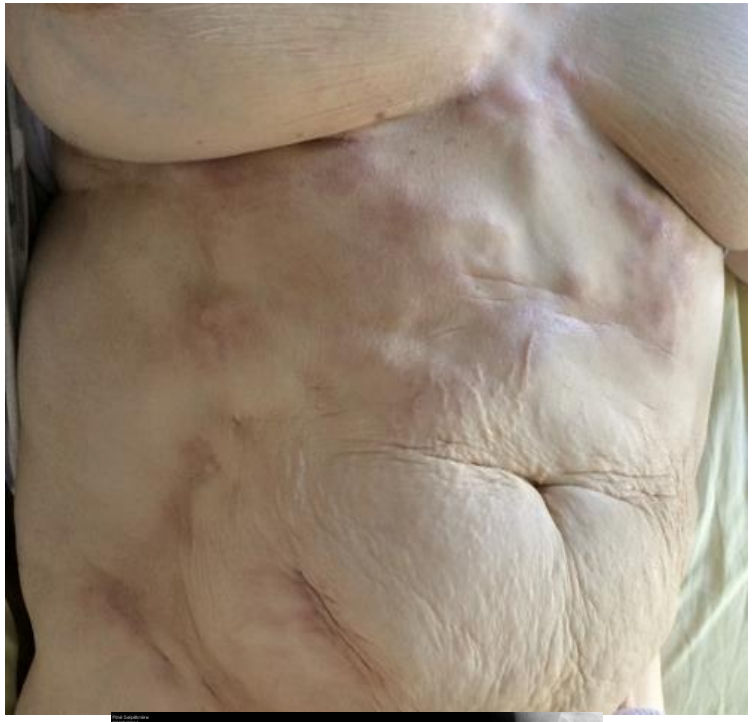


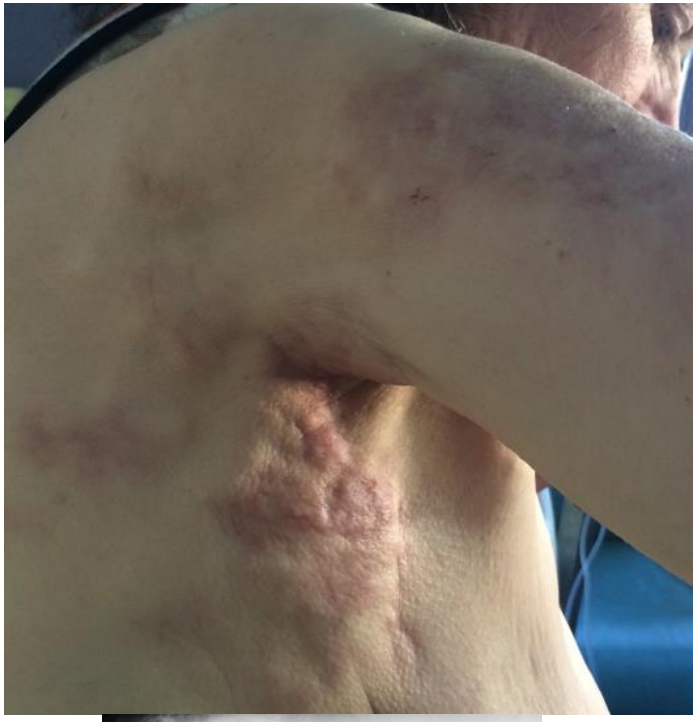


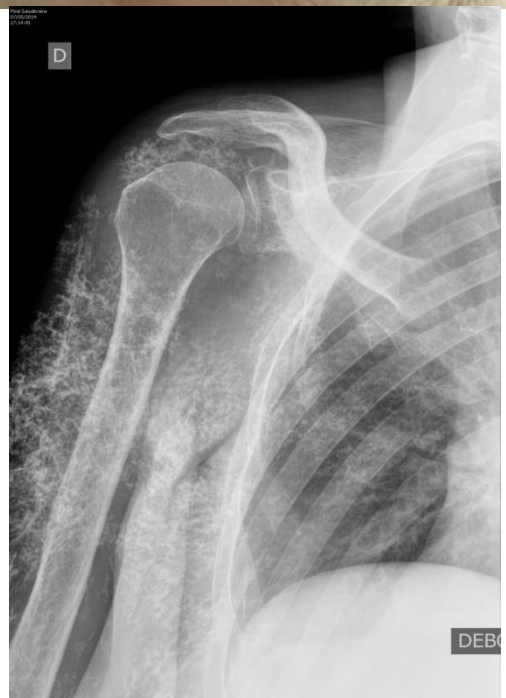








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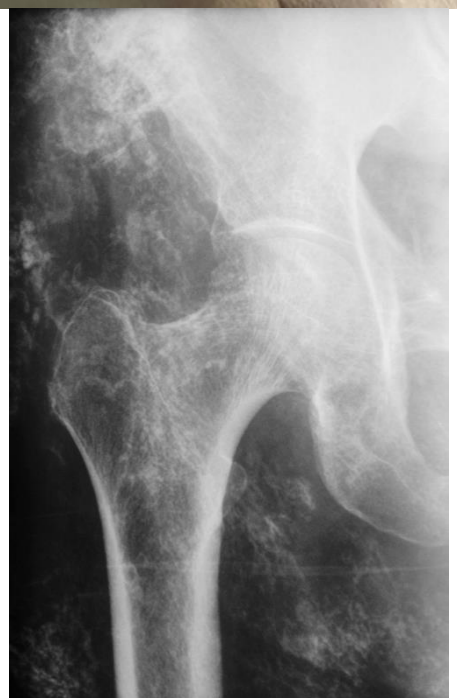

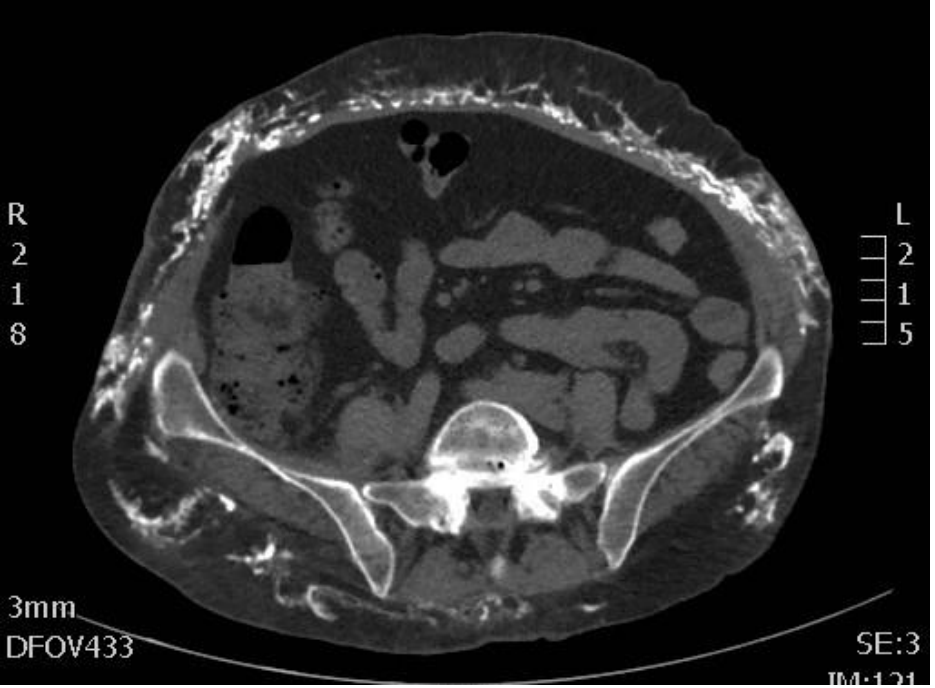
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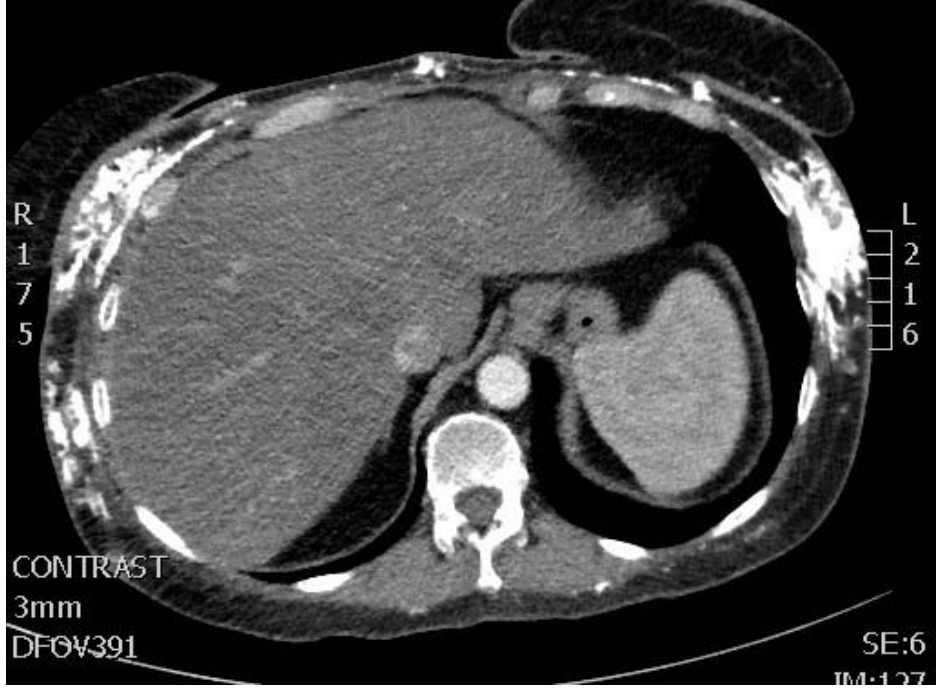
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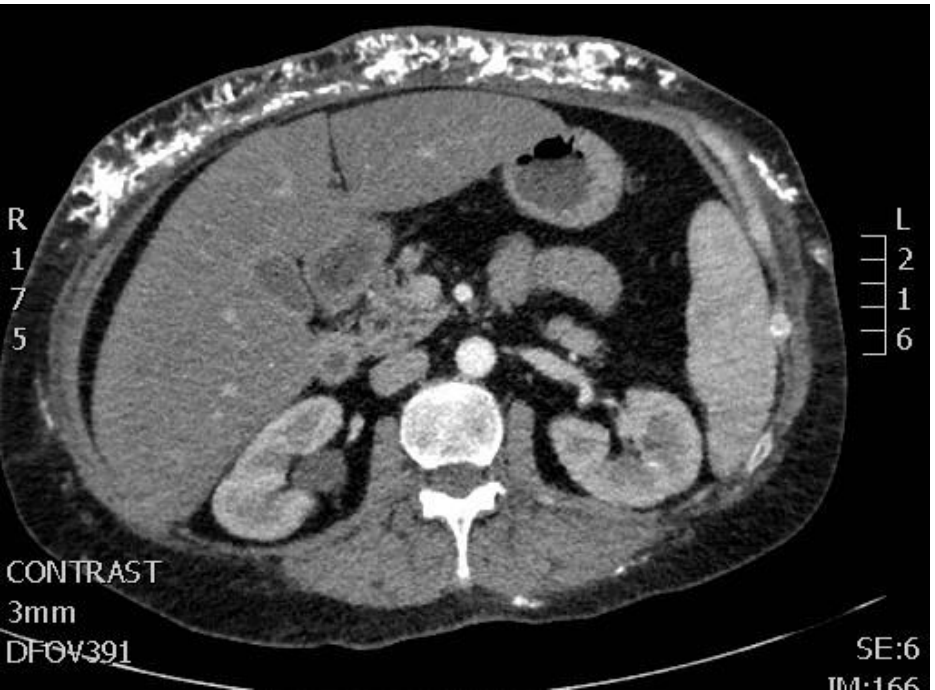
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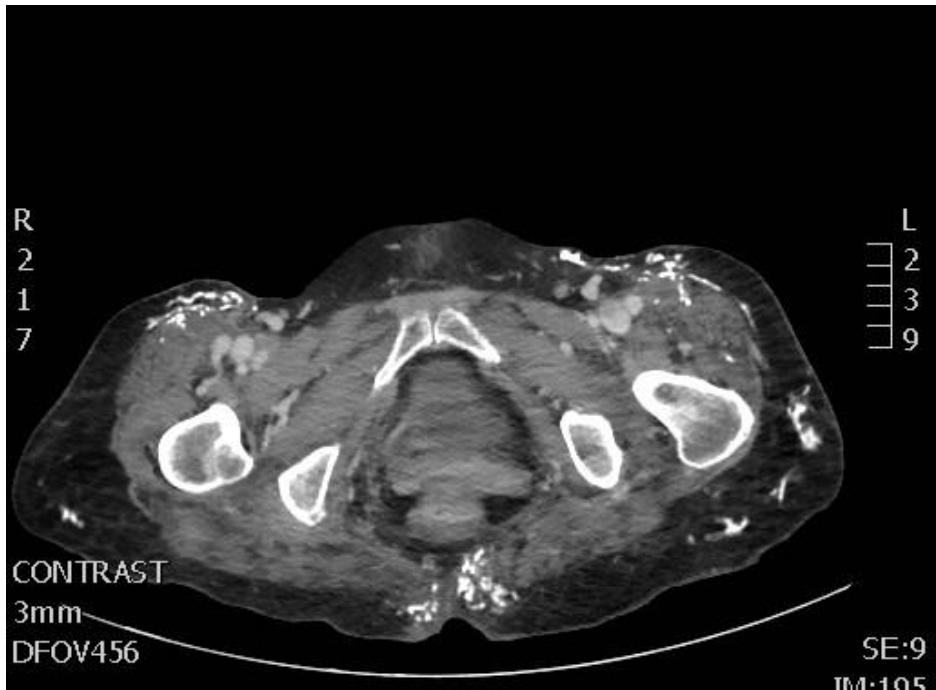
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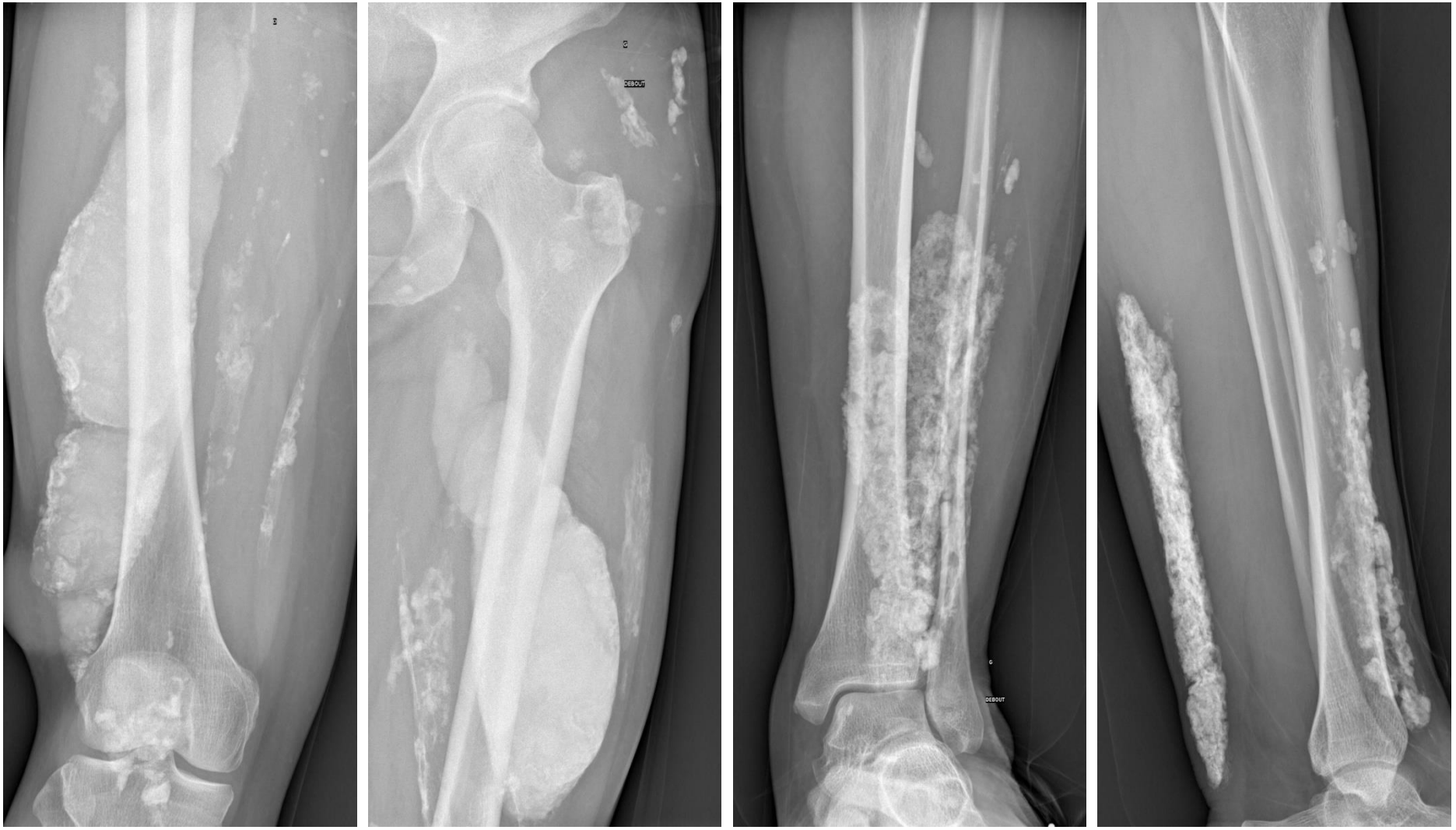
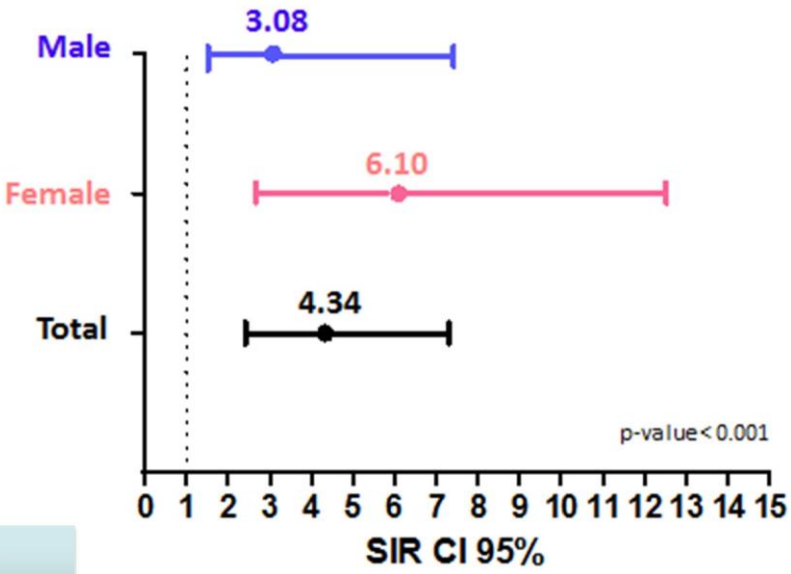


➡ **Trois patients avec des anti-NXP2**

DM with anti-Mi2



Cancer in patients with anti-Mi2 dermatomyositis (n=12/65)

Age at diagnosis of cancer (years)	Sex	Time between myopathy and cancer diagnosis (years)	Type of cancer	Tumour extension	Survival
79	M	0.1	Lung small-cell carcinoma	Metastatic	Alive
58	M	1.1	Prostate adenocarcinoma	Localized	Alive
85	F	0.7	Breast carcinoma	Metastatic	Dead
59	M	-0.7	Rectal adenocarcinoma	Localized	Alive
62	F	0.4	Fallopian tube carcinoma	Metastatic	Alive
62	F	1.1	Anal carcinoma	unknown	Alive
64	M	0.2	Lung carcinoma	Metastatic	Alive
68	F	0.5	Gastrointestinal stromal tumor	Localized	Alive
65	F	1.3	Pancreas adenocarcinoma	Metastatic	Alive
37	F	-1.1	Breast carcinoma	Metastatic	Alive
78	F	-1.6	Renal cell carcinoma	unknown	Dead
66	M	0.1	Colon adenocarcinoma	Localized	Alive

Poster: 1112

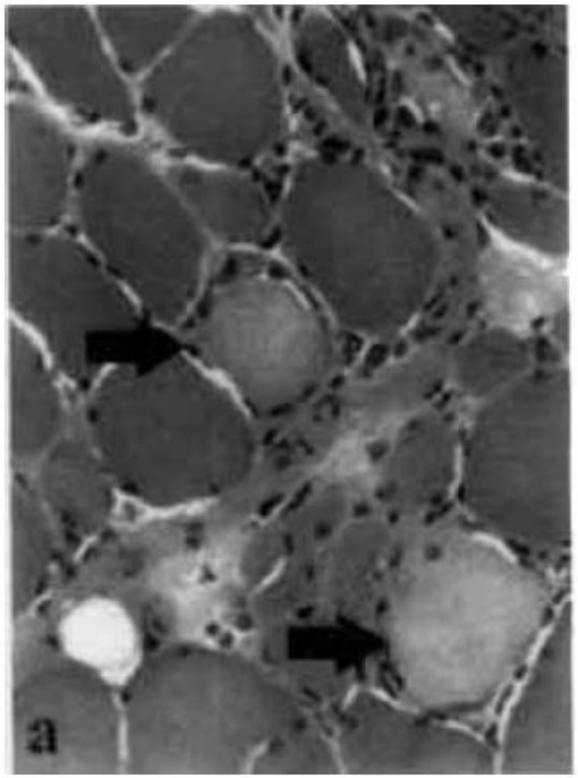
Paraneoplastic necrotizing myopathy

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

MNAI, auto-Ac et cancers

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]

- Occurrence of malignancy by calculating the standardized incidence ratio within 3 years, either before or after, the diagnosis of myopathy.
- Comparison of numbers of observed cancers to those expected in the general population sharing the same age and gender.

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

Table 2 Cancer in patients with immune mediated necrotizing myopathy

Serotype	Age at diagnosis of cancer (years)	Sex	Time between myopathy and cancer diagnosis (years)	Type of cancer	Tumour extension	Survival
HMGCR	81	F	−1.1	lung carcinoma	localized	dead
HMGCR	62	M	−0.2	renal carcinoma	localized	alive
HMGCR	71	F	0.4	breast cancer	localized	alive
HMGCR	69	F	1.0	ovarian carcinoma	localized	dead
HMGCR	67	F	2.2	oesophagus cancer	localized	alive
HMGCR	86	F	2.6	breast cancer	localized	alive
HMGCR	67	F	6.4	breast carcinoma	localized	alive
HMGCR	68	M	11.1	gastric carcinoma	localized	alive
HMGCR	33	F	13.2	breast carcinoma	localized	alive
SRP	55	F	−13.8	endometrial carcinoma	localized	alive
SRP	79	M	−1.7	hepatocellular carcinoma	localized	dead
SRP	73	F	1	breast carcinoma	localized	alive
SRP	67	M	10.2	bladder carcinoma	localized	alive
MSA−	71	F	−5.6	non Hodgkin lymphoma	metastatic	alive
MSA−	66	F	−0.4	anal carcinoma	localized	alive
MSA−	77	H	0.1	hepatocellular carcinoma	localized	dead
MSA−	79	M	0.4	gastric carcinoma	metastatic	dead

- Malignancy occurred in 29% of MSA - patients, 17% of anti-HMGCR + and 8% of anti-SRP + patients.
- Mean age at the diagnosis of cancer was 73 ± 6 years in MSA -, 67 ± 15 years in anti-HMGCR+ , and 68 ± 10 years in anti-SRP + patients.

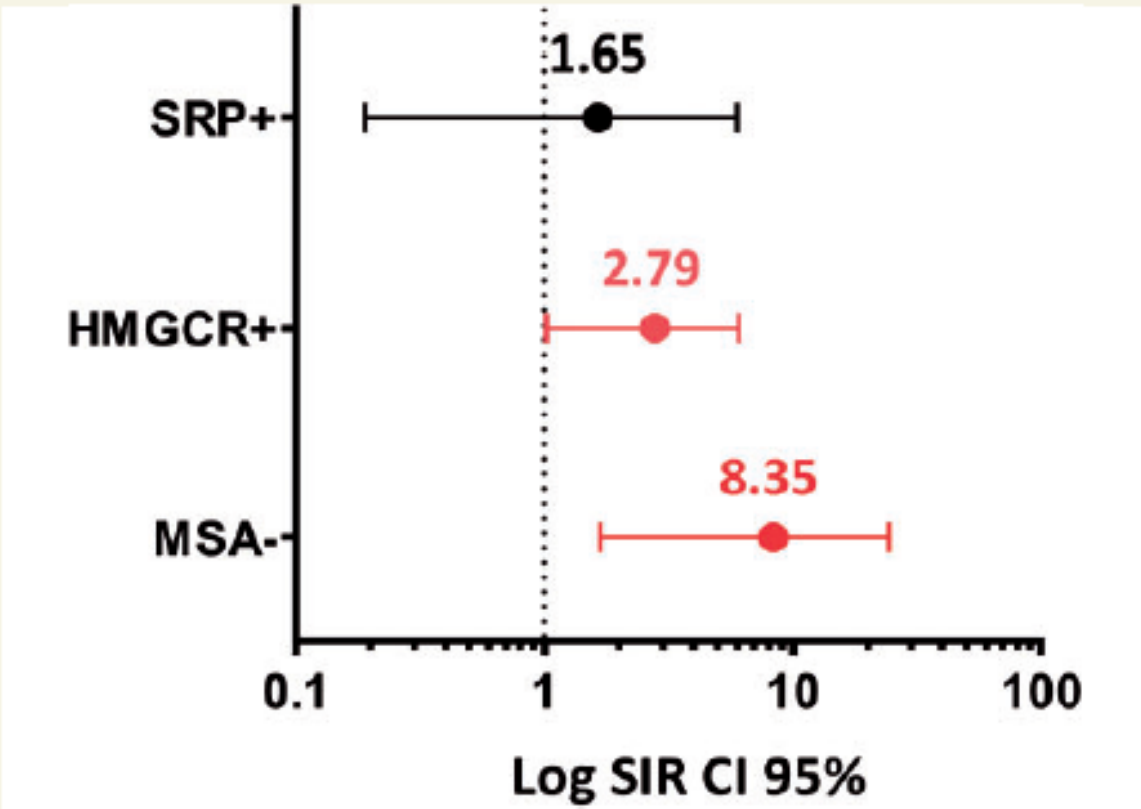


Figure 1 Risk of cancer in patients with immune-mediated necrotizing myopathy compared to the general population. Risk of malignancy was measured using standardized incidence ratio (SIR) 3 years before or after the diagnosis of myopathy and compared to the general population of the same age and gender structure. Values for the anti-SRP +, anti-HMGCR +, and MSA− patients are represented with 95% confidence interval (CI). An increased risk of cancer was observed in MSA− and HMGCR + patients ($P < 0.01$ and $P = 0.02$, respectively).

Conclusions on prognosis

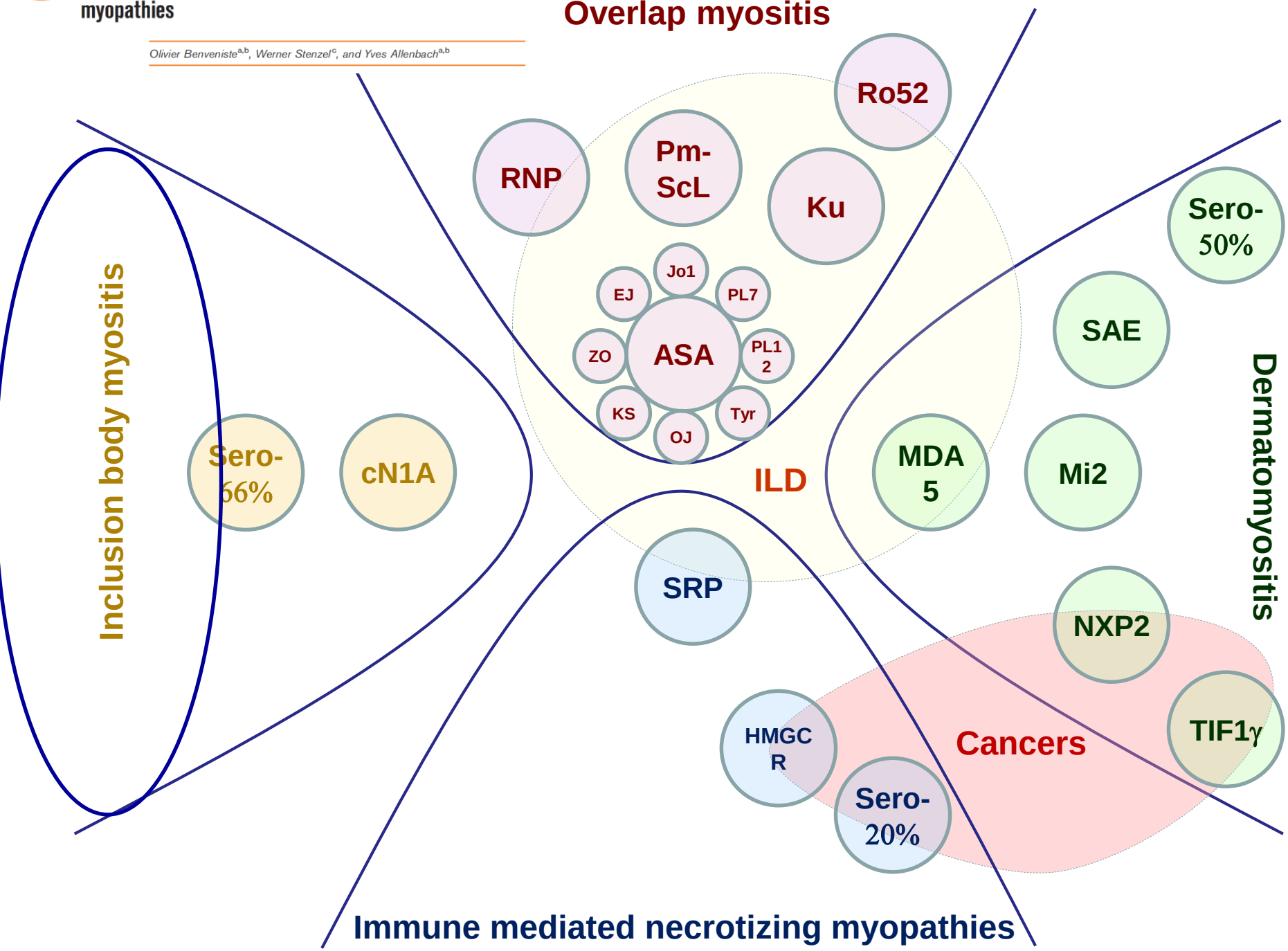
- Risk of cancer:
  - Increase with age
  - Anti-TIF1-γ, anti-NXP2, anti-Mi2 (?)
  - seronegative IMNM, Anti-HMGCR

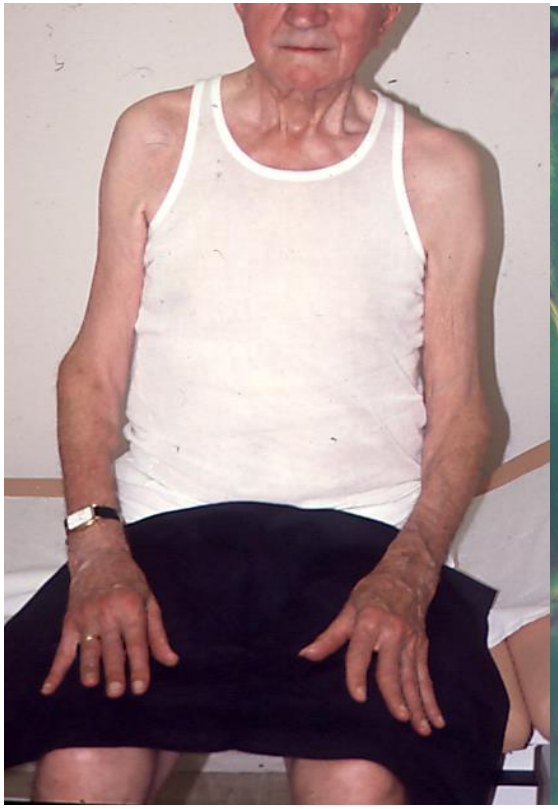
- Severity of ILD
  - Anti-MDA5
  - ASA: anti- PL7/PL12/EJ… > anti-Jo1
  - Anti-Ku, anti-Pm-ScL…

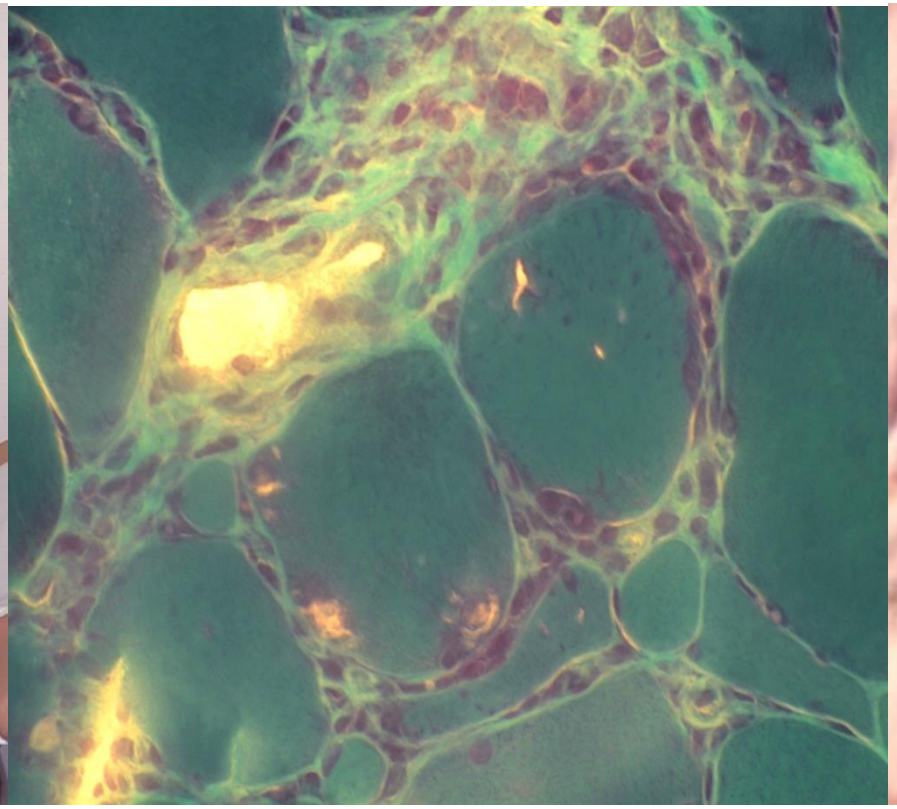
- Pronounced muscle damage
  - Anti-SRP > young anti-HMGCR > other IIM
  - Anti-FHL1

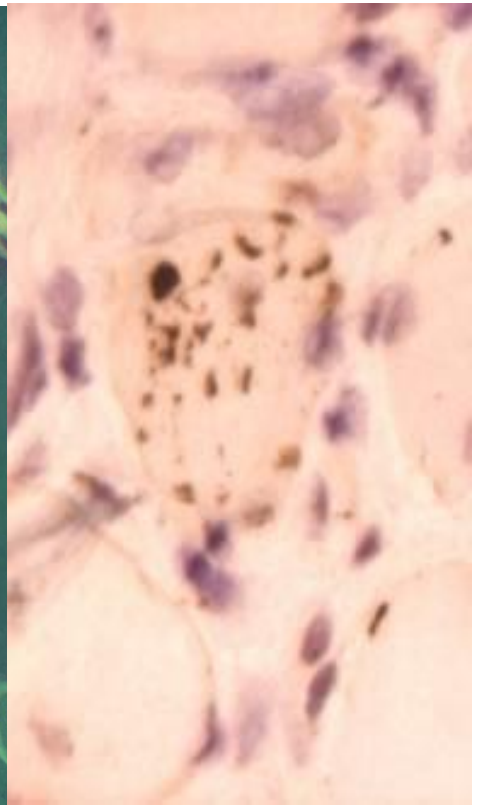
Current Opinion
Advances in serological diagnostics of inflammatory myopathies

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









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††

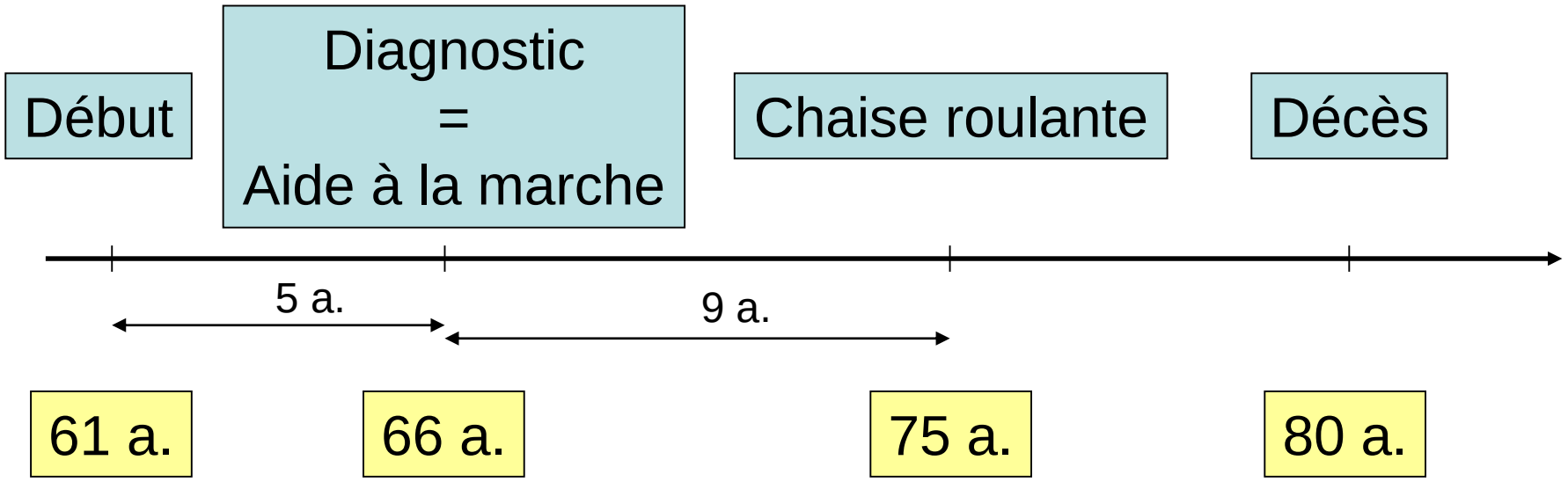
Neurology, 1995

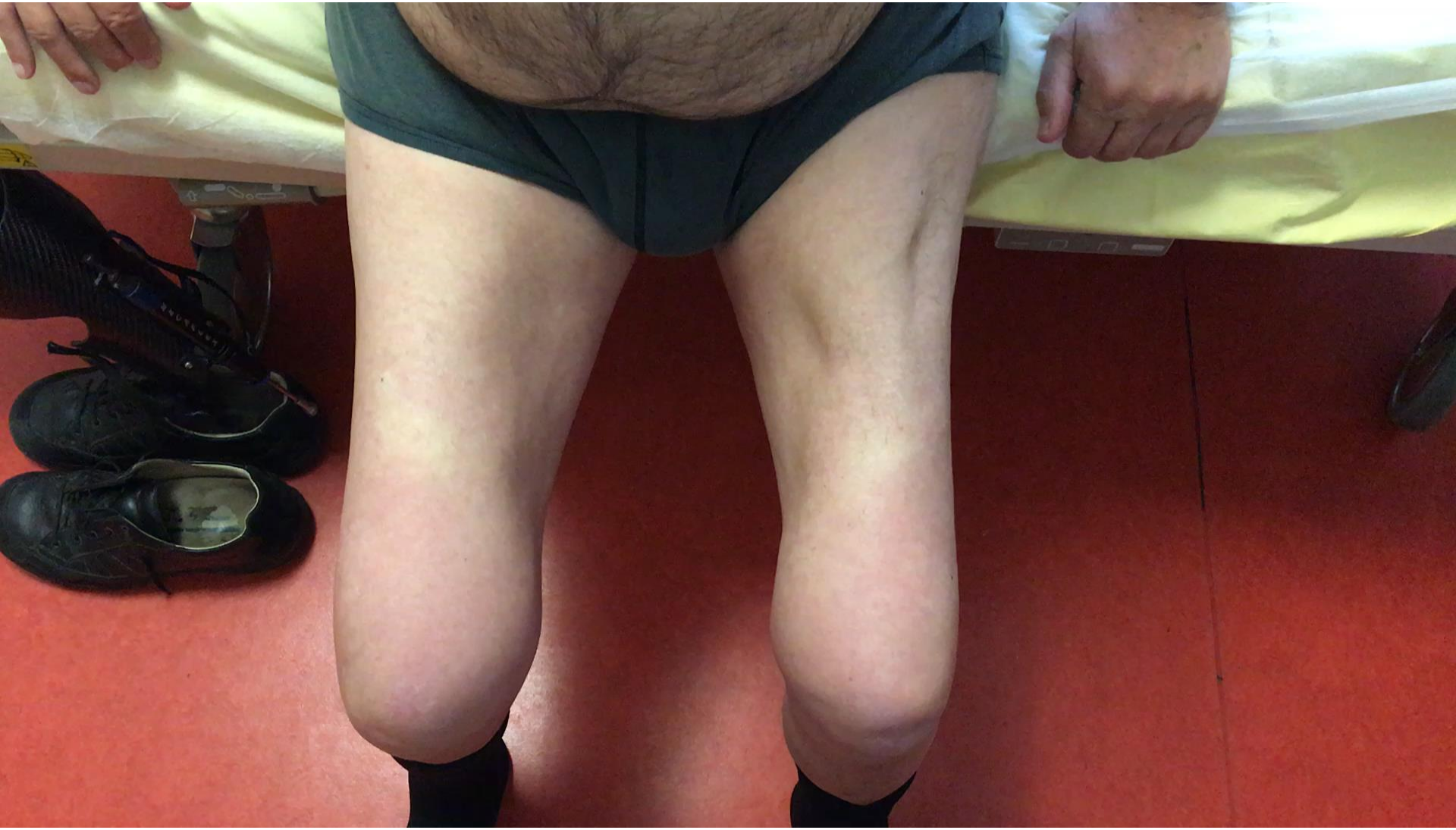
Brain Advance Access published October 12, 2011
doi:10.1093/brain/awr213 Brain 2011: Page 1 of 9 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Long-term observational study of sporadic inclusion body myositis

Olivier Benveniste,[1,2,3] Marguerite Guiguet,[4] Jane Freebody,[5] Odile Dubourg,[1,6] Waney Squier,[5] Thierry Maisonobe,[6] Tanya Stojkovic,[1] Maria Isabel Leite,[5] Yves Allenbach,[2,3] Serge Herson,[1,2,3] Stefen Brady,[5] Bruno Eymard[1,2] and David Hilton-Jones[5]

n = 136





sIBM clinical features/ diagnosis criteria

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Neuromuscular Disorders 22 (2012) 980–986

www.elsevier.com/locate/nmd

Quadriceps strength is a sensitive marker of disease progression in sporadic inclusion body myositis

Yves Allenbach [a,1], Olivier Benveniste [a,b,*,1], Valérie Decostre [c], Aurélie Canal [c], Bruno Eymard [b], Serge Herson [a,b], Coralie Bloch-Queyrat [a], Jean-Yves Hogrel [c]

Available online at www.sciencedirect.com

ScienceDirect

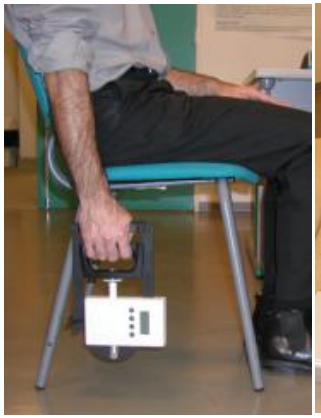
Neuromuscular Disorders xxx (2014) xxx–xxx

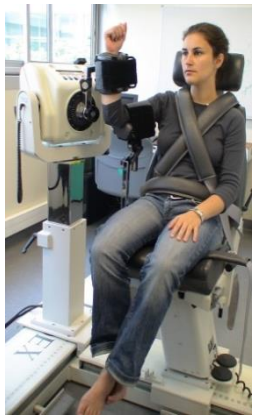
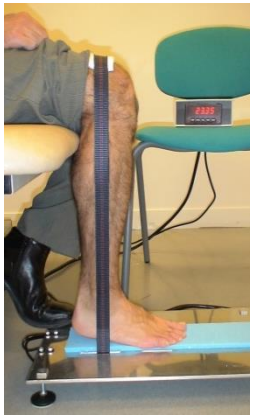
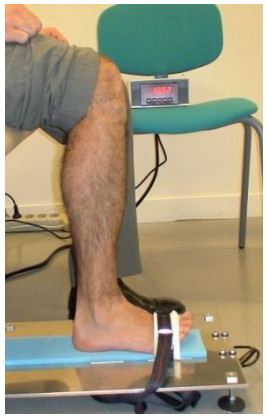
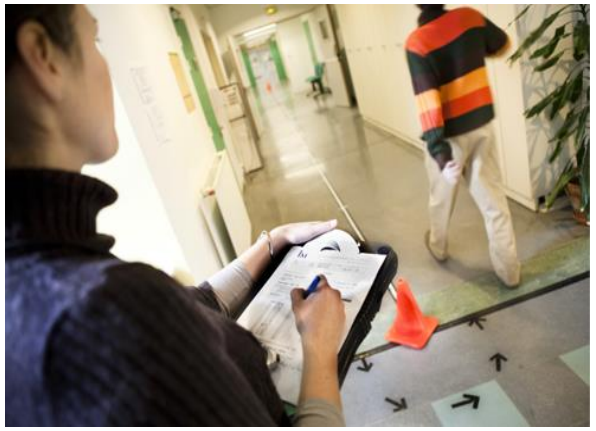
www.elsevier.com/locate/nmd

Four-year longitudinal study of clinical and functional endpoints in sporadic inclusion body myositis: Implications for therapeutic trials

Jean-Yves Hogrel [a,*], Yves Allenbach [a,b], Aurélie Canal [a], Gaëlle Leroux [b], Gwenn Ollivier [a], Kuberaka Mariampillai [a,b], Laurent Servais [a], Serge Herson [a,b], Valérie Decostre [a], Olivier Benveniste [a,b]

Evaluation



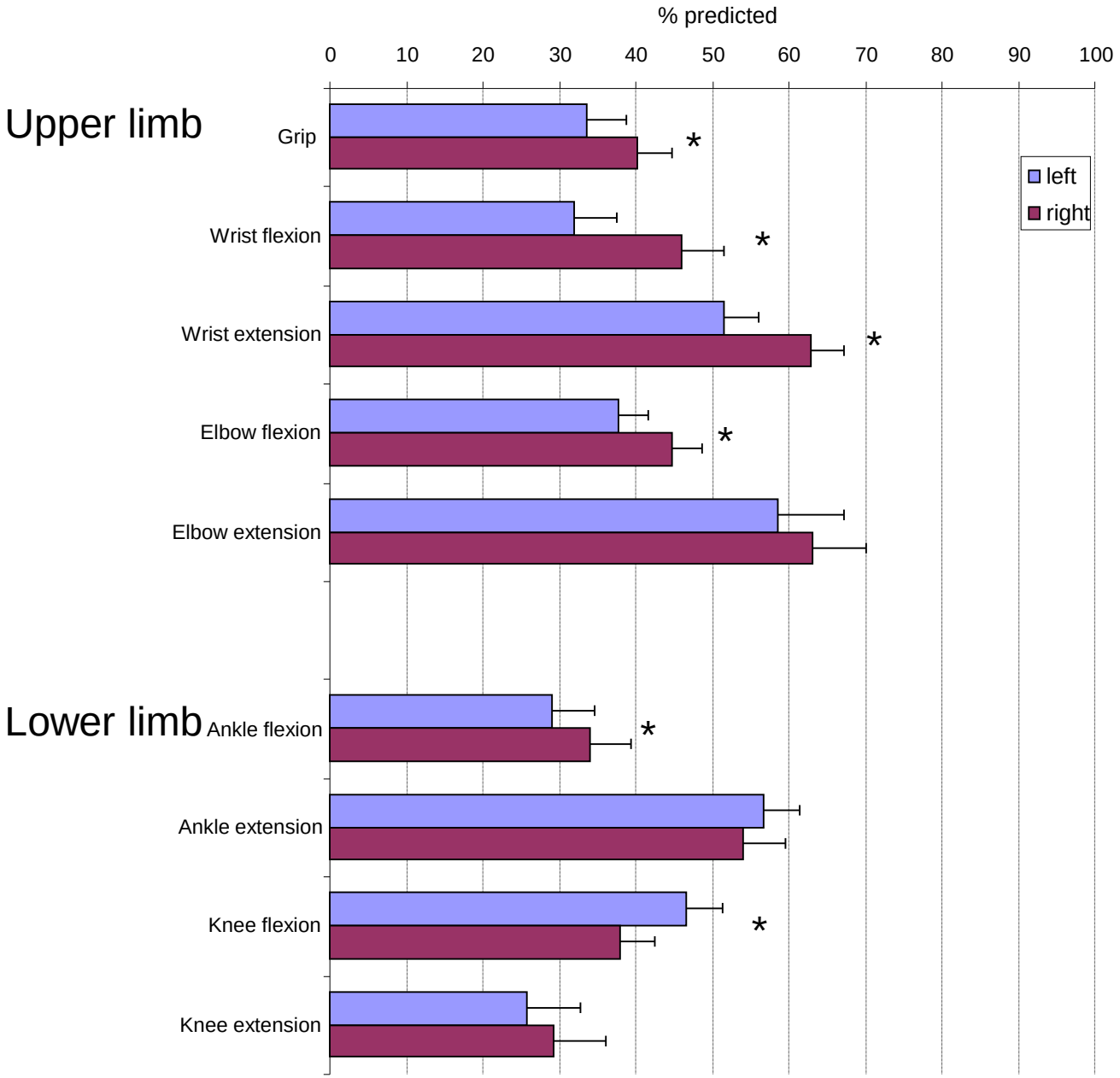






9 months

4 years

Visit 1 Visit 2 Visit 3

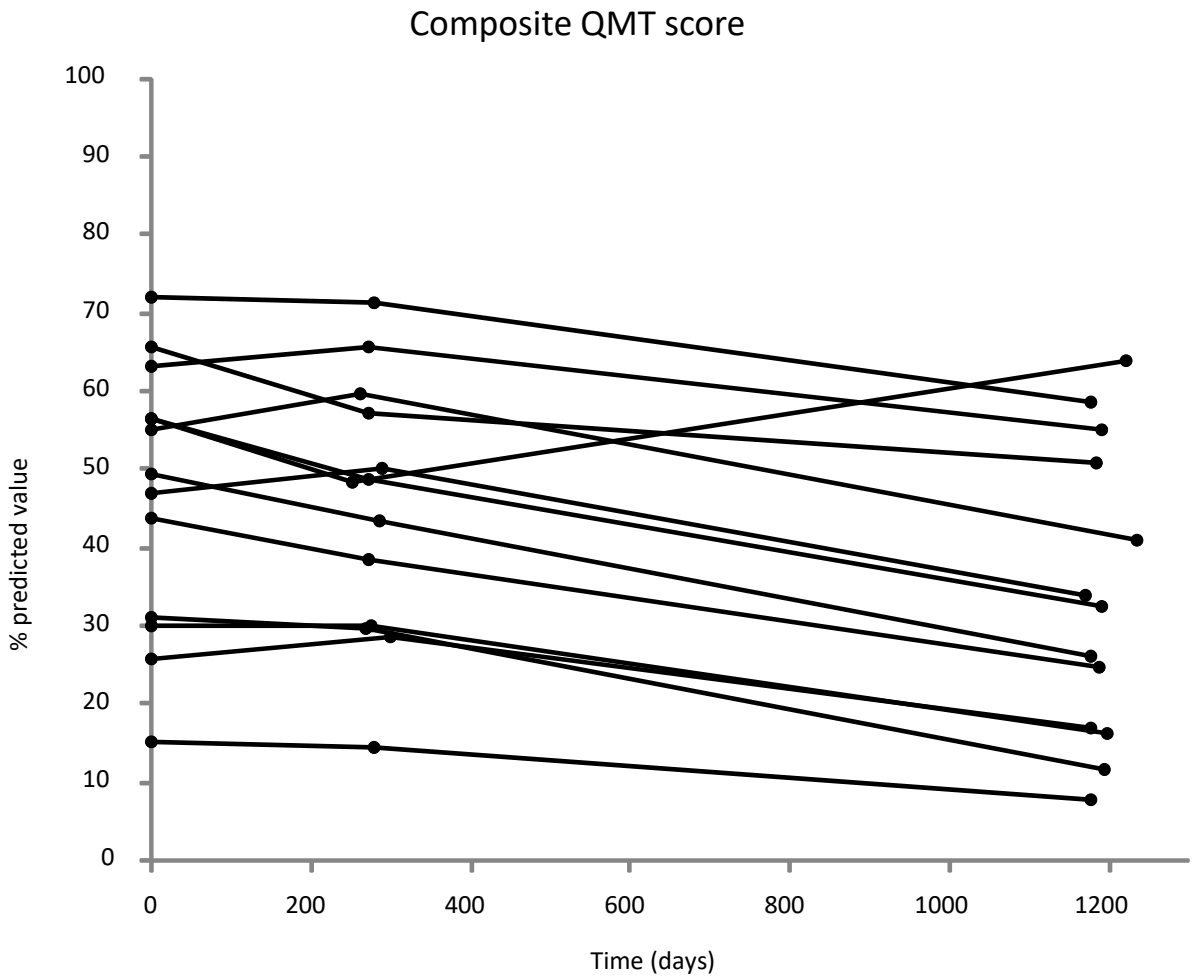
Mesure de la force à J0



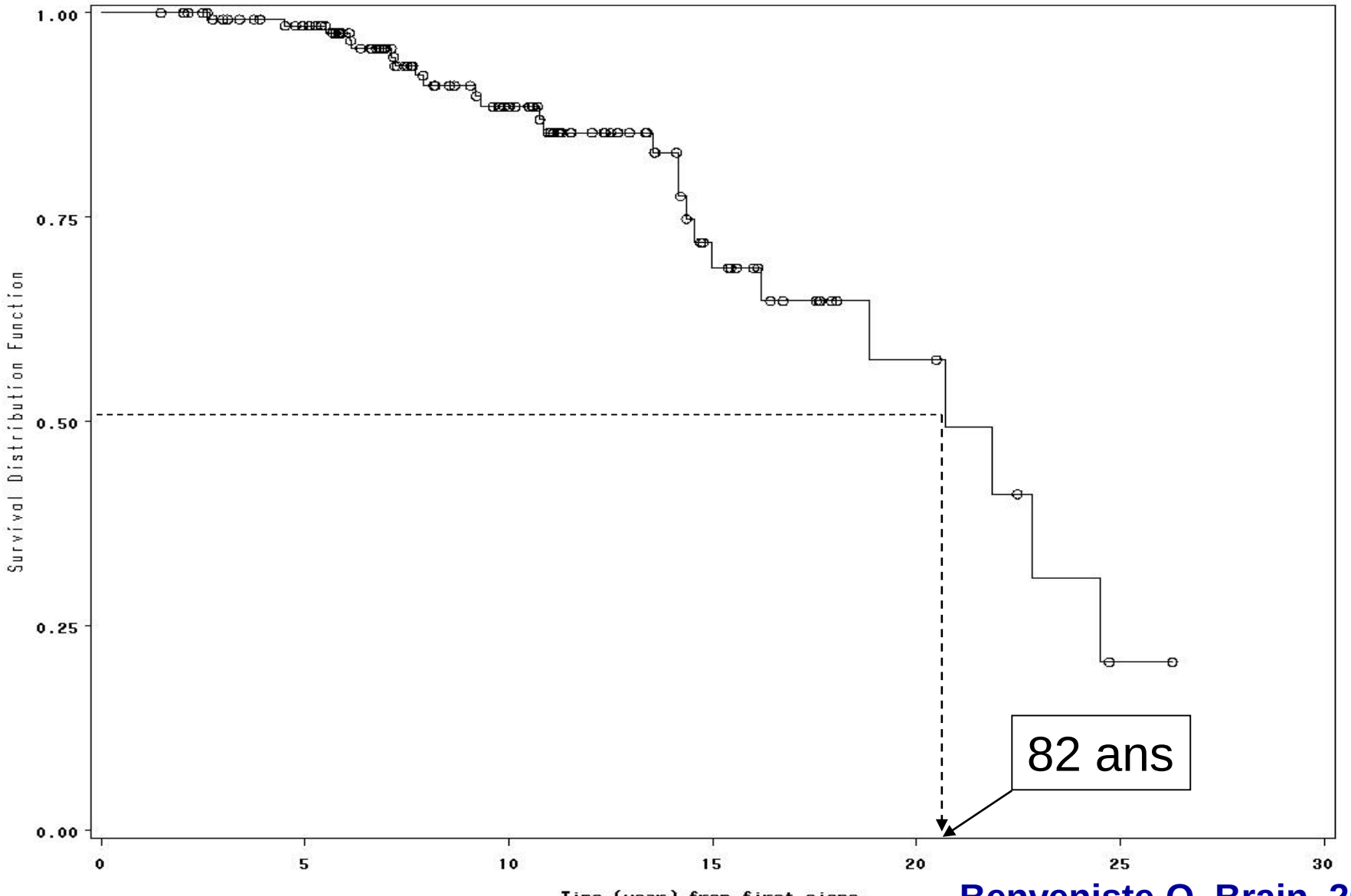
Changement après 9 mois

	Baseline	% change over 9 months	p value
QMT			
Composite score upper limb	37.99	-4.35	0.205
Hand grip	31.99	-4.66	0.070
Wrist flexion	38.62	-2.84	0.469
Wrist extension	57.88	-4.12	0.679
Elbow flexion	44.07	-5.80	0.098
Elbow extension	60.75	-5.75	0.148
Composite score lower limb	44.18	-6.51	0.109
Ankle flexion	37.43	-6.17	0.433
Ankle extension	67.07	-2.95	0.605
Knee flexion	48.11	-6.88	0.163
Knee extension	**27.55**	**-12.79**	**0.026**
Composite score total	40.71	-3.30	0.301

Evolution sur 4 ans

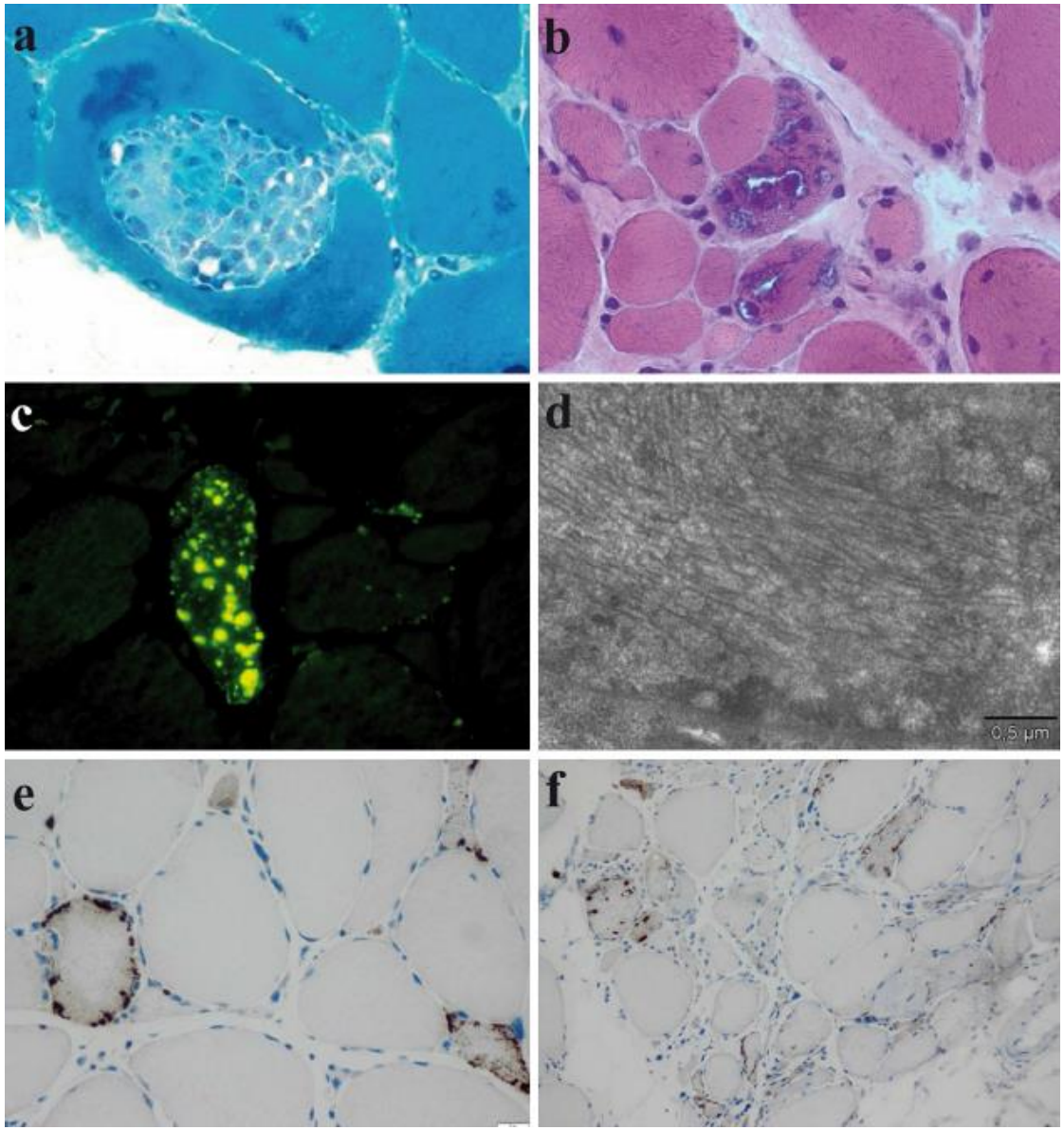


Survie depuis les premiers signes



Benveniste O, Brain, 2011

Histologie



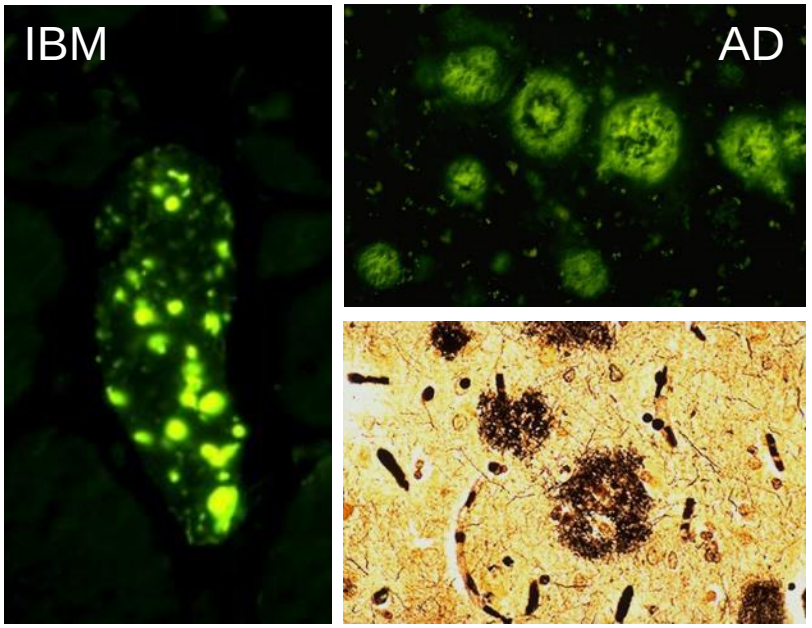
Benveniste O, Acta Neuropath, 2015

Contenu des inclusions protéiques

Many proteins related to neurodegenerative diseases:

- β-amyloid and βAPP
- phosphorylated tau
- α1ACT
- α-synuclein
- prion protein
- ApoE
- αβ-crystallin
- Parkin
- copper zinc superoxide dismutase
- manganese superoxide dismutase
- apoptotic regulators (Bcl-2, Bcl-x and BAX)
- Lipoprotein receptors
- Ubiquitins

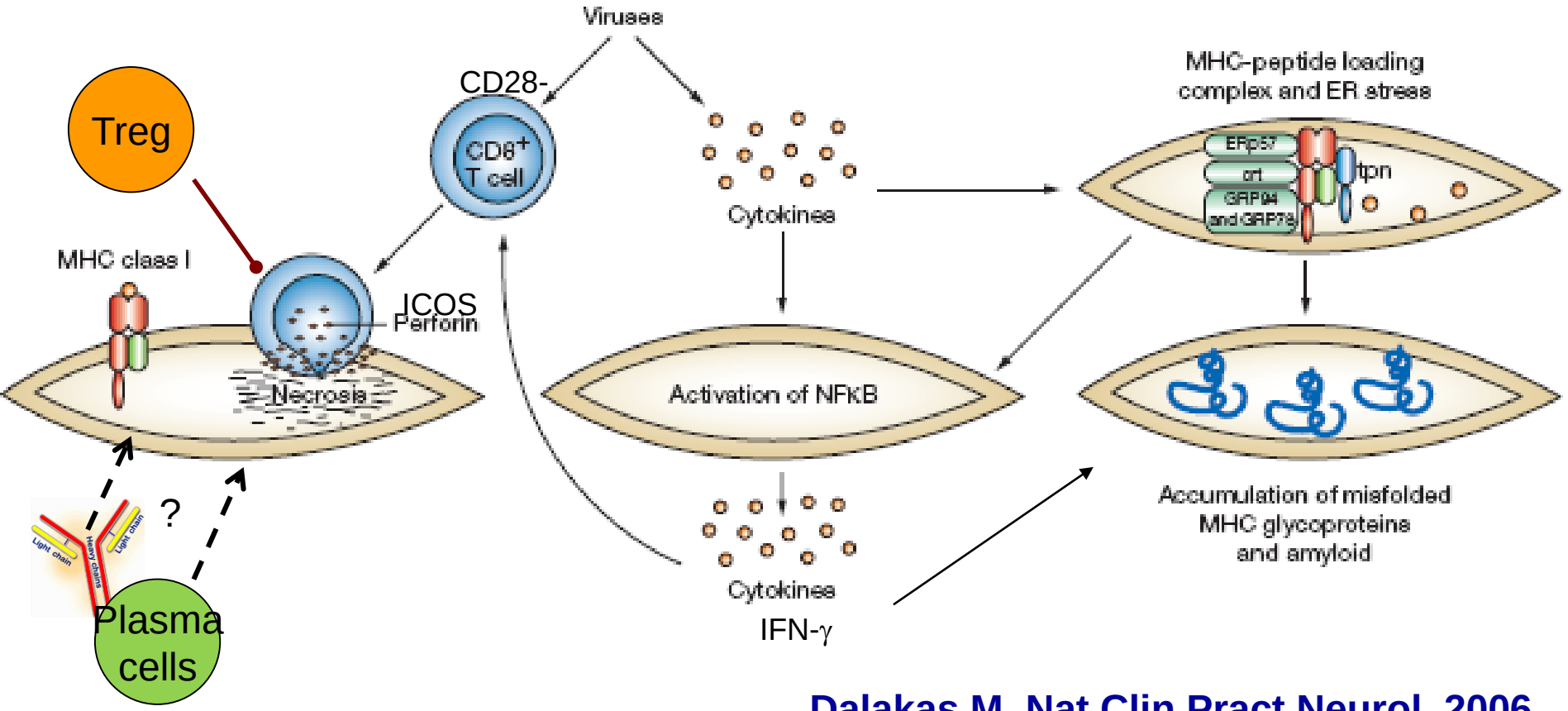
Amyloid deposits



Werner Stenzel

Unanswered question

Is IBM a degenerative or an inflammatory myopathy?



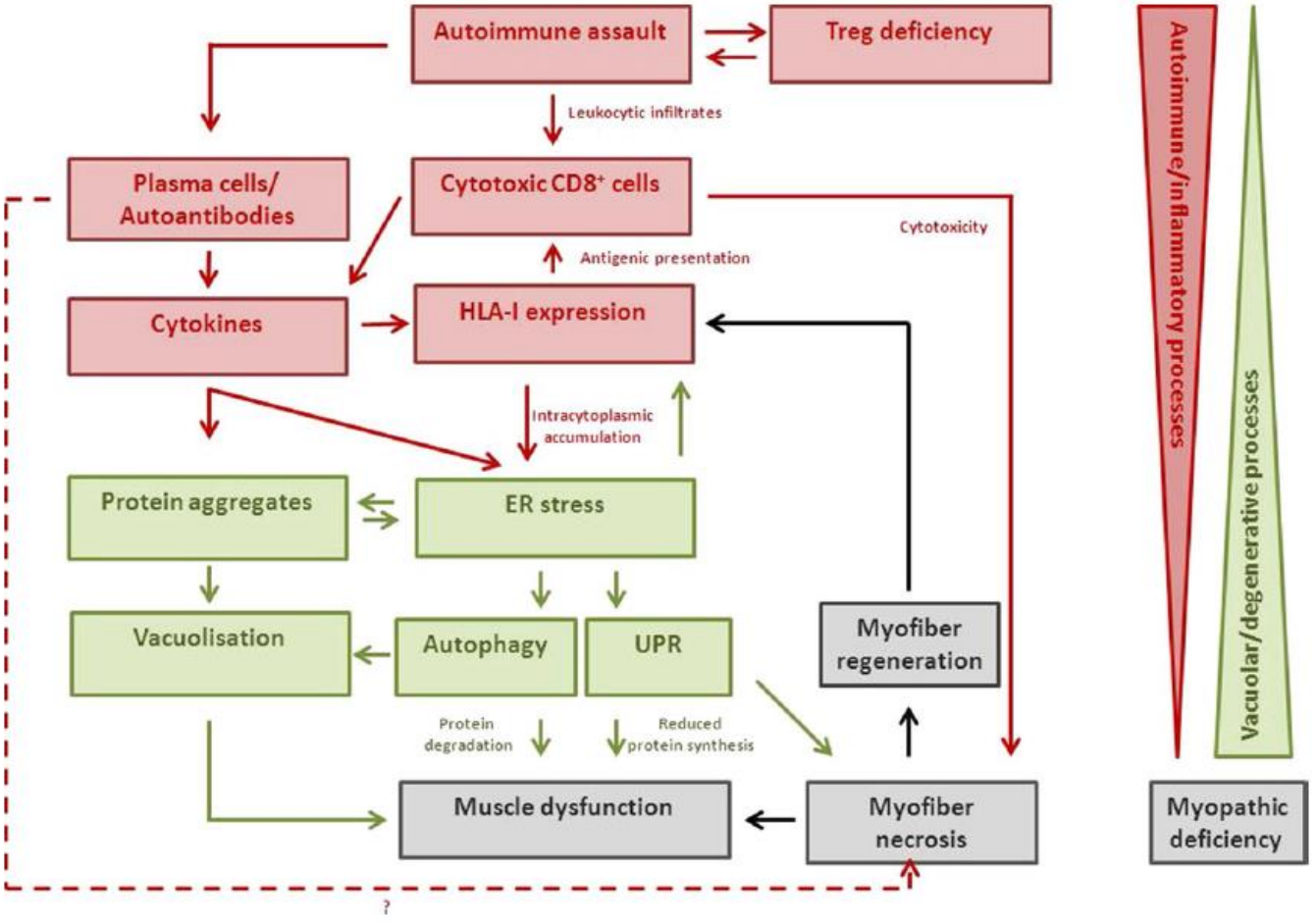
Dalakas M, Nat Clin Pract Neurol. 2006

Acta Neuropathol
DOI 10.1007/s00401-015-1384-5

REVIEW

Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken

Olivier Benveniste · Werner Stenzel · David Hilton-Jones · Marco Sandri · Olivier Boyer · Baziel G. M. van Engelen



Anti-cN1A

ANN NEUROL 2013;73:397–407

Autoantibodies to Cytosolic 5′-Nucleotidase 1A in Inclusion Body Myositis

Helma Pluk, PhD,[1]* Bas J. A. van Hoeve, MD,[2]* Sander H. J. van Dooren, PhD,[1]*

ANN NEUROL 2013;73:408–418

Cytosolic 5′-Nucleotidase 1A Autoimmunity in Sporadic Inclusion Body Myositis

H. Benjamin Larman, PhD,[1,2,3,4,5]* Mohammad Salajegheh, MD,[6,7]*

ARD Online First, published on February 24, 2015 as 10.1136/annrheumdis-2014-206691

EXTENDED REPORT

Disease specificity of autoantibodies to cytosolic 5′-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases

Megan K Herbert,[1] Judith Stammen-Vogelzangs,[1] Marcel M Verbeek,[2,3]

Table 1 Sensitivity and specificity of anti-cN-1A autoantibodies

Sera	Number	Anti-cN-1A reactivity*	
		n	Per cent
Inclusion body myositis	238	88	37
Polymyositis/dermatomyositis	185	8	4
Polymyositis/scleroderma overlap	12	0	0
Neuromuscular diseases	93	4	4
Sjögren's syndrome	22	8	36
Systemic lupus erythematosus	44	9	20
Scleroderma	44	1	2
Rheumatoid arthritis	44	1	2
Multiple sclerosis	40	2	5
Type 1 diabetes	40	0	0
Disease controls†	*458*	*16*	*3*

*Reactivity with at least one of the three cN-1A peptides higher than cut-off.
†Disease controls: total of all disease control groups except IBM, SLE and SjS.
cN-1A, cytosolic 5′-nucleotidase 1A; IBM, inclusion body myositis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus.

Arthritis Care & Research
Vol. 68, No. 1, January 2016, pp 66–71
DOI 10.1002/acr.22600

BRIEF REPORT

Cytosolic 5′-Nucleotidase 1A As a Target of Circulating Autoantibodies in Autoimmune Diseases

THOMAS E. LLOYD,[1] LISA CHRISTOPHER-STINE,[1] IAGO PINAL-FERNANDEZ,[2] ELENI TINIAKOU,[1] MICHELLE PETRI,[1] ALAN BAER,[1] SONYE K. DANOFF,[1] KATHERINE PAK,[3] LIVIA A. CASCIOLA-ROSEN,[1] AND ANDREW L. MAMMEN[4]

24/135 DM patients (18%)

Neuromuscular Disorders 20 (2010) 414–421

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Workshop report

International Workshop on Inclusion Body Myositis held at the Institute of Myology, Paris, on 29 May 2009

Olivier Benveniste[a,*], David Hilton-Jones[b]

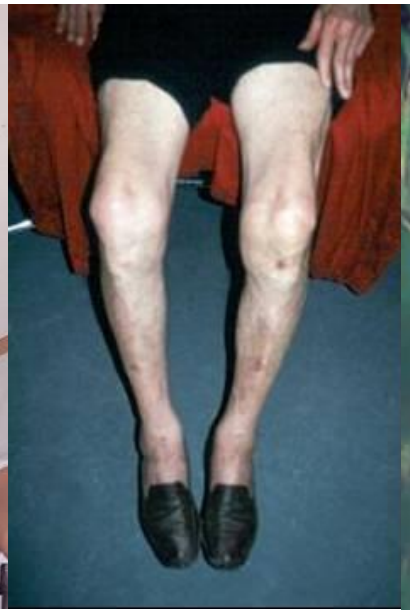
Revised diagnostic criteria for sIBM.

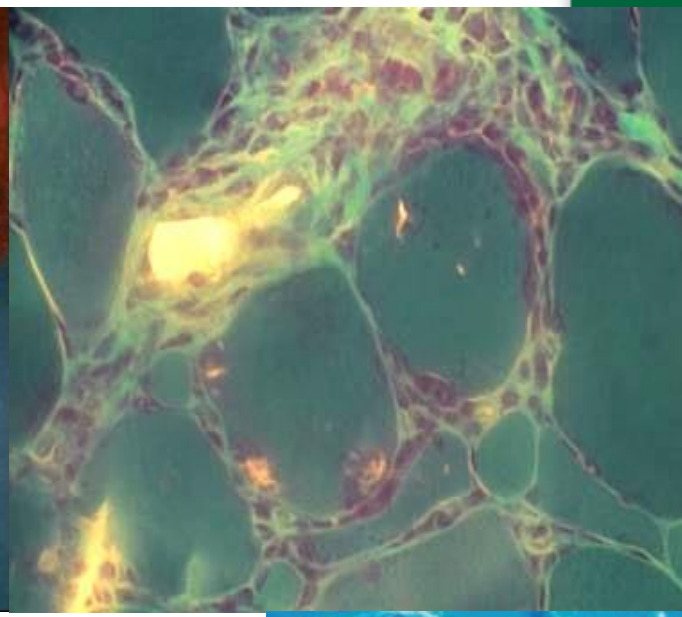
Clinical and laboratory features	Classification	Pathological features
Consistent with IBM	Pathologically defined IBM	Endomysial exudate Partial invasion Vacuoles Congo-red or crystal violet or hyperphosphorylated tau (SMI-31) p62/SQSTM1 or TDP43 or 15–18 nm filaments
Duration >6 months Age >30 years EMG consistent Quads weakness > hip flex and FF weakness > should abd	Clinically defined IBM	Endomysial exudate or ↑ MHC1 no Congo-red or SMI-31 or 15–18 nm filaments
Duration >6 months Age >30 years EMG consistent Quads weakness > hip flex or FF weakness > should abd	Possible IBM	Endomysial exudate or ↑ MHC1 no Congo-red or SMI-31 or 15–18 nm filaments

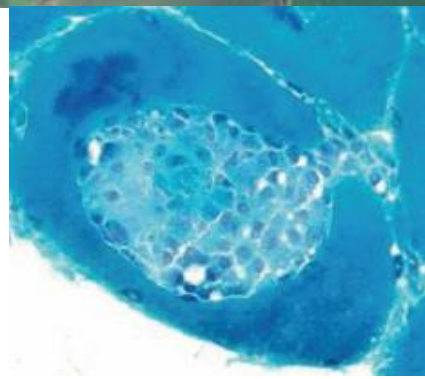
Evaluation and construction of diagnostic criteria for inclusion body myositis

Neurology 2014

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

Brain Advance Access published October 12, 2011

doi:10.1093/brain/awr213 Brain 2011: Page 1 of 9 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Long-term observational study of sporadic inclusion body myositis

Olivier Benveniste,[1,2,3] Marguerite Guiguet,[4] Jane Freebody,[5] Odile Dubourg,[1,6] Waney Squier,[5] Thierry Maisonobe,[6] Tanya Stojkovic,[1] Maria Isabel Leite,[5] Yves Allenbach,[2,3] Serge Herson,[1,2,3] Stefen Brady,[5] Bruno Eymard[1,2] and David Hilton-Jones[5]

n = 136

Description des traitements reçus par 71 (52%) des patients

Molecules and duration	Results
Corticosteroids (prednisone, 1 mg/kg/day) (n=63)	65 (92%)
Intravenous Immunoglobulins (n=39)	40 (56%)
Azathioprine (n=17)	19 (27%)
Methotrexate (n=21)	23 (32%)
Combination of treatment Corticosteroids only Corticosteroids and other drugs Other drugs only	 19 (27%) 46 (65%) 6 (8%)
Duration of treatment, months [n=69]	41 [13.0-89.2] ~ 3.5 years

Comparison entre les patients traités ou non

Status at the last visit	Untreated (n=65)	Treated (n=71)	p
CK, u/ml (n=87)	367 [219 -649]	209 [117-559]	0.11
Grip test (n=76)	13.4 [11.0-17.2]	13.5 [9.0-18.0]	0.84
Walton (n=113)	4 [3-6]	6 [3-6]	0.007
RMI (n=88)	11 [9-13]	10 [4-11]	0.004
IWCI (n=71)	50 [30-65]	40 [25-50]	0.04
Current handicap for walking (n=136) None 1 or 2 canes Wheelchair	 20 (31%) 26 (40%) 19 (29%)	 13 (18%) 26 (37%) 32 (45%)	0.10

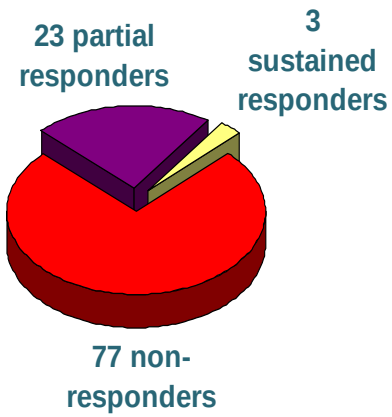
O Benveniste. Brain, 2011

Estimates of covariate effect on each transition in the multi-state model

	Transition	HR (95%CI)	p
Age at first symptoms (> 60 yrs vs <60 yrs)	No handicap – walking with aid No handicap – wheelchair Walking with aid – wheelchair Alive - Death	1.98 (1.27-3.08) 0.62 (0.19-2.07) 1.35 (0.68-2.71) 3.65 (1.22-10.92)	0.003 0.44 0.39 0.02
Treatment (Yes vs No)	No handicap – walking with aid No handicap – wheelchair Walking with aid – wheelchair Alive - Death	2.05 (1.30-3.25) 2.09 (0.70-6.24) 1.74 (0.92-3.30) 1.47 (0.67-3.22)	0.002 0.18 0.09 0.34

Corticothérapie et IBM

- **Retrospective**
  - 112 pts in 15 trials (6 single cases)
  - retrospective diagnoses in some
  - doses 20 to 100mg
  - 2 weeks to 2 years
  - insufficient info on dosing regime



Corticothérapie et IBM

- **Prospective**
  - 2 open label trials
  - 8/8 deteriorated ***(RJ Barohn, neurology 1995)***
  - 36/36 deteriorated at M4 (60 mg/d prednisone ± Ig IV) ***(Dalakas, Neurology, 2001)***
    - No significative change of the QMT or MRC score

Pilot trial of etanercept in the treatment of inclusion-body myositis

R. J. Barohn, L. Herbelin, J. T. Kissel, W. King, A. L. McVey, D. S. Saperstein and J. R. Mendell

Neurology 2006;66;123-124; originally published online Dec 16, 2005;

- 9 patients: 25 mg subcutaneously twice weekly
- Duration: 17 ± 6.1 months

- No effect:
  - Patients MVIC composite score: –0.36 (SD 0.26)
  - Control group (placebo subjects from beta-interferon 1a trials): –0.19 (SD 0.74, $p > 0.05$)

IBM: 6 études contrôlées prospectives

Authors	N	Intervention	Efficacy
Dalakas, 1997	19	IVIg or placebo	No, 3 mo
Walter, 2000	22	IVIg or placebo	No, 6 mo
Dalakas, 2001	34	CS + IVIg or placebo	No, 3 mo
Muscle study Group, 2001 and 2004	57	Beta IFN or placebo	No, 6 mo
Rutkove, 2002	19	Oxandrolone or placebo	No, 3 mo
Badsrising, 2002	44	MTX or placebo	No, 12 mo

Traitement des IBM, en pratique :

- Kinésithérapie +++

- Si patient « jeune », évolution rapide, biopsie très inflammatoire…
  - Prednisone (1 mg/kg/j)
  - MTX
- Pour une durée finie (3 à 6 mois)

- Si trouble de la déglutition
  - IgIV
  - Myotomie cricoïdienne

afssaps
Agence française de sécurité sanitaire des produits de santé

HAS
HAUTE AUTORITÉ DE SANTÉ

Situation temporairement acceptable

Myosite à inclusions avec dysphagie grave

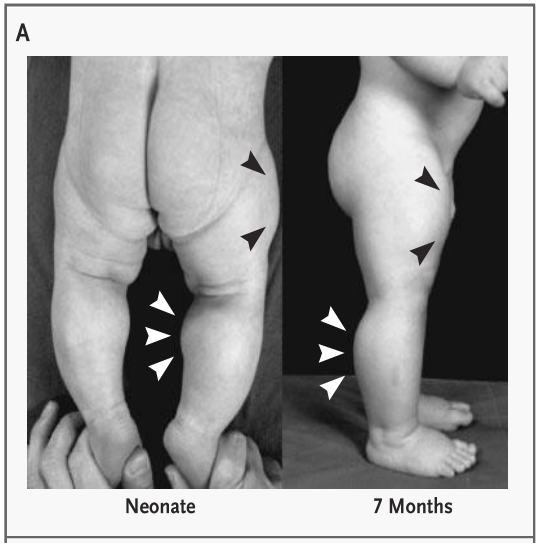
Anti-myostatin

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

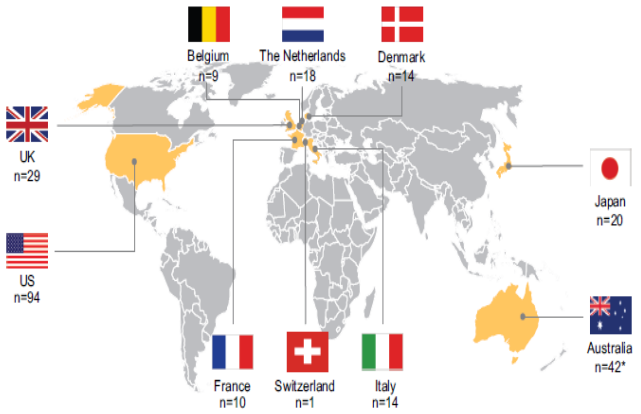
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jin Lee, M.D., Ph.D.

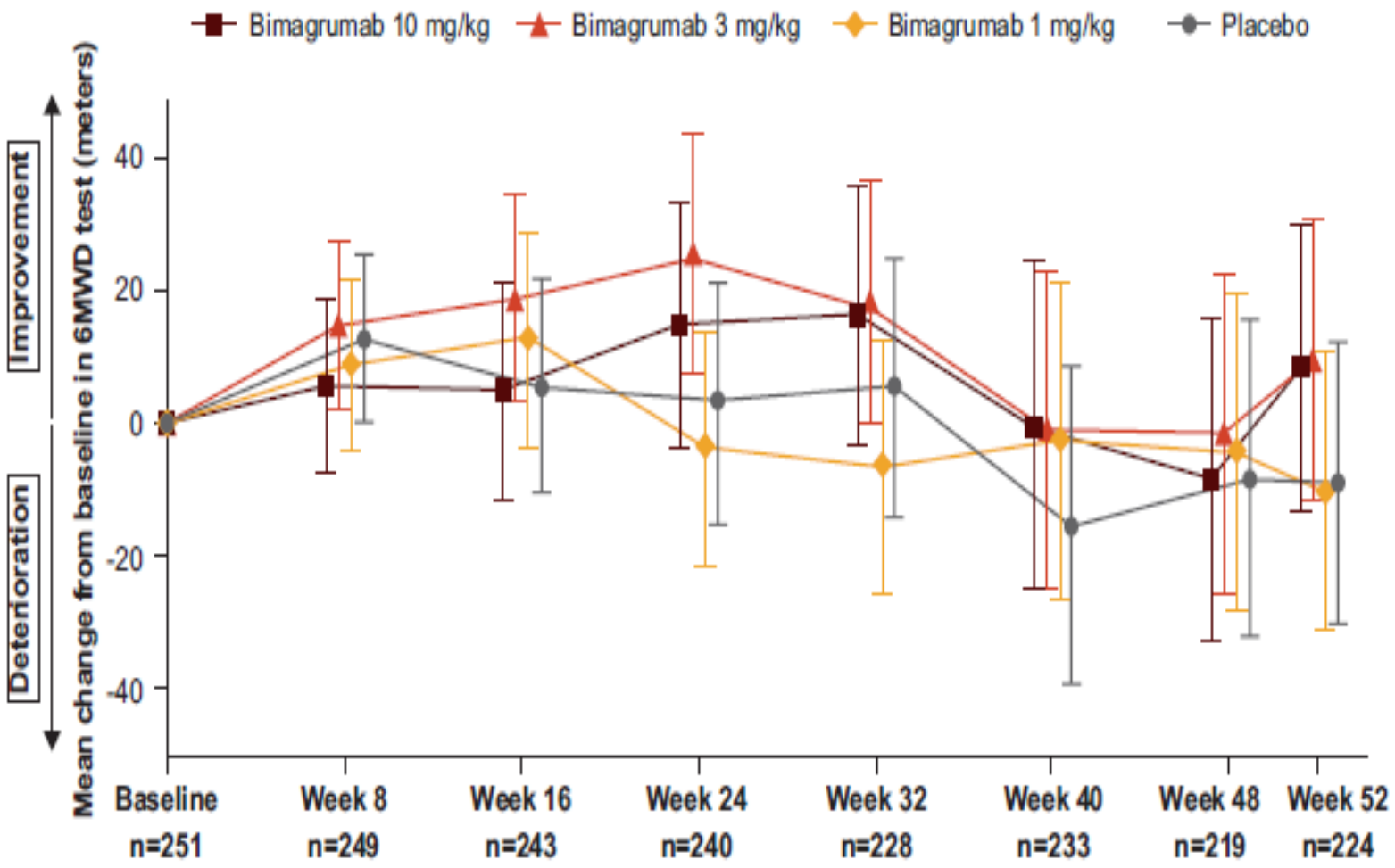


Efficacy and Safety of Bimagrumab/BYM338 at 52 Weeks on Physical Function, Muscle Strength, Mobility in sIBM Patients (RESILIENT)

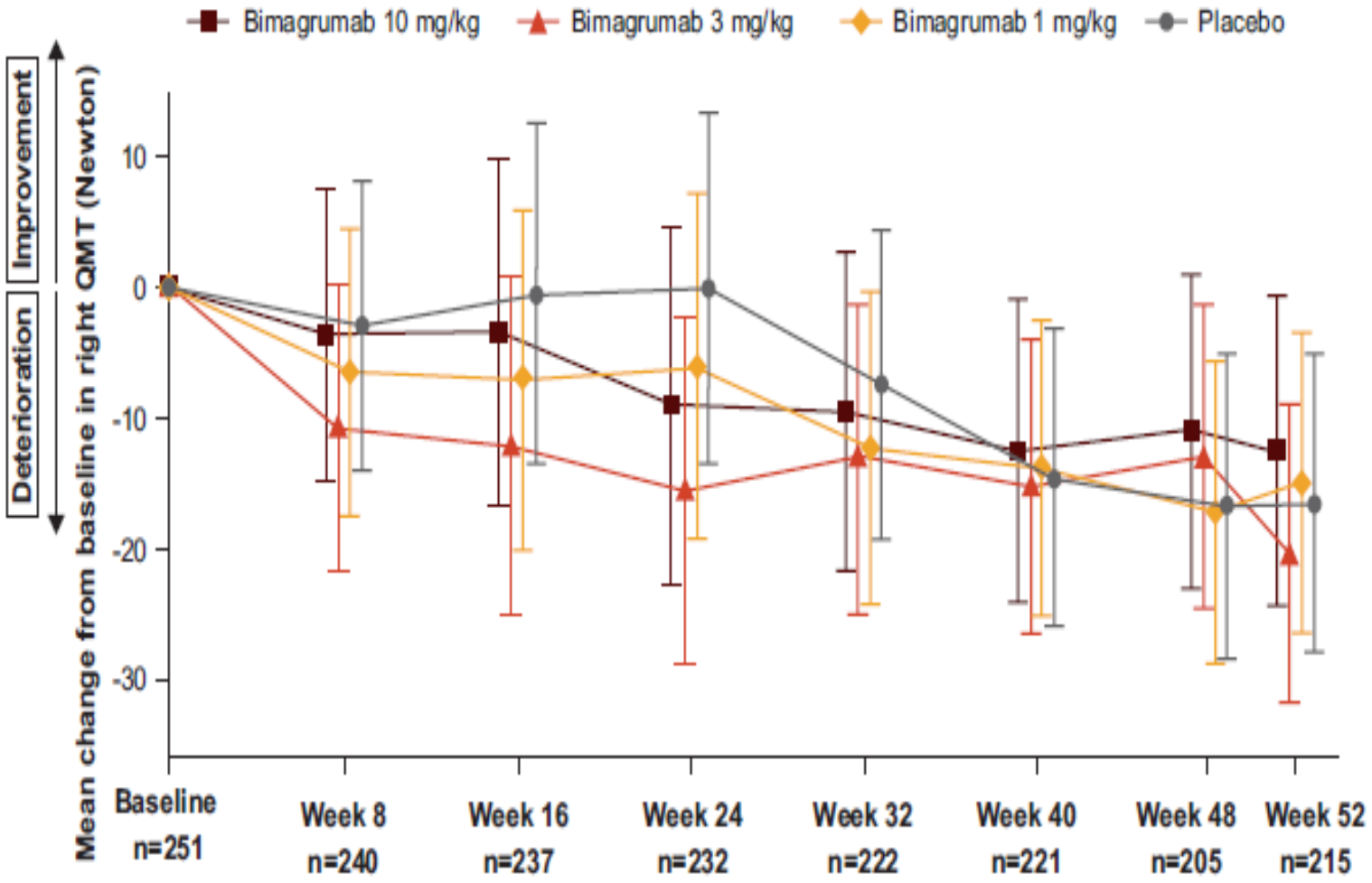
Phase II/III: 240 patients
Sponsor: Novartis Pharmaceuticals
ClinicalTrials.gov Identifier: NCT01925209



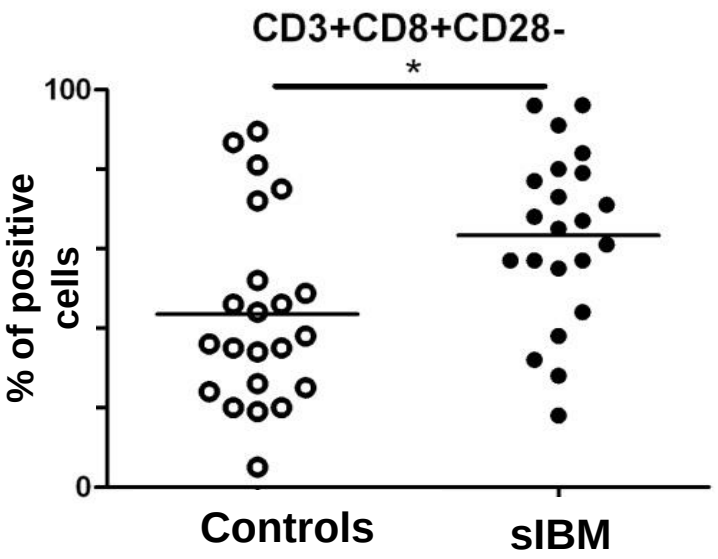
6MWD

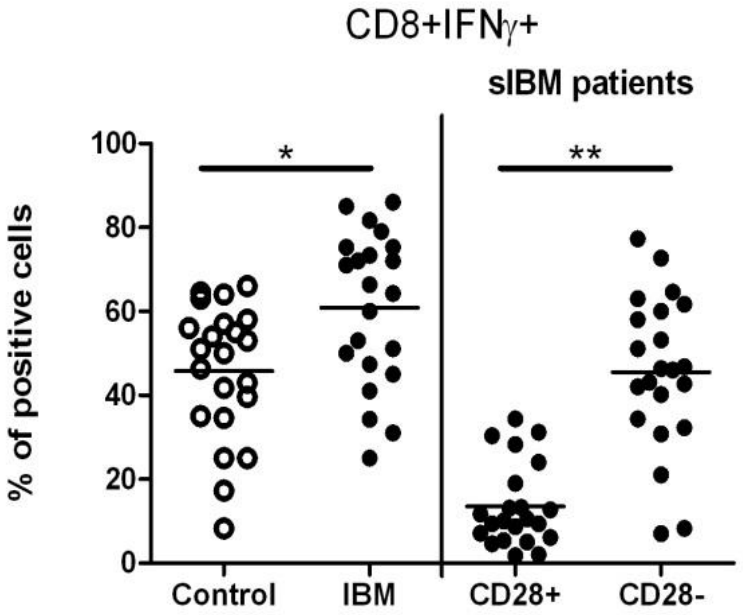

Bimagrumab 10 mg/kg
Bimagrumab 3 mg/kg
Bimagrumab 1 mg/kg
Placebo
Improvement
Deterioration
Mean change from baseline in 6MWD test (meters)
40
20
0
-20
-40
Baseline
n=251
Week 8
n=249
Week 16
n=243
Week 24
n=240
Week 32
n=228
Week 40
n=233
Week 48
n=219
Week 52
n=224

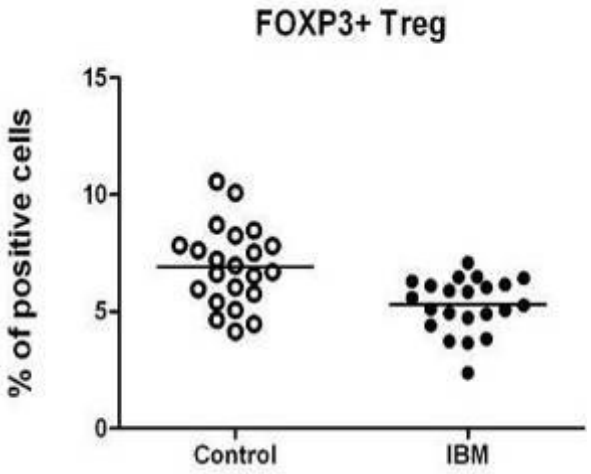
Quadriceps strength (QMT)

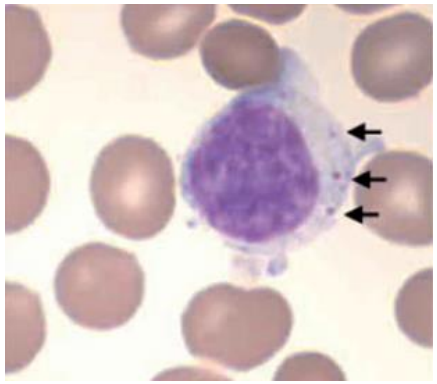


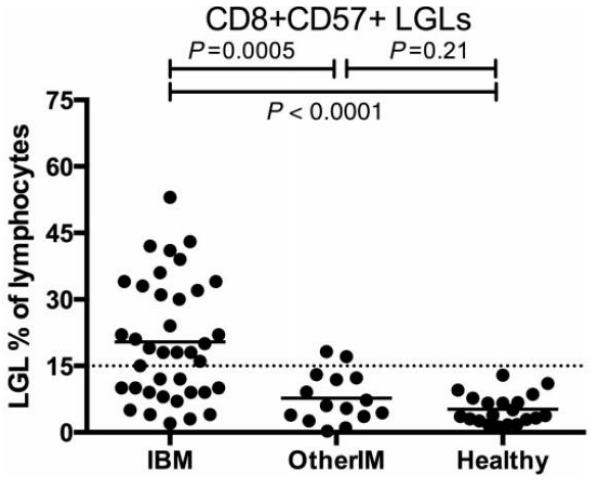
Rational for the use of rapamycin = sirolimus







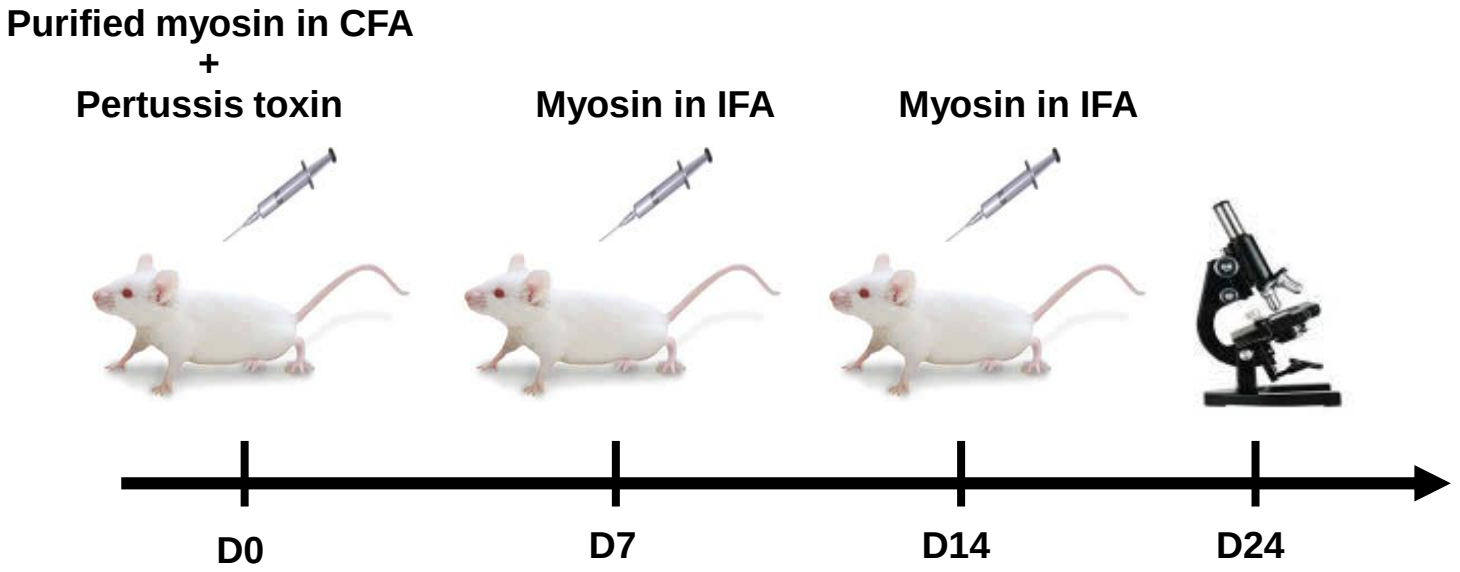


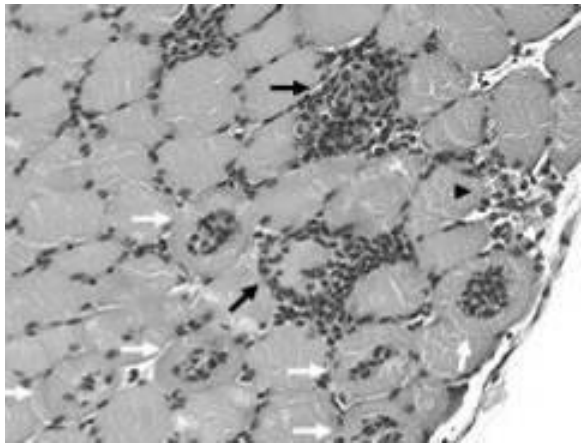


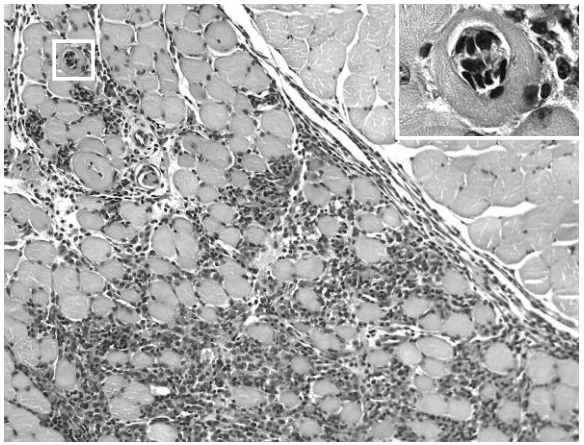
Y Allenbach, PLoS One 2014

SA Greenberg, Brain 2016

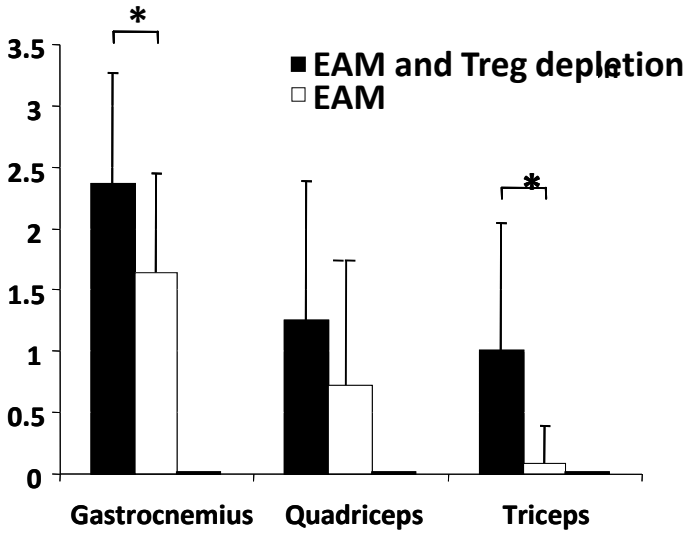
Model of Autoimmune Experimental Myositis





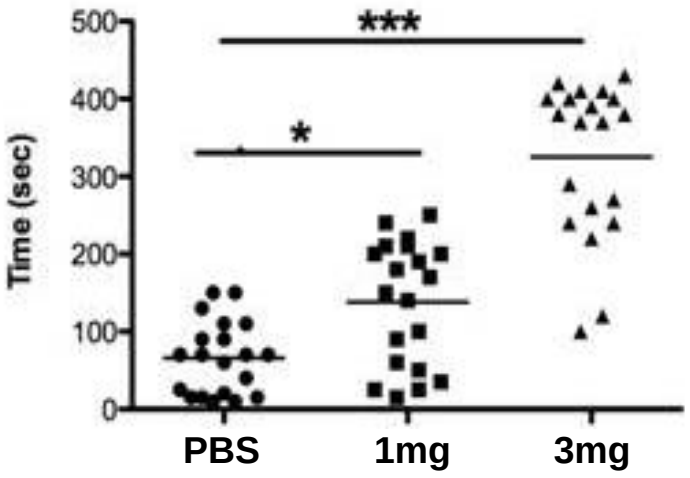


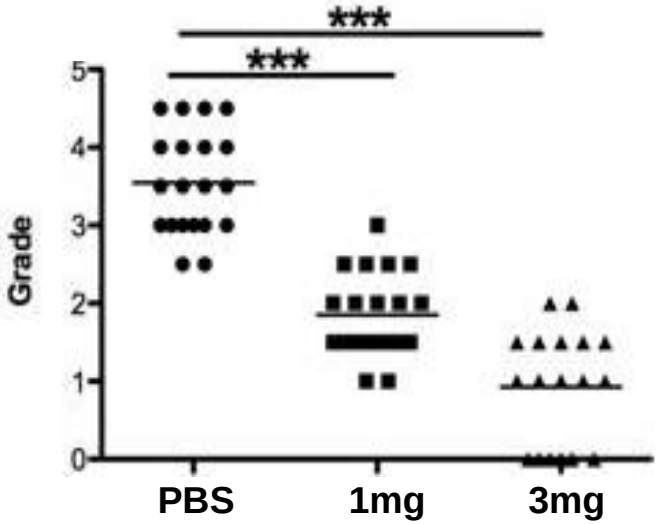
Transfer

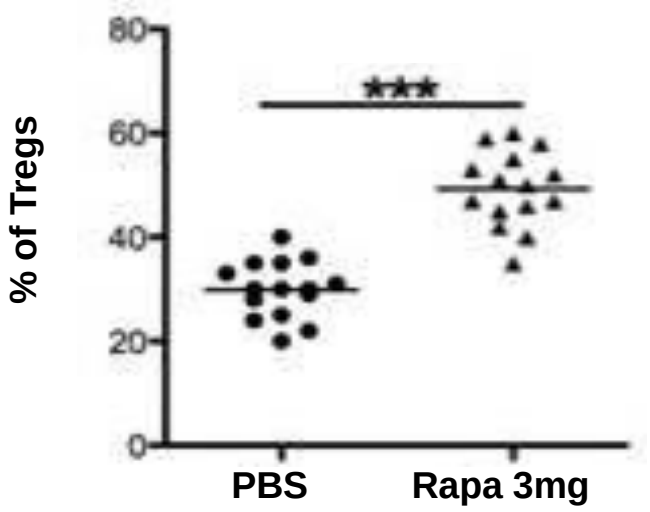


Y Allenbach, Am J Pathol 2009

Effect of Rapamycin in our mouse model







N Prevel: PLoS One 2014

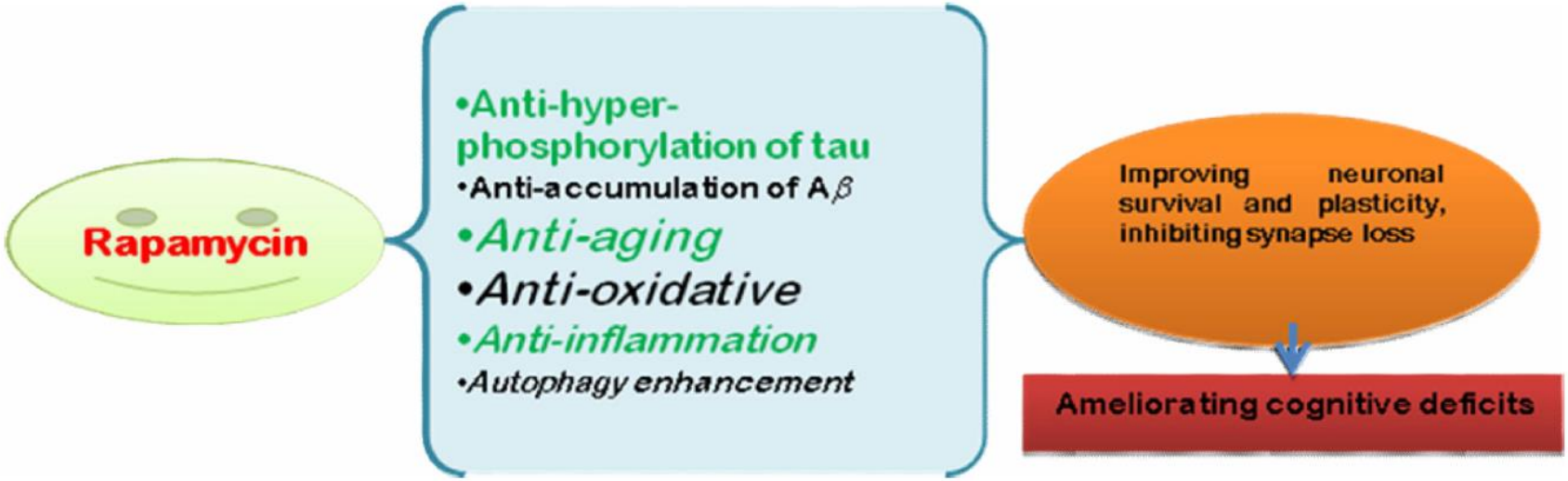
J Biochem Pharmacol Res. 2013 June ; 1(2): 84–90.

Rapamycin, Autophagy, and Alzheimer's Disease

Zhiyou Cai[a,*] and **Liang-Jun Yan**[b]

[a]Department of Neurology, Lu'an People's Hospital, the Lu'an Affiliated Hospital of Anhui Medical University, Lu'an, Anhui Province, China, 237005

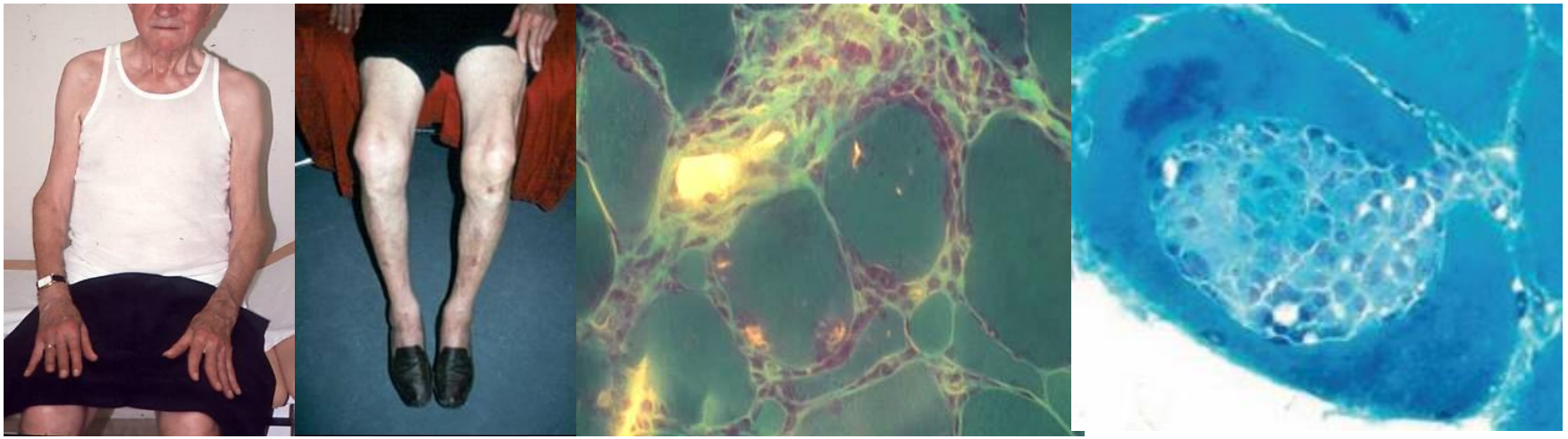
[b]Department of Pharmacology and Neuroscience and Institute for Aging and Alzheimer's Disease Research, University of North Texas Health Science Center, Fort Worth, Texas, USA



RAPAMI

- Prospective, randomized, controlled, double blind, monocentric, phase IIb trial evaluating the efficacy at 52 week of rapamycin in 22 patients compared to 22 with placebo.
- Rapamycin/placebo oral solution: 2mg/kg/day, adapted to rapamycinemia

- **Inclusion Criteria: IBM**



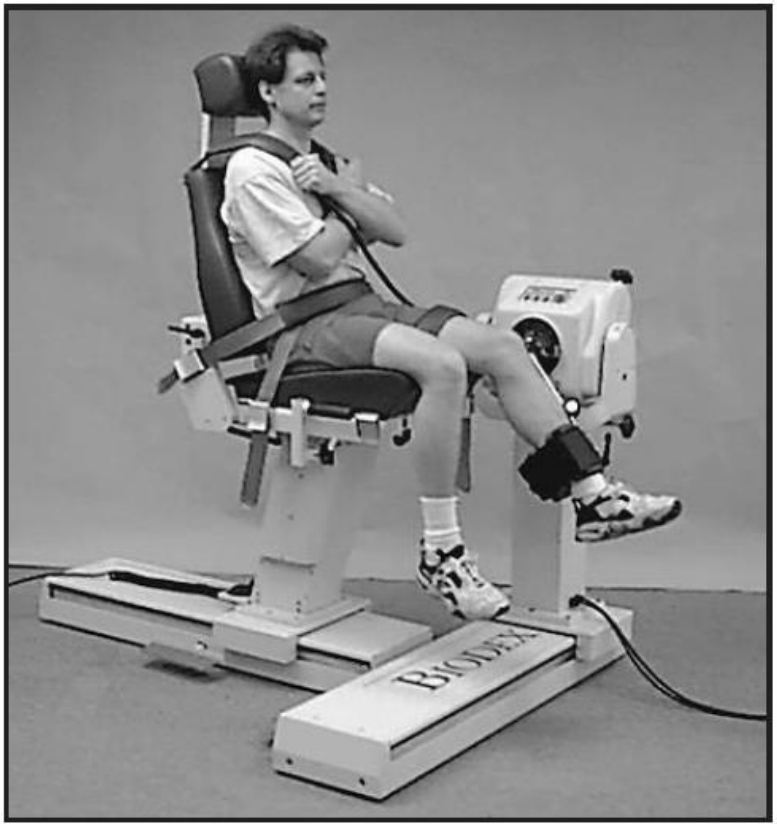
- Finger flexor **or** quadriceps weakness, **and**
- Endomysial inflammation, **and**
- Invasion of nonnecrotic muscle fibres **or** rimmed vacuole ***TE Lloyd, Neurol 2014***

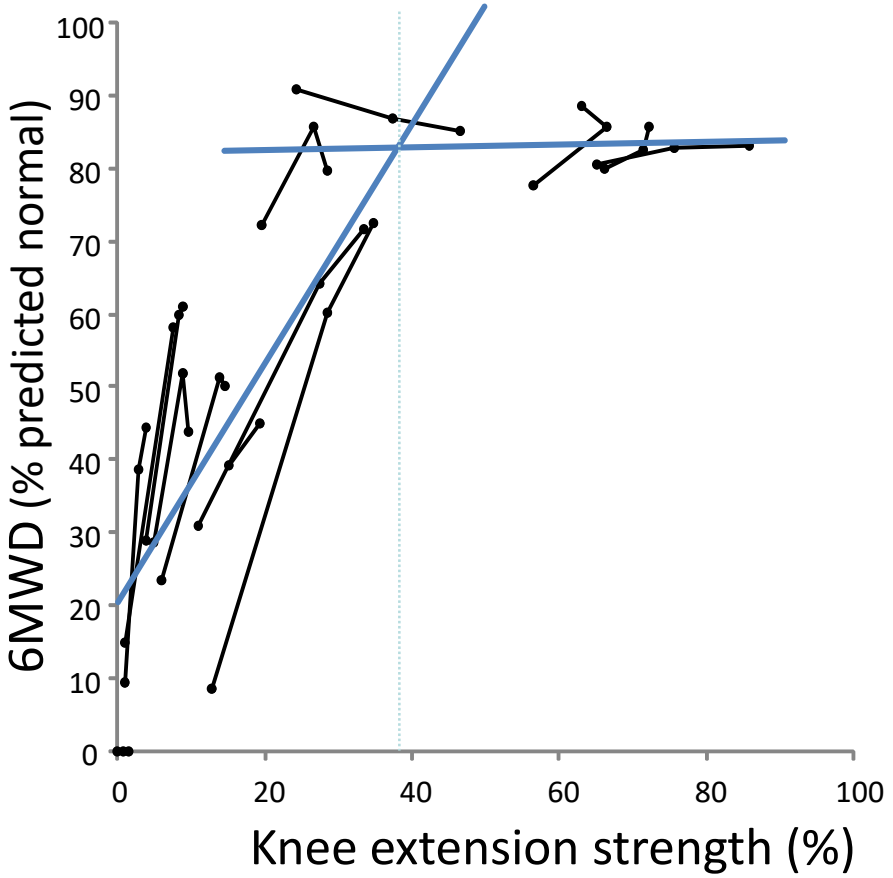
Exclusion criteria

- **Impossiblility to walk 10 meters**
- Hypersensitivity to rapamycin or one compound of the oral solution
- Severe respiratory insufficiency (FVC < 50% and/or FEV1 < 50%)
- Severe chronic kidney disease (Estimated Glomerular Filtration Rate < 15 ml/min and/or proteinuria > 0.3 g/24h)
- Chronic liver disease (cirrhosis and/or ALT/AST > 2.5 normal values)
- Cancer non in remission (necessitating specific treatment) during the past 12 months
- Connective Tissue Disease non in remission (necessitating specific treatment) during the past 12 months
- Pregnancy
- Seropositivity for HIV, HCV or HBV
- Total cholesterolemia > 8 mmol/l
- Triglyceridemia > 5 mmol/l
- Hemoglobinemia < 11 g/dL
- Thrombopenia < 100 000/mm3
- Neutropenia < 1500/ mm3
- Lymphopenia < 1000/ mm3

Primary endpoint

- Stabilization of maximal voluntary quadriceps isometric strength assessed with a dynamometer (Biodex System3 pro).



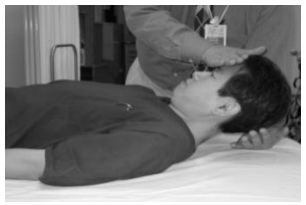


Y Allenbach, JY Hogrel, Neuromusc Dis 2012 & 2014

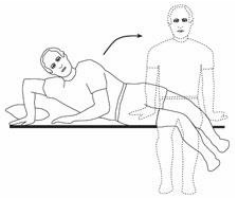
Secondary endpoints

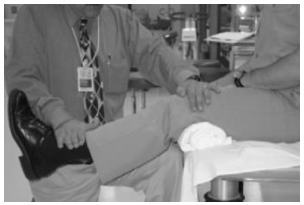
- Safety,
- Other muscle groups strength (QMT),
- Distance walked in 6 minutes (6MWD),
- Pulmonary functional tests (FVC),
- Functional scales (IBMWCI),
- Questionnaires (IBMFRS, nbr of falls)
- Muscle quality assessed by quantitative MRI.

IBM weakness composite index (IBMWCI)



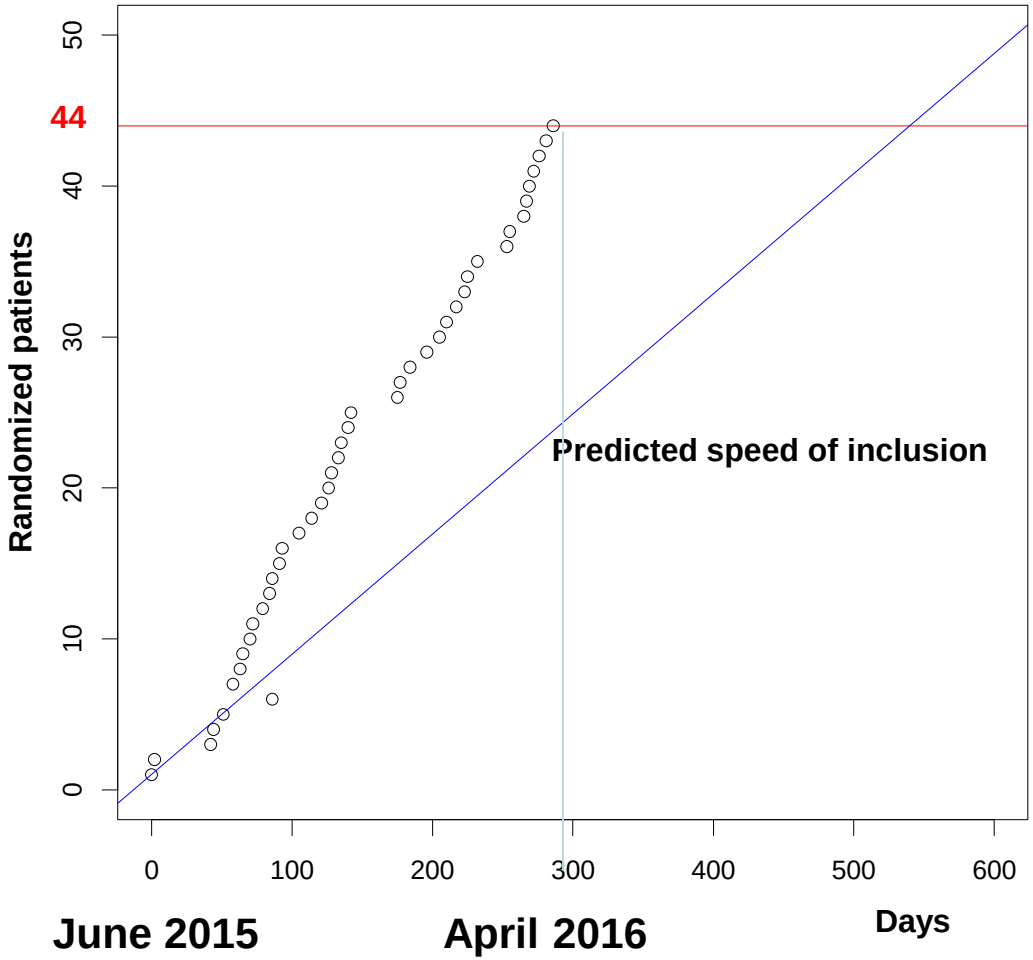
Measured parameters	
Arms outstretched forwards (s)	
150	15
100	10
50	5
<50	0
Legs held outstretched at 45° supine (s)	
75	15
50	10
25	5
<25	0
Neck flexors, lying in bed	
Against resistance	10
Without resistance	5
Impossible	0
From lying in bed to standing	
Without support	10
With support	5
Impossible	0
Walk	
Normal	10
With cane(s) or walker	5
Impossible (wheelchair)	0
From sitting position in a chair to standing	
Without support	10
With support	5
Impossible	0
Force of finger flexors	
MRC = 5	10
MRC = 3 or 4	5
MRC = 0, 1 or 2	0
Force of the quadriceps	
Normal (MRC = 5/5)	10
Decreased (MRC = 3 or 4)	5
Weak (MRC = 0, 1 or 2)	0
Swallowing	
Normal	10
Moderate or intermittent difficulties	5
Severe or permanent difficulties	0
Total	/100





O Benveniste, Brain 2011

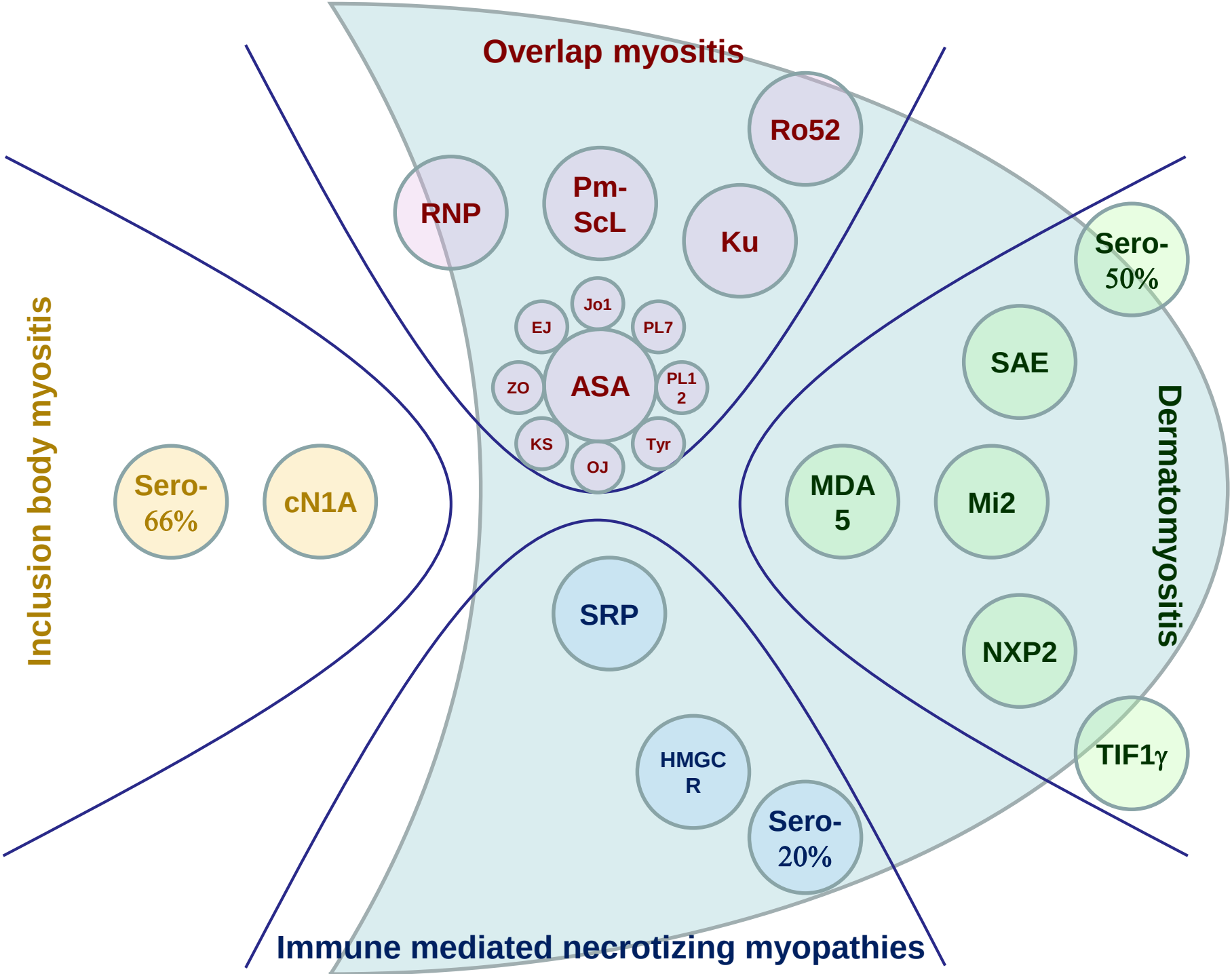
Inclusions of the 44 IBM patients



- Last day of one year treatment of the 44th patient: April 28th 2017
- Data base locked: July 15th 2017

At inclusion

	Rapamycin N=22		Placebo N=22		
	Mean	SD	Mean	SD	p
Sex	12 ♂	10 ♀	11 ♂	11 ♀	0.7
Age (y)	67	7.6	65	8.6	0.5
Disease duration	2.9	3	3.3	2.7	0.4
6MWD (m)	380	129	333	125	0.2
Quad (Nm)	29	21	37	33	0.6
Grip (daN)	16	8	13	10	0.2
FVC (%)	109	21	104	19	0.5
IBMWCI (max 100)	65	12	60	20	0.4
IBMFRS (max 40)	32	3.5	31	6.2	0.2
CK	384	342	716	898	0.3
Anti-cN1A+	7		9		0.3

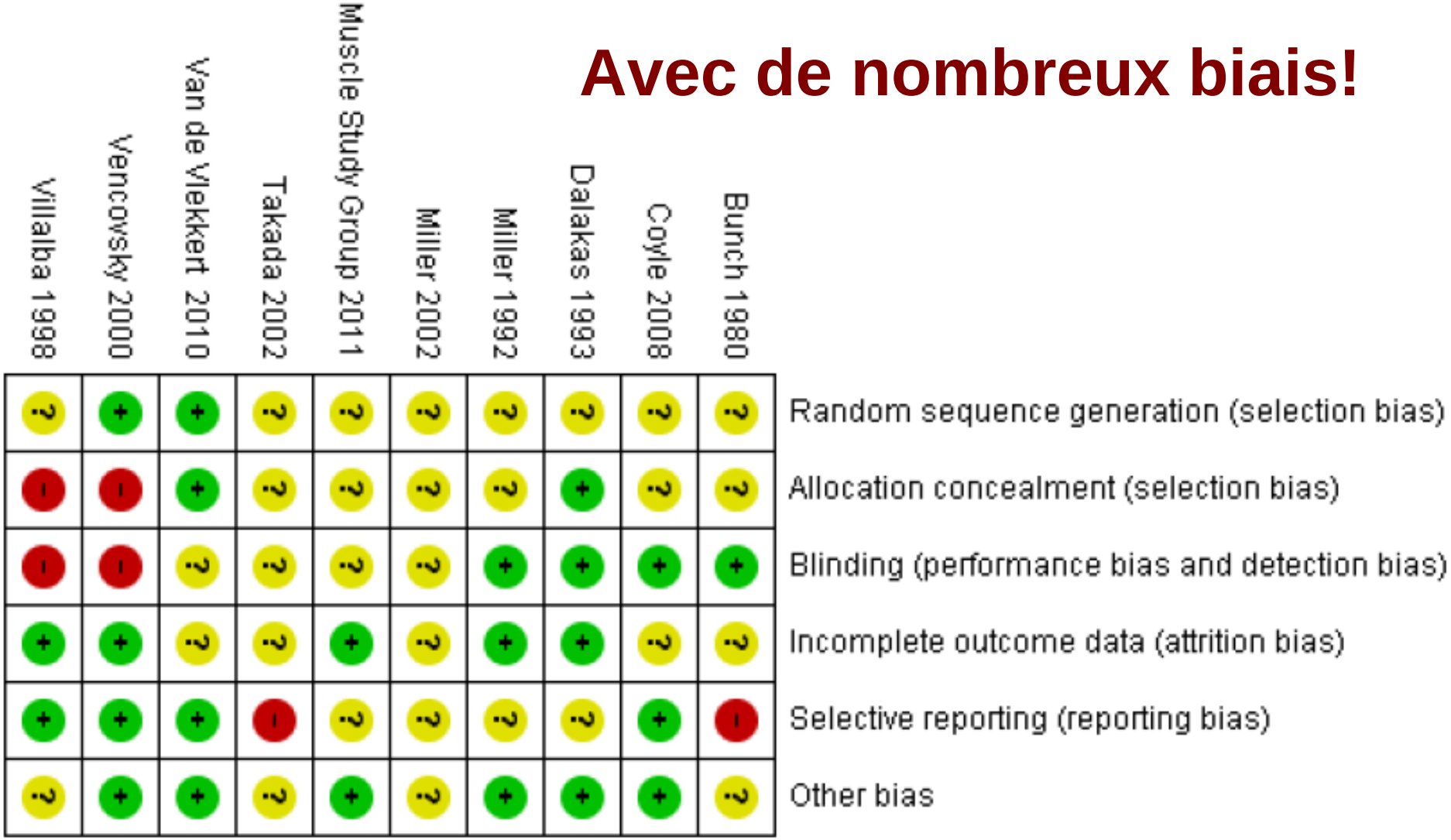

Overlap myositis
Ro52
RNP
Pm-ScL
Ku
Jo1
EJ
PL7
ZO
ASA
PL12
KS
Tyr
OJ
Sero-50%
SAE
Dermatomyositis
Inclusion body myositis
Sero-66%
cN1A
MDA5
Mi2
SRP
NXP2
HMGCR
TIF1γ
Sero-20%
Immune mediated necrotizing myopathies

Avant 2013, seuls 10 essais randomisés controllés (PM/DM)

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	No? 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

Differents critères de jugement : MMT en 5 à 13 points sur 18 à 26 muscles

Avec de nombreux biais!



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

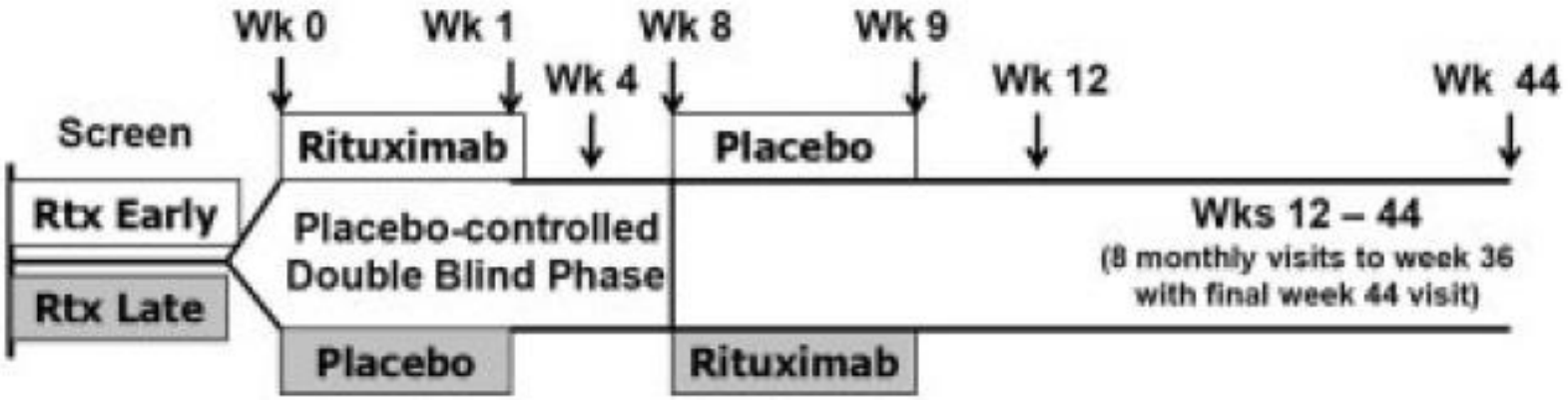
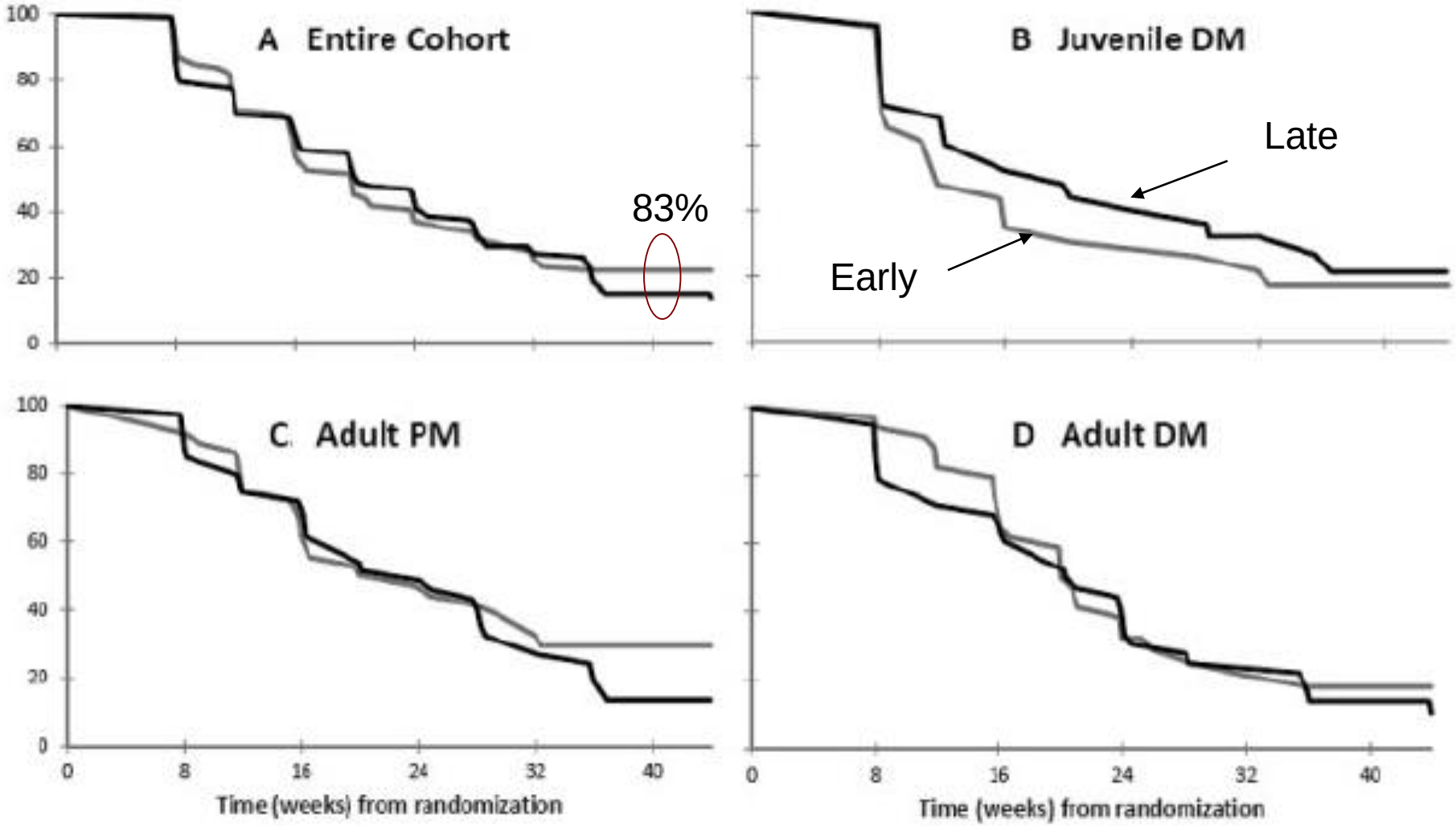


Table 1. Baseline demographic and clinical characteristics and core set measures, by treatment group*

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)

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 26 (2016) 523–534

www.elsevier.com/locate/nmd

Workshop report

213th ENMC International Workshop: Outcome measures and clinical trial readiness in idiopathic inflammatory myopathies, Heemskerk, The Netherlands, 18–20 September 2015

Olivier Benveniste [a,b,*], Lisa G. Rider [c,**] on behalf of the ENMC Myositis Outcomes Study Group [#]

EUROPEAN NEURO MUSCULAR CENTRE

Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies

Lisa Christopher-Stine

Current Opinion in Rheumatology 2010, 22:623–626

- Also, for outcome measures?

- Around the table
  - 18 experts, 7 specialties (dermatology (1), internal medicine (4), neurology (6), pediatric rheumatology (2), physiotherapy (1), pneumology (1), and rheumatology (3))
  - 8 countries (Belgium, France, Norway, The Netherlands, Spain, Sweden, the United Kingdom, and the United States of America)
  - 3 patient representatives (UK, France, Netherlands)

R. Aggarwal (rheumatologist, USA); Y. Allenbach (internist, France); O. Benveniste (internist, France); J. de Bleecker (neurologist, Belgium); H. Devilliers (internist, France); D. Hilton-Jones (neurologist, UK); J-Y. Hogrel (bio-engineer, France); I. Lundberg (rheumatologist, Sweden); A. Mammen (neurologist, USA); C. Oddis (rheumatologist, USA); G. Padberg (research director ENMC); L. Rider (pediatric rheumatologist, USA); M. Rose (neurologist, UK); H. Sanner (pediatric rheumatologist, Norway); A. Selva O Callaghan (internist, Spain); M. de Visser (neurologist, The Netherlands); A. Wells (pulmonologist, UK); V. Werth (dermatologist, USA).

Critères d'inclusion pour les essais futurs

Recommandations du groupe:

- Classer les patients par phénotype, anapath et les Acs !

Par ex : anti-synthetase ≠ DM ou PM

- Recruter des groupes homogènes de patients !

1. **IBM**
2. **DM adulte** (exclure anti-MDA5, anti-Tif1γ…)
3. **DMJ**
4. **Anti-Synthetase** (par ex anti-Jo1)
5. **MNAI** (anti-SRP ou HMGCR)

(6. **PM**)

Medical Research Council

Table I. *Medical Research Council scale. Aids to examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationery Office; 1976*

0	No contraction
1	Flicker or trace contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

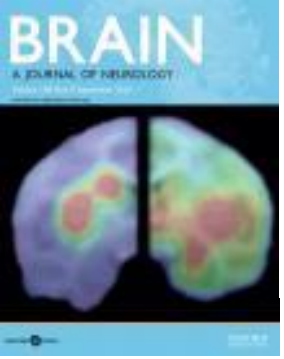
Mesure de l'amplitude du movement « Range of motion »

MRC–Adaptation A(13)

5	Normal strength
5-	Uncertain muscle weakness
4+	Inability to resist against maximal pressure throughout ROM
4	Ability to resist against moderate pressure throughout ROM
4-	Ability to resist against minimal pressure throughout ROM
3+	Ability to move through full ROM AG and resist against minimal pressure through partial ROM, then contraction breaks abruptly
3	Ability to move through full ROM AG
3-	Ability to move through > 50% ROM AG
2+	Ability to move through < 50% ROM AG
2	Ability to move through full ROM GE
2-	Ability to move in any arc of motion with GE
1	Visible or palpable muscle contraction
0	No contraction palpable

MMT Kendal et MRC

MRC–Adaptation A(13)		Kendall "10-point" Scale(4;24)	
5	Normal strength	10	Holds test position against strong pressure
5-	Uncertain muscle weakness	n/a	
4+	Inability to resist against maximal pressure throughout ROM	9	Holds test position against moderate to strong pressure
4	Ability to resist against moderate pressure throughout ROM	8	Holds test position against moderate pressure
4-	Ability to resist against minimal pressure throughout ROM	7	Holds test position against slight to moderate pressure
3+	Ability to move through full ROM AG and resist against minimal pressure through partial ROM, then contraction breaks abruptly	6	Holds test position against slight pressure
3	Ability to move through full ROM AG	5	Holds test position (no pressure)
3-	Ability to move through > 50% ROM AG	4	Gradual release from test position
2+	Ability to move through < 50% ROM AG	3	Moves through < 100% ROM AG, or through full ROM GE against resistance, or through full ROM GE and holds against resistance
2	Ability to move through full ROM GE	2	Moves through full ROM GE
2-	Ability to move in any arc of motion with GE	1	Moves through < 100% ROM GE
1	Visible or palpable muscle contraction	T	Visible or palpable muscle contraction
0	No contraction palpable	0	No contraction palpable



OCCASIONAL PAPER

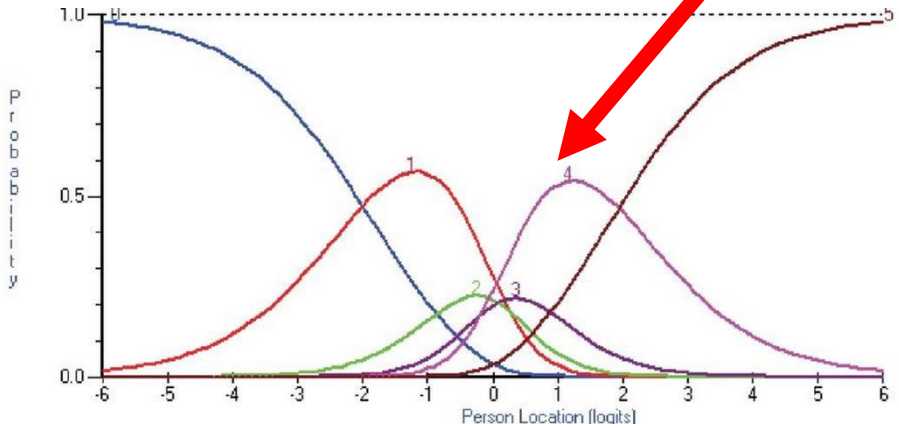
Modifying the Medical Research Council grading system through Rasch analyses

Els Karla Vanhoutte,[1] Catharina Gerritdina Faber,[1] Sonja Ingrid van Nes,[2] Bart Casper Jacobs,[2] Pieter Antoon van Doorn,[2] Rinske van Koningsveld,[3] David Reid Cornblath,[4] Anneke Jelly van der Kooi,[5] Elis
Willem Lodew
Elisabeth van
Hendrik Boot,
Ingemar Sergi

For a given level of whole muscular strength

(0 on the arbitrary unit -6 to +6 scale)

The probability of scoring 1, 2, 3, or 4 was almost the same !



Concerns regarding **MMT8**

- Evaluation of gluteus medius and quads
- Kendall with 10 point scale

- 7: holds test position against slight to moderate pressure,
- 8: moderate pressure,
- 9: moderate to strong pressure

Proposition of the group (to be evaluated): **MMT5 vs. MMT8**

- Deltoids, biceps brachii, psoas, hamstrings, neck flexors
- Use 0-3 scoring: 0=paralysis; 1=severe weakness; 2=slight weakness; and 3=normal strength (compare to 0-10 scoring)

Critères de jugement pour les essais

DOI-IMACs

20% or more in 3 of 6 outcome measures, with no more than 2 variables worsening by ≥25% (excluding MMT)

Core set domain	Method of assessment
Physician's global activity assessment	Horizontal 10-cm VAS
Patient's/parent's global activity assessment	Horizontal 10-cm VAS
Muscle strength	MMT, including proximal, distal, and axial muscles assessed on 0–10-point or expanded 0–5-point scale
Physical function	HAQ; for pediatrics C-HAQ and CMAS
Muscle-associated enzymes	At least 2 of CK, LDH, AST, ALT, or aldolase tests
Extramuscular activity assessment	Extramuscular portion of the Myositis Disease Activity Assessment Tool (MDAAT)

Accelerometer (GENEActiv device)

- proven in both small scale studies and large international cohorts
- can collect data for periods of 7 days to over a month
- Specific software for analysis
- is **scientifically validated** (107 publications) http://www.geneactiv.org/resources-support/publications/

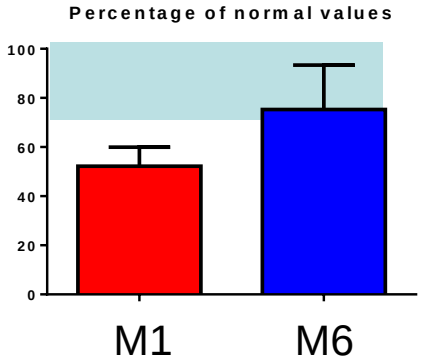
439 clinical trials with accelerometers (clinical trial.gov):

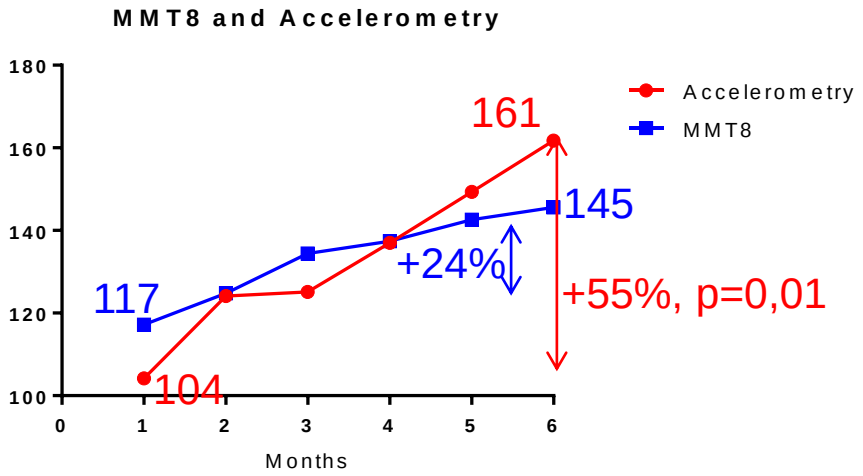
physical activity, obesity, heart disease, cancer, muscle disease (n=3), …

From Rider et al, 2004

Et demain : application smart phone?

N=5 IIM patients (2 DM, 3 IMNM), starting prednisone+MTX+IVIg

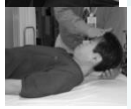




Accelerometry is promising!

Evaluation de la force

N=51 IIM patients, evaluated at D0 & M6

	Testing	SRM	ES	% pt improv
 Shoulder abduction	+ 1.0	1.10	0.9	58%
 Elbow flexion	+ 0.6	0.95	0.91	50%
 Neck flexion	+ 1.0	0.88	0.82	47%
 Limb abduction	+ 0.7	0.71	0.65	25%
 Knee flexion	+ 0.7	0.82	0.78	43%
 Knee extension	+ 0.5	0.52	0.53	25%
 Thigh flexion	+ 1.2	1.24	0.98	63%

Evaluation de la force

N=51 IIM patients, evaluated at D0 & M6

	Testing	SRM	ES	% pt improving
 Stand up from handless chair				77 %
 Ability to squat				20 %
 Nb of standing up from a chain in 60s	+ 7	0.84	0.73	
 Barré	+ 73	1.01	0.78	
 Mingazzini	+ 32	1.0	0.90	
 Ability to cross legs				67 %

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]

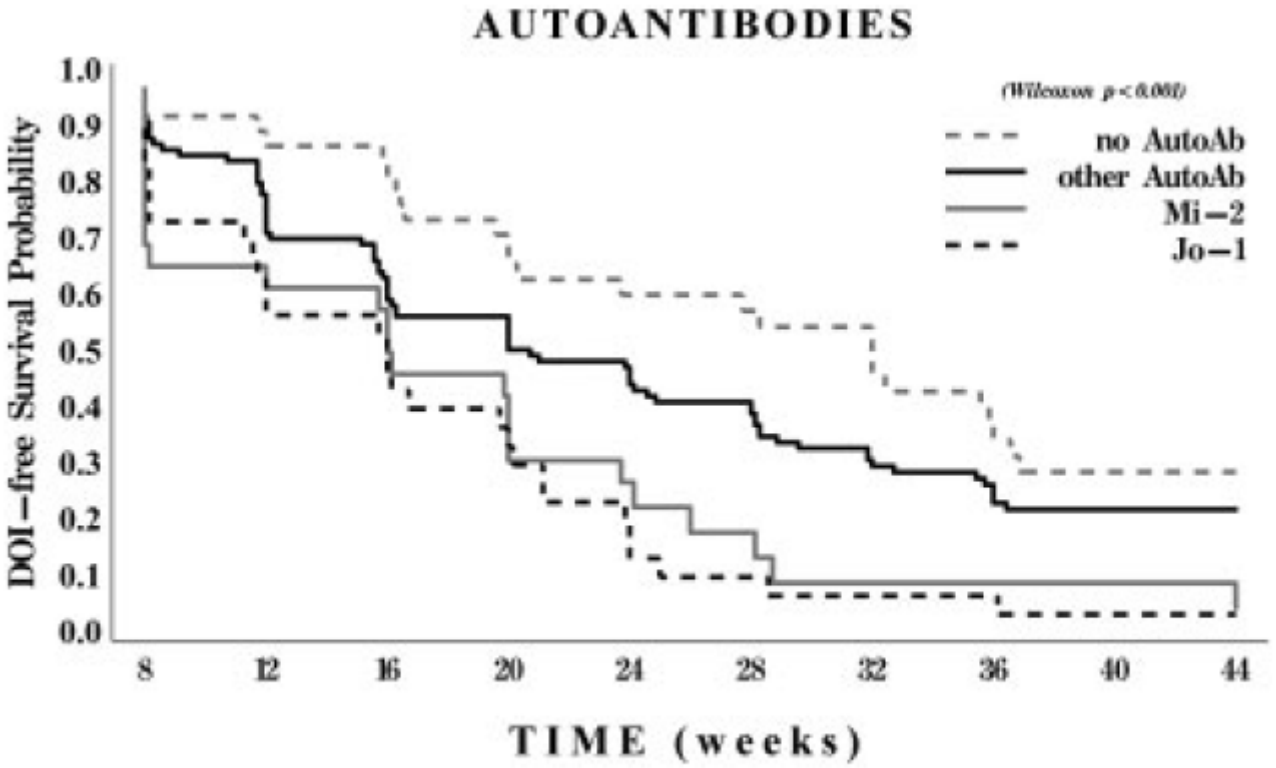


Figure 1. Kaplan-Meier curves for probability of meeting the definition of improvement (DOI) according to myositis autoantibody

RESEARCH ARTICLE

Efficacy of Rituximab in Refractory Inflammatory Myopathies Associated with Anti- Synthetase Auto-Antibodies: An Open-Label, Phase II Trial

PLoS One. 2015 Nov 5;10(11):e0133702

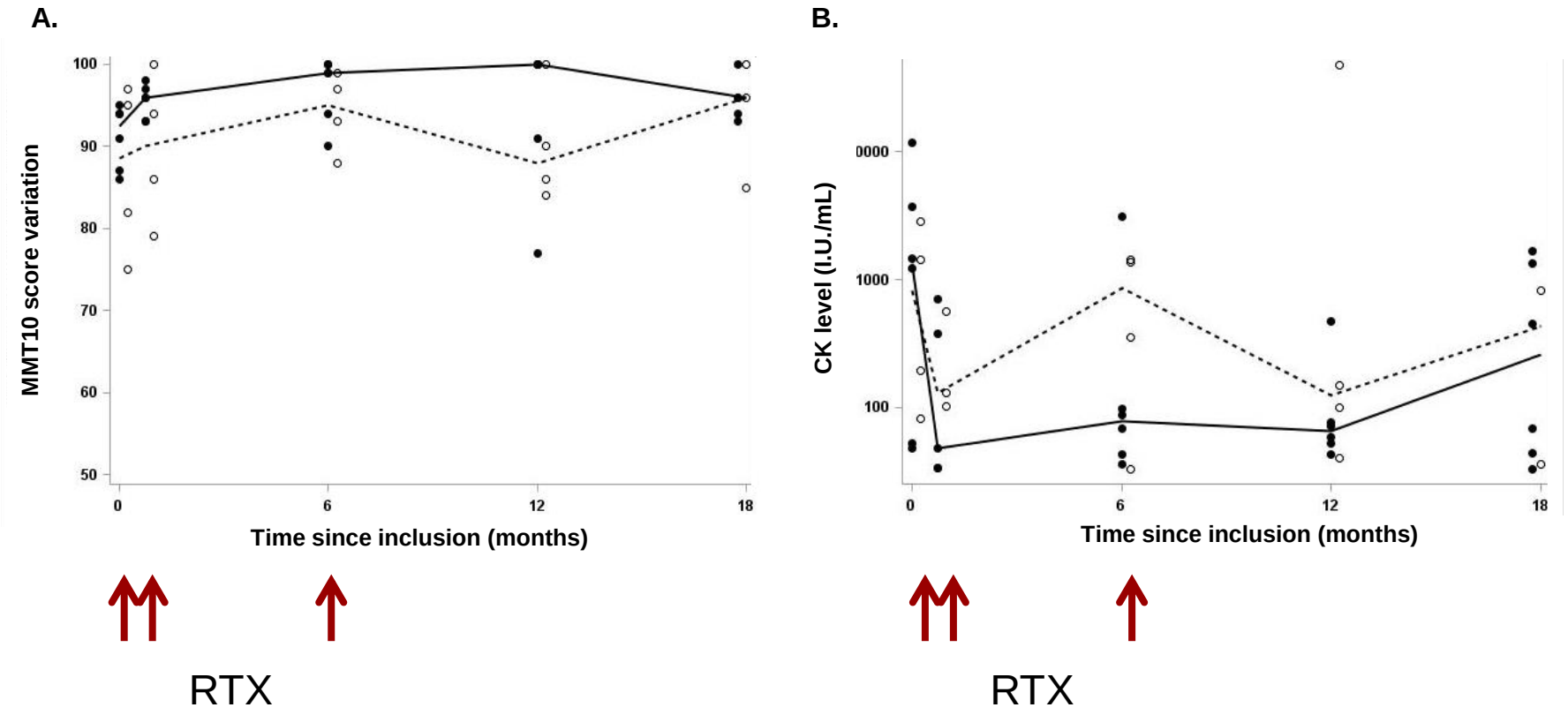
Yves Allenbach[1]*, Marguerite Guiguet[2], Aude Rigolet[1], Isabelle Marie[3], Eric Hachulla[4], Laurent Drouot[5], Fabienne Jouen[5], Serge Jacquot[5], Kuberaka Mariampillai[1], Lucile Musset[6], Philippe Grenier[7], Herve Devilliers[8], Adrian Hij[9], Olivier Boyer[5], Serge Herson[1], Olivier Benveniste[1]

RTX: 1 g à J0, J15 et M6

Table 1. Patients characteristics, muscular evaluation, and treatment administration at baseline and month 12.

#	Sex	Age (yrs)	Disease duration (yrs)	Traitements before enrollement	Treatments at inclusion	Kendall score/100		CK (I.U./L)	
						M0	M12	M0	M12
1	M	20	2	CT, MTX, AZA, MMF, RTX	CT, AZA	94	100	11718	58
2	M	56	1	CT, MTX, AZA, IVIg, MMF	CT, MMF	87	100	53	72
3	M	54	0.5	CT, AZA, CYC, IVIg	CT	75	86	605	148
4	M	30	1	CT, AZA, IVIg	CT, MTX, IVIg	94	100	3704	43
5	W	58	4	CT, IVIg, MMF	CT, MMF	91	77	822	470
6	W	46	3	CT, IVIg, MMF	CT	99	84	75	47857
7	M	42	4	CT, MTX, AZA, IVIg	CT, AZA	86	91	48	53
8	M	64	8	CT, MTX, AZA, IVIg	CT, AZA	82	90	193	40
9	M	58	8	CT, AZA, IVIg	CT, AZA, IVIg	99	100	141	77
10	M	59	2	CT, MTX, AZA, IVIg	CT	95	100	2840	99

Evaluations musculaires



50% d'amélioration

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

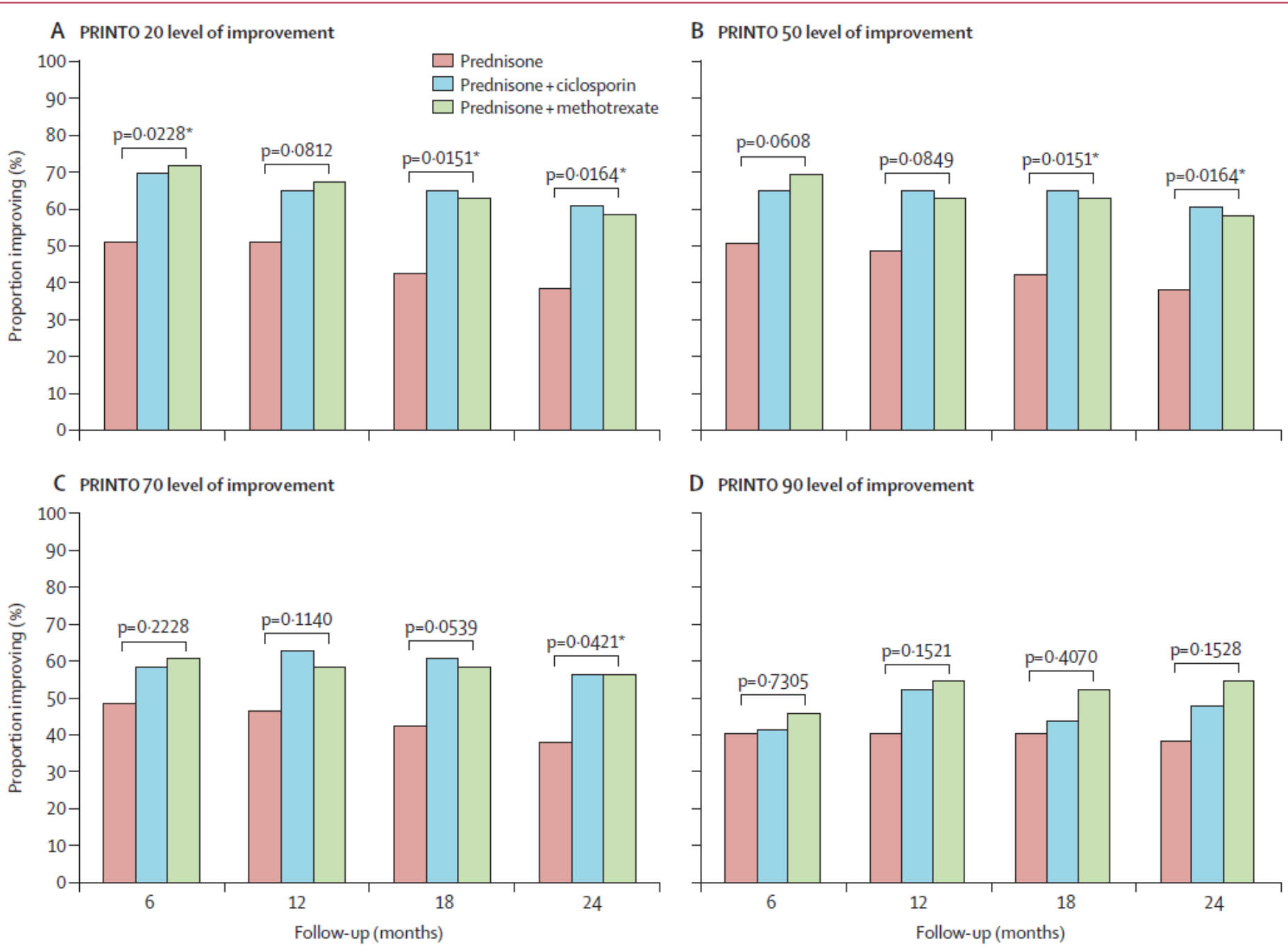
	Prednisone (n=47)	Prednisone plus ciclosporin (n=46)	Prednisone plus methotrexate (n=46)
Women	26 (55%)	26 (57%)	30 (65%)
Men	21 (45%)	20 (43%)	16 (35%)
Ethnic origin			
White European	32 (68%)	32 (70%)	29 (63%)
Hispanic	8 (17%)	5 (11%)	6 (13%)
Other	2 (4%)	5 (11%)	6 (13%)
Unknown	5 (11%)	4 (9%)	5 (11%)
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
0
10
20
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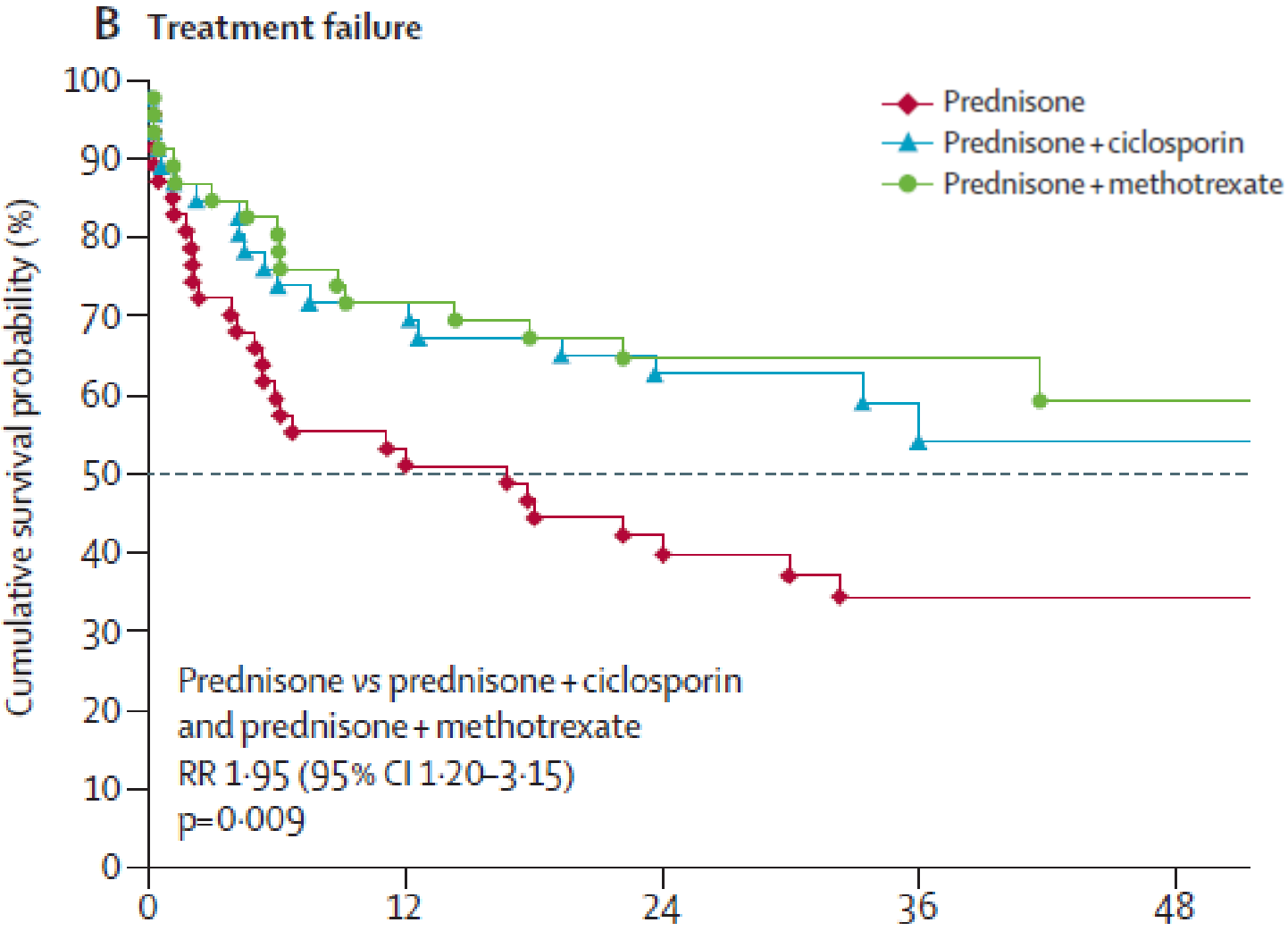
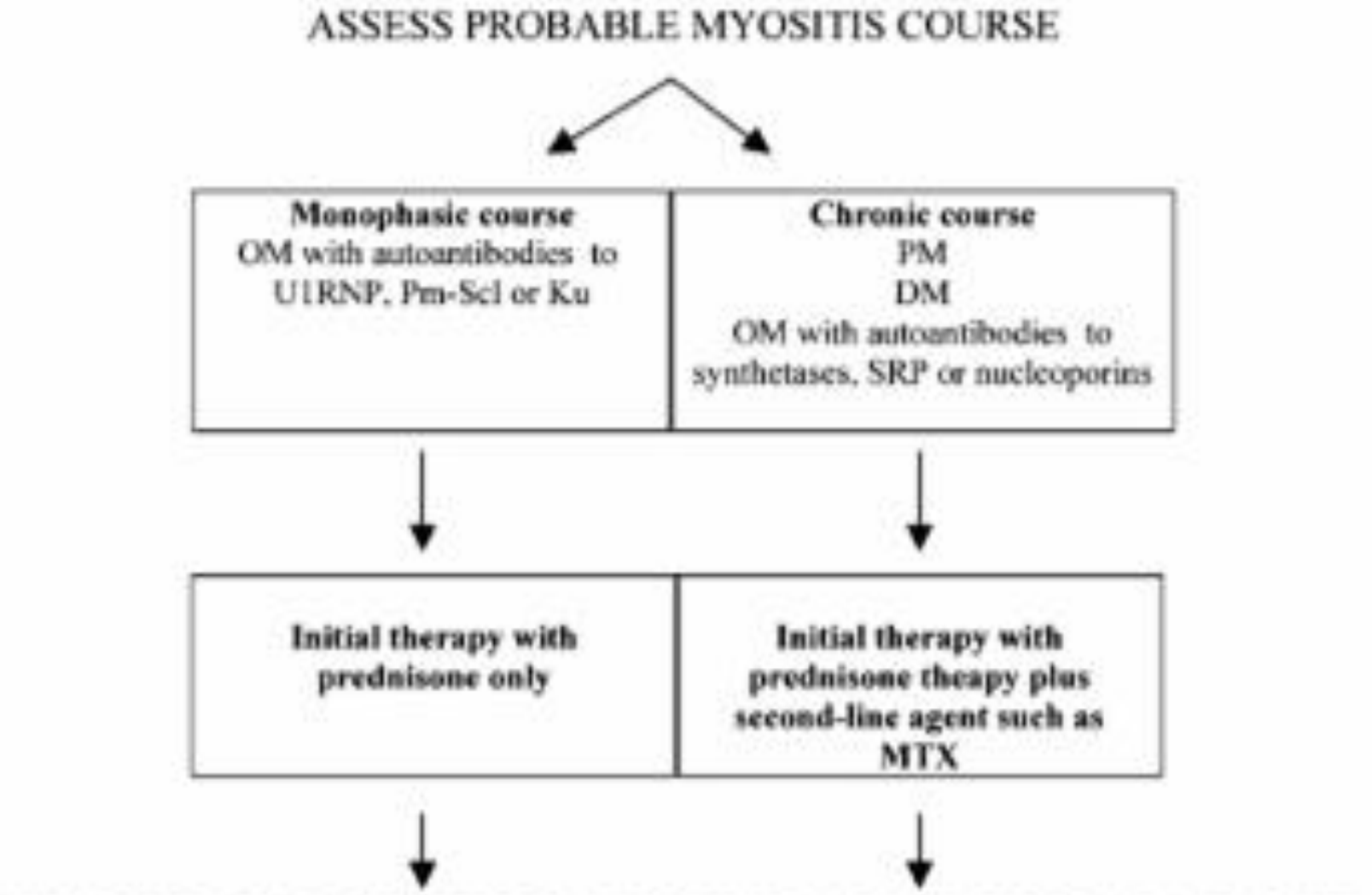
40
50
60
70
80
90
100
6
12
18
24



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.

	Prednisone (n=47)	Prednisone plus ciclosporin (n=46)	Prednisone plus methotrexate (n=46)	p
Adverse events	51	128	74	..
Median (range) adverse events per patient	0 (0–8)	1·5 (0–20)	1 (0–8)	0·004
Patients with serious adverse event	1 (2%)	5 (11%)	2 (4%)	0·17
Patients with adverse event leading to permanent or temporary withdrawal	1 (2%)	10 (22%)	10 (22%)	0·009
Skin and subcutaneous tissue disorders	10 (21%)	27 (59%)	9 (20%)	<0·0001
Hypertrichosis	5 (11%)	8 (17%)	1 (2%)	0·04
Hirsutism	1 (2%)	11 (24%)	1 (2%)	0·0002
Alopecia	1 (2%)	4 (9%)	2 (4%)	..
Gastrointestinal disorders	9 (19%)	24 (52%)	9 (20%)	0·0004
Nausea	3 (6%)	4 (9%)	4 (9%)	..
Abdominal pain or abdominal pain upper*	2 (4%)	7 (15%)	0	0·008
Infections and infestations	5 (11%)	14 (30%)	14 (30%)	0·03
Endocrine disorders	9 (19%)	6 (13%)	9 (20%)	..
Cushing's syndrome or Cushingoid*	9 (19%)	6 (13%)	9 (20%)	..
Investigations	3 (6%)	8 (17%)	6 (13%)	..
Weight increased	3 (6%)	1 (2%)	3 (7%)	..
Blood creatinine increased	0	3 (7%)	0	..
Nervous system disorders	3 (6%)	9 (20%)	2 (4%)	..
Headache	1 (2%)	5 (11%)	1 (2%)	..
General disorders and administration site conditions	1 (2%)	9 (20%)	2 (4%)	0·008
Musculoskeletal and connective tissue disorders	1 (2%)	5 (11%)	4 (9%)	..
Psychiatric disorders	2 (4%)	5 (11%)	4 (9%)	..
Metabolism and nutrition disorders	3 (6%)	4 (9%)	4 (9%)	..
Vascular disorders	2 (4%)	7 (15%)	1 (2%)	..
Cardiac disorders	0	3 (7%)	1 (2%)	..
Tachycardia	0	3 (7%)	0	..
Eye disorders	0	3 (7%)	3 (7%)	..

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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Traitement des PM/DM/MNAI, en pratique :

- Prednisone (1 mg/kg/j) 6 semaines puis diminution
- MTX (ou Azat)
- Si gravité IgIV (3 à 6 cures)

| 3 ans…

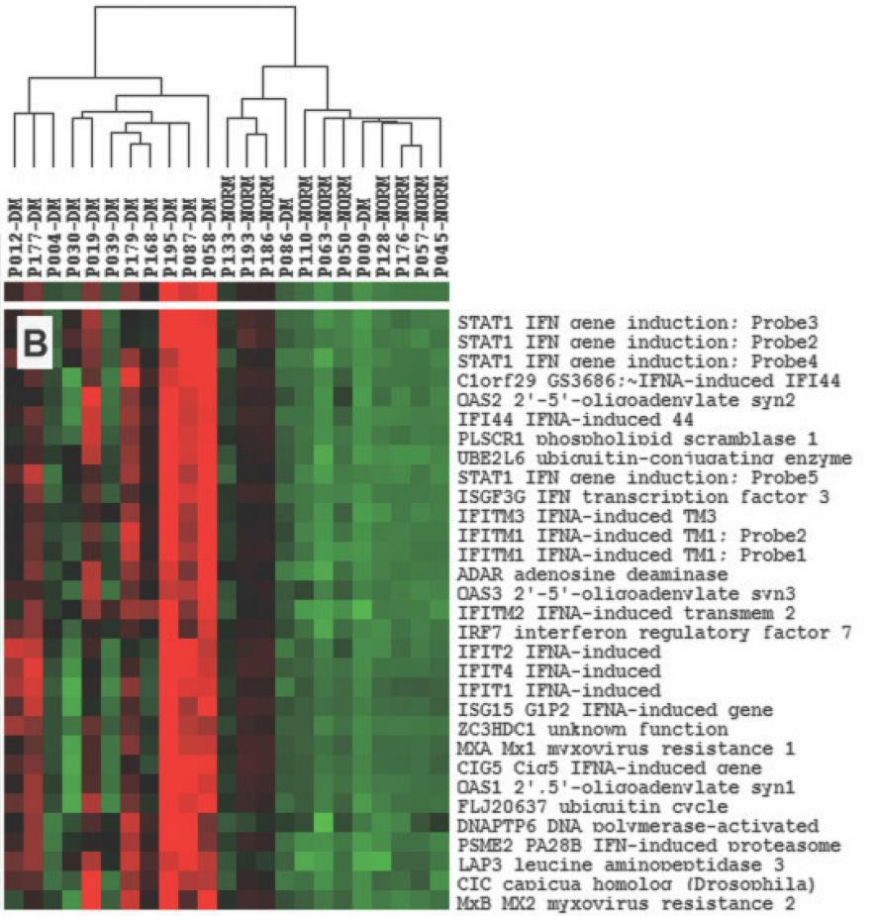
- Puis : MTX + Azat, MMF, EDX, **RTX (si auto-Ac)**…

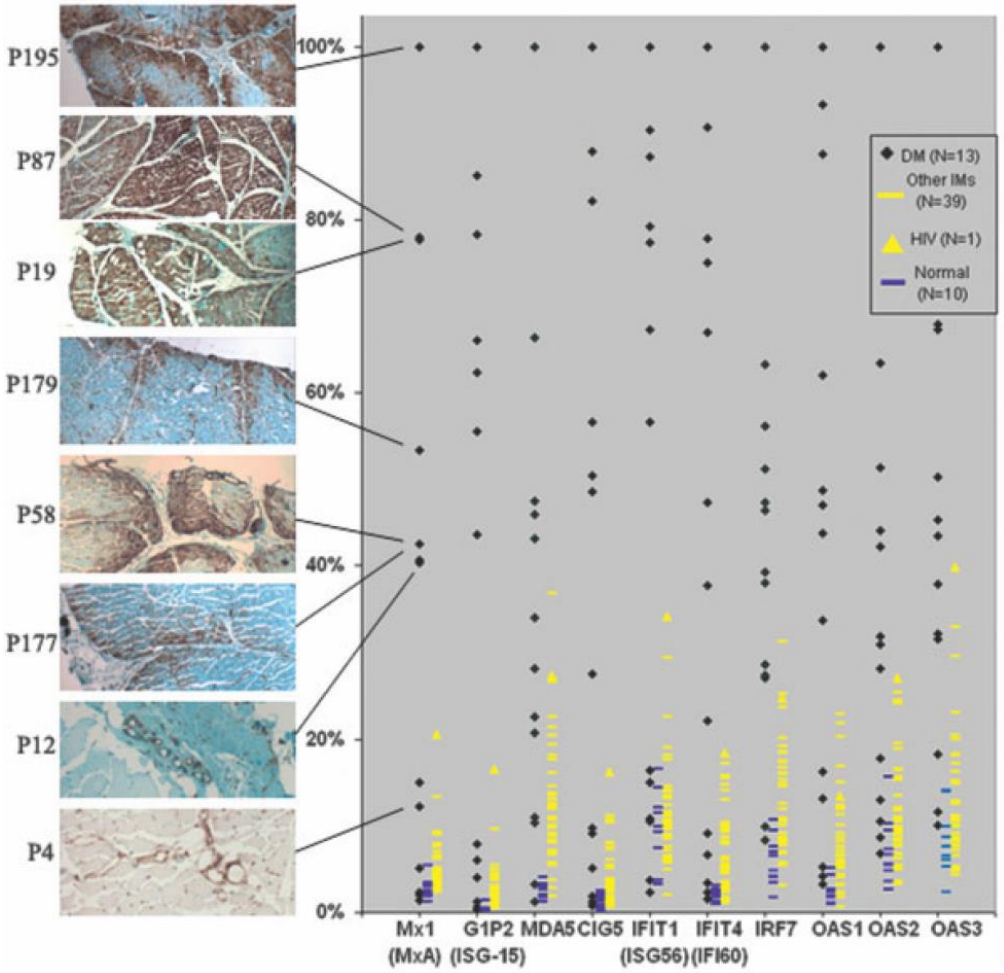
A définir :

- Place du RTX pour les différentes MAI?
- Place du RTX en monothérapie?
- Schéma du traitement d'entretien : 1g tous les 6 mois?
- Durée du traitement d'entretien par RTX: 3 ans?

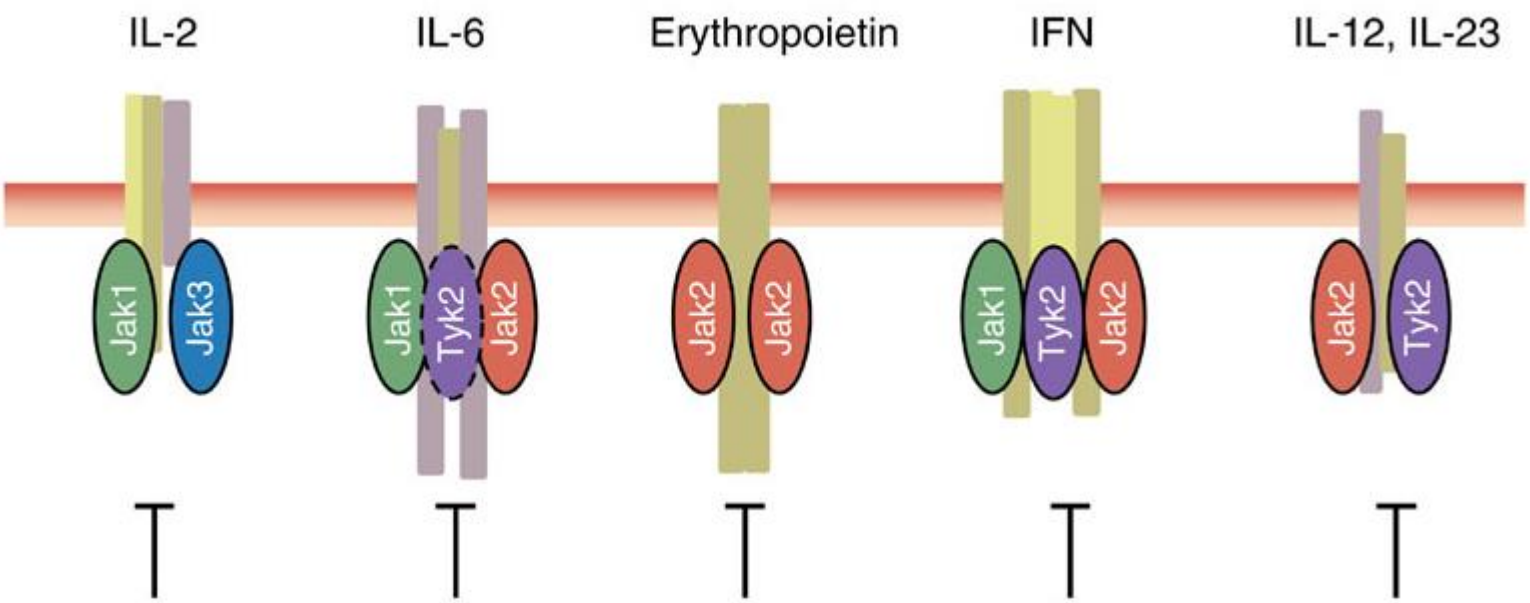
Interferon-α/β–Mediated Innate Immune Mechanisms in Dermatomyositis

Greenberg et al 2005. Ann Neurol.





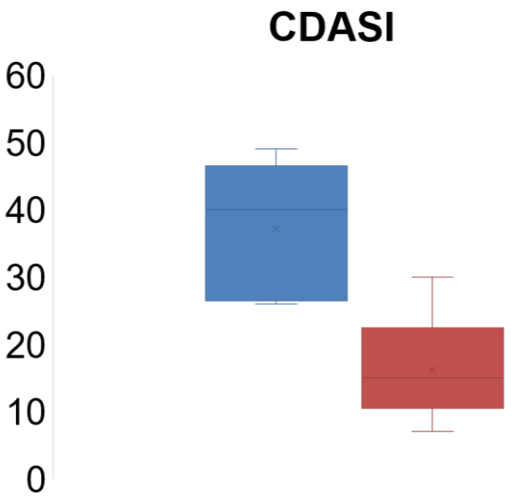
JAK inhibitors pathways

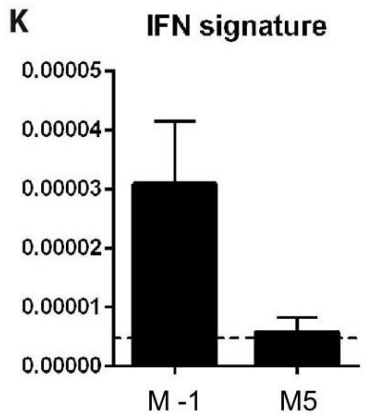


	IL-2	IL-6	Erythropoietin	IFN	IL-12, IL-23
Jak1 inhibitor	+	+	−	+	−
Jak2 inhibitor	−	+	+	+	+
Jak3 inhibitor	+	−	−	−	−
Tyk2 inhibitor	−	+	−	+	+

Jakinibs

Drug	Target	Status	Diseases
Ruxolitinib (INC424)	JAK1, JAK2	*FDA approved* Phase II Phase IIb	RA Various cancers Psoriasis (topical)
Tofacitinib (CP690550)	JAK3>JAK1>> (JAK2)	*FDA approved* Phase III Phase II	RA Psoriasis, Ulcerative colitis Spondyloarthritis, JIA Transplant rejection
Oclacitinib (PF03394197)	JAK1	*FDA approved*	Canine allergic dermatitis
ABT494	JAK1	Phase II	RA, Crohn's
Baricitinib (INCB28050, LY3009104)	JAK1, JAK2	Phase II	RA, Psoriasis, Diabetic nephropathy, autoinflammatory disease
Filgotinib (GLPG0634)	JAK1	Phase II	RA, Crohn's disease
INCB039110	JAK1, JAK2	Phase II	Psoriasis, RA
Peficitinib (ASP015K)	pan-JAK	Phase II	Psoriasis, RA
R333	JAK/SYK	Phase II	Discoid lupus (topical)
GLG0778	JAK1	Phase II	SLE
GSK2586184	JAK1	Phase II	SLE, Psoriasis
Decernotinib (VX509)	JAK3	Phase IIb	RA





L Ladislau, Brain 2018

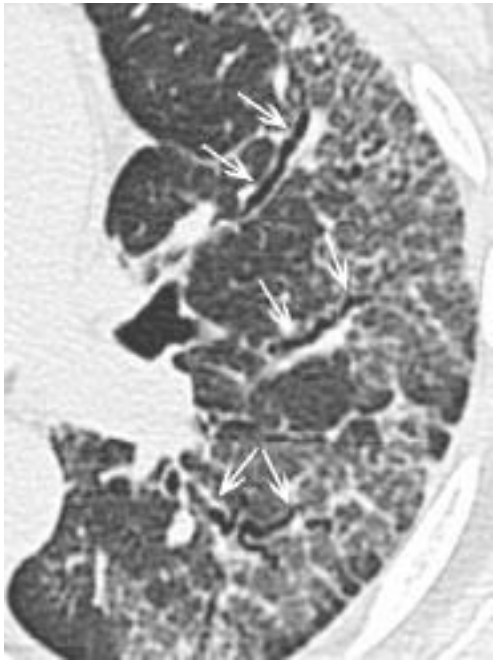
Antisynthetase Syndrome with Anti-Jo1 Antibodies in 48 Patients: Pulmonary Involvement Predicts Disease-modifying Antirheumatic Drug Use

RALUCA STANCIU, MARGUERITE GUIGUET, LUCILE MUSSET, DIANE TOUITOU, CATHERINE BEIGELMAN, AUDE RIGOLET, NATHALIE COSTEDOAT-CHALUMEAU, YVES ALLENBACH, BAPTISTE HERVIER, ODILE DUBOURG, THIERRY MAISONOBE, JEAN-LUC CHARUEL, ANTHONY BEHIN, SERGE HERSON, ZAHIR AMOURA, PHILIPPE GRENIER, and OLIVIER BENVENISTE

J Rheumatol 2012

- Follow-up: 4,5 years
  - No need of DMARD: 14 patients (29%)
  - Need of DMARD: 34 patients (71%)

- Predictive factors of DMARD need:
  - Mechanic's hands: p=0.02
  - high CK (6000 vs. 1000): p=0.002
  - NSIP score (7 vs. 4): p=0.04
  - TLV (57% vs. 70%): p=0.02



PID

Rheumatology 2007;46:124–130
Advance Access publication 4 June 2006
doi:10.1093/rheumatology/kel112

Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/ dermatomyositis

Y. Yamasaki[1], H. Yamada[1], M. Yamasaki[1], M. Ohkubo[1], K. Azuma[1], S. Matsuoka[2], Y. Kurihara[2], H. Osada[3], M. Satoh[4] and S. Ozaki[1]

17 patients, all under corticosteroids
Median follow-up: 32 mois
Good response: 70% !

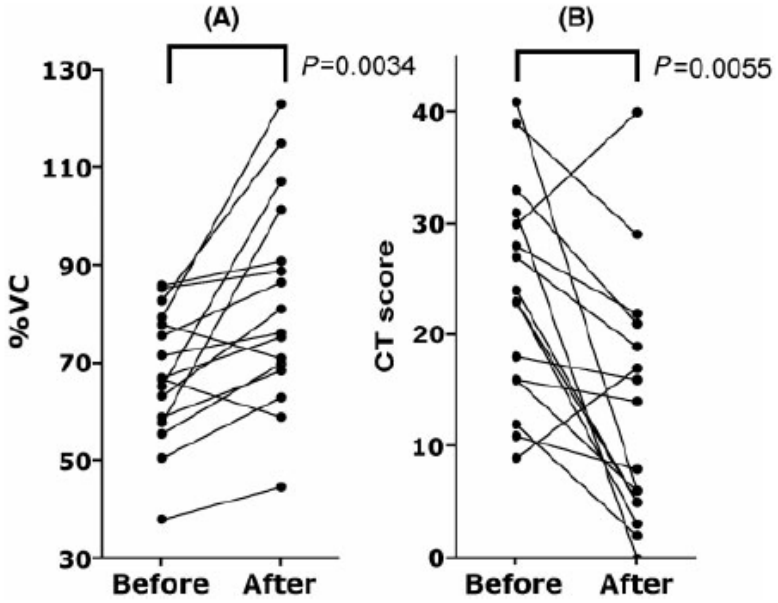


FIG. 1. Percent VC (A) and CT score (B) before and after IVCYC. The VC% improved significantly ($P=0.0034$ by Wilcoxon signed-rank test) after the IVCYC therapy. The CT score improved in 14/16 patients after the IVCYC therapy ($P=0.0055$ by Wilcoxon signed-rank test).

A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/ dermatomyositis

Respiratory Medicine 2013

Isabel C. Mira-Avendano [a,*], Joseph G. Parambil [a], Ruchi Yadav [b], Valeria Arrossi [c], Meng Xu [d], Jeffrey T. Chapman [e], Daniel A. Culver [a]

46 patients: 24 CYC, 13 AZA, 9 MMF

Equivalent efficacy

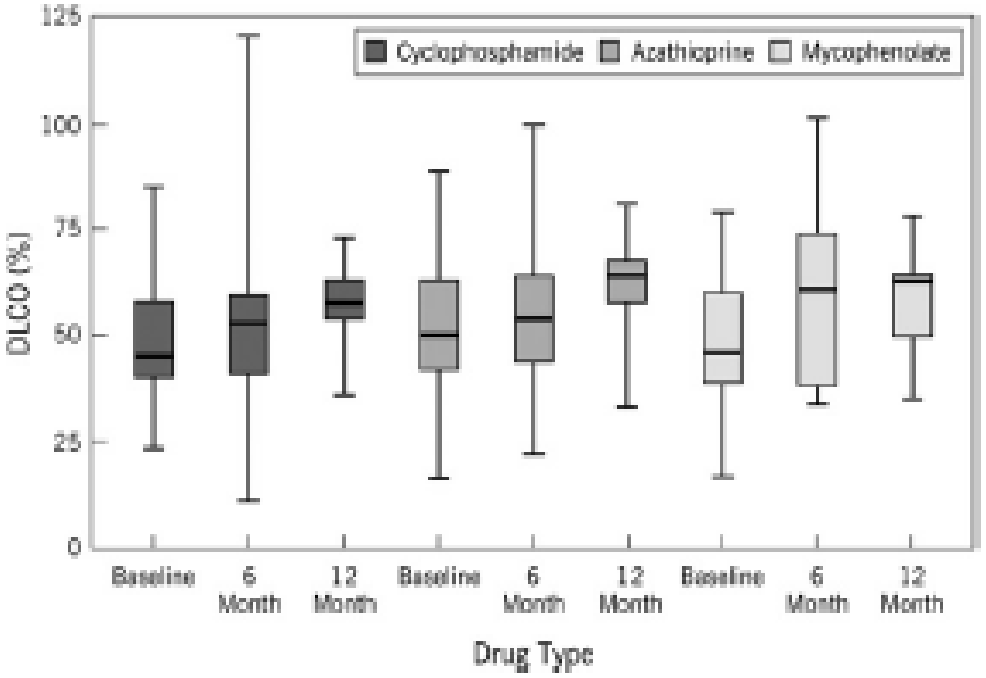


Figure 2 Percentage DLCO after 6 and 12 months of treatment.

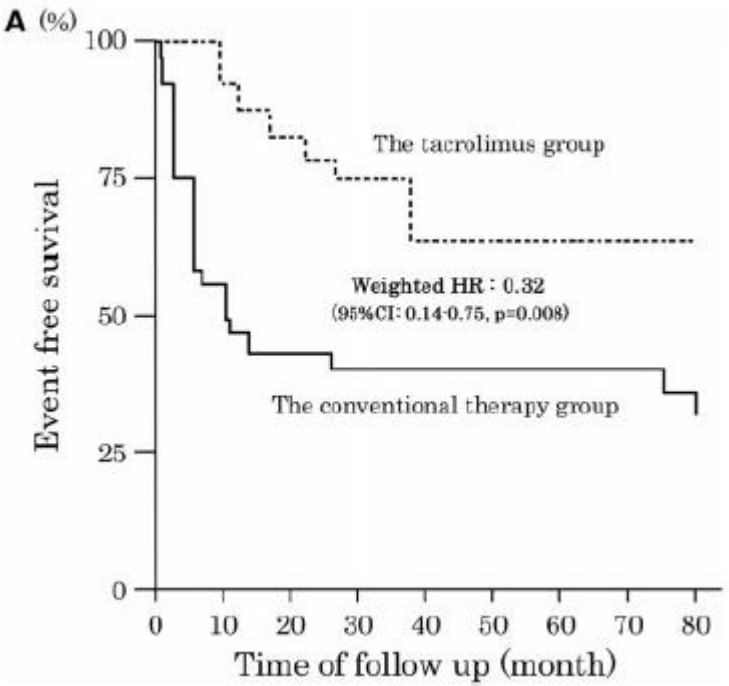
RHEUMATOLOGY

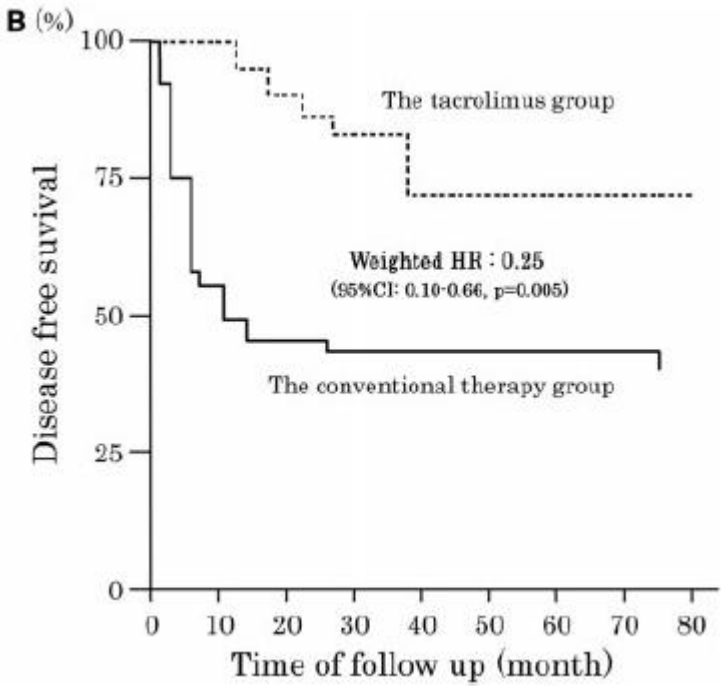
Rheumatology 2015;54:39–44
doi:10.1093/rheumatology/keu166
Advance Access publication 24 April 2014

Concise report

The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis

Takashi Kurita[1], Shinsuke Yasuda[1], Koji Oba[2], Toshio Odani[1], Michihito Kono[1],



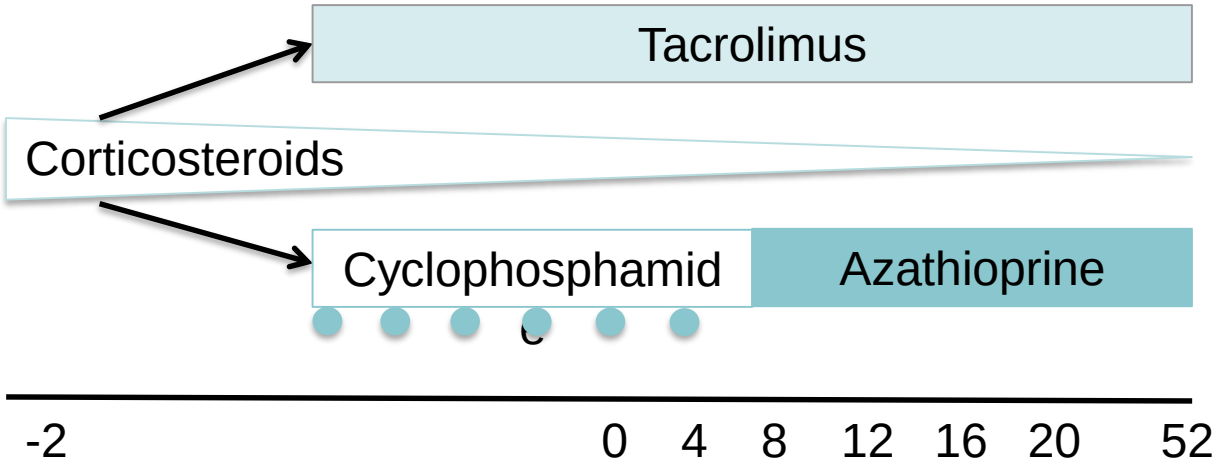


n=25
EDX: 9

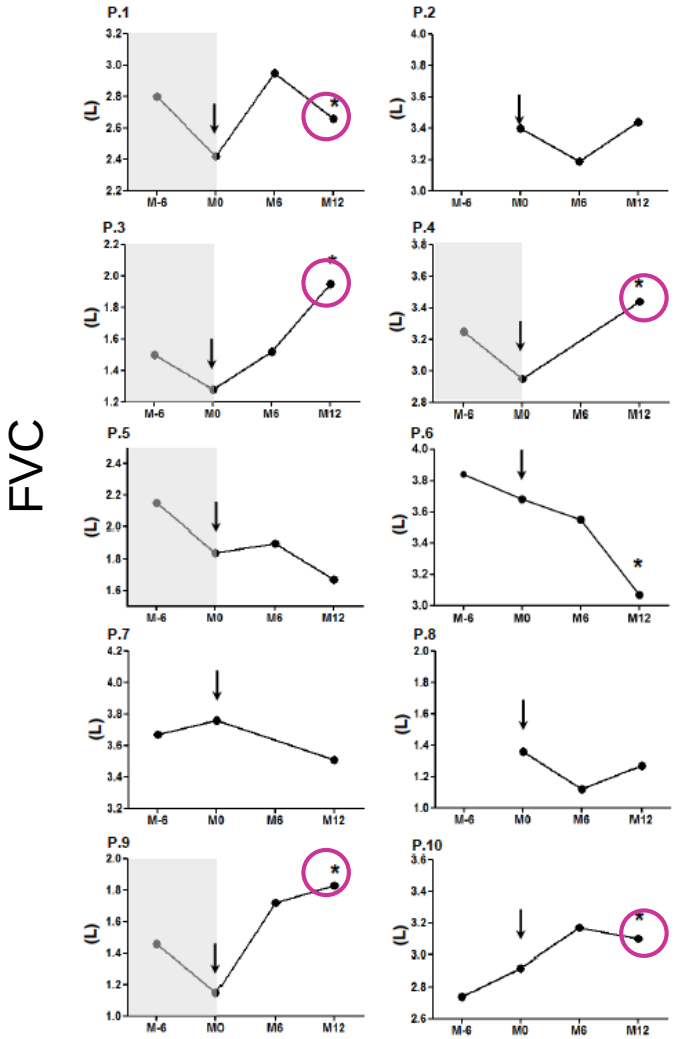
n=24
CSA: 7
EDX: 2

CATR.PAT Study, PHRC 2014

- Mars 2018
- PID avec un antisynthetase
- 88 patients



FORCE trial, Prospective IIb,
Y. Allenbach, PLoS One (2015)



10 refractory patients:

- In 50% significative improvement of the FVC...
- No clear improvement on CT scan or DLCO
- Very good tolerance

Anti-CD25

Basiliximab may improve the survival rate of rapidly progressive interstitial pneumonia in patients with clinically amyopathic dermatomyositis with anti-MDA5 antibody

Jing Zou,[1] Ting Li,[2] Xingfang Huang,[2] Sheng Chen,[2] Qiang Guo,[2] Chunde Bao[2]

[1]Department of Pneumology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China
[2]Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Letter, ARD 2014, n=4

En pratique traitement de la PID

ICU

1. Corticosteroids IV-oral
2. Cyclophosphamide
   Anticalcineurines
3. Plasma exchanges

Severe ILD

1. Corticosteroids IV-oral
2. Cyclophosphamide
   Anticalcineurines

Then: MMF or AZA

2nd line: anti-CD20

Non severe ILD

1. Corticosteroids oral
2. MMF, AZA or MTX

Vaccinations
Rehabilitation

The Myositis Association in France: GIMI

AFMTÉLÉTHON
INNOVER POUR GUERIR

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