# PID associées aux Myopathies Inflammatoires

*DU Cochin mai 2019*

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**A. Selon vous quelles affirmations concernant les PID associées aux MI sont exactes ?**

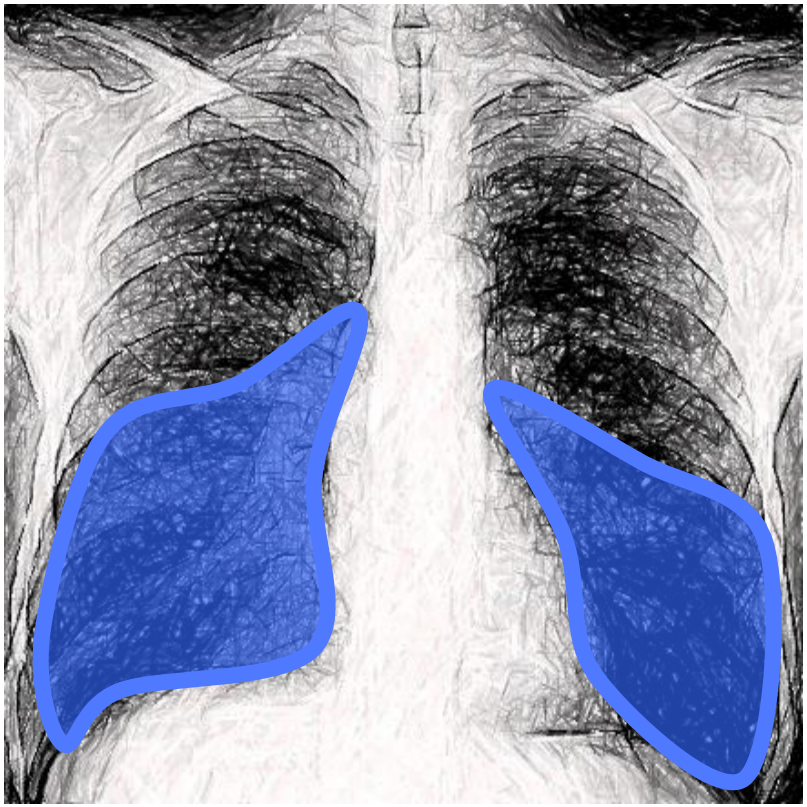
1. Il s'agit du principal facteur de morbi-mortalité
2. On les rencontre au cours de toutes les MI
3. La PIC est la forme la plus fréquente
4. Nécessite une confirmation histologique
5. La PID conditionne les traitements

**B. Vous recevez un patient déficitaire (myogène) et dyspnéique (PID). Parmi ceux-ci quels sont les éléments pronostiques péjoratifs ?**

1. Le type d'auto-Ab spécifique de la myosite
2. La rapidité de survenue de la PID
3. La mesure de la CV aux EFR
4. Le pattern radiologique
5. Hypertension pulmonaire

**C. Mr John P, présente une PID associée à une myosite de chevauchement, NYHA III, CV 55%, DLCO 51%. Votre traitement de choix est:**

1. Bolus corticoïdes puis oraux, en monothérapie
2. Corticothérapie et Immunosuppresseurs
3. Vaccinations à jour, PnC, HI, Grippe annuelle
4. Traitement préventif de la Pneumocyctose
5. Echanges plasmatiques, IV-Ig puis id 2.



**20-86% -> 2/3**

**Variabilité dépendante des modalités diagnostiques**

**-PID Infraclinique : 18% - 30%**

**-PID postérieure Myosite : 17%-39%**

*Fathi M. ARD 04*

*Marie I. AR 11*

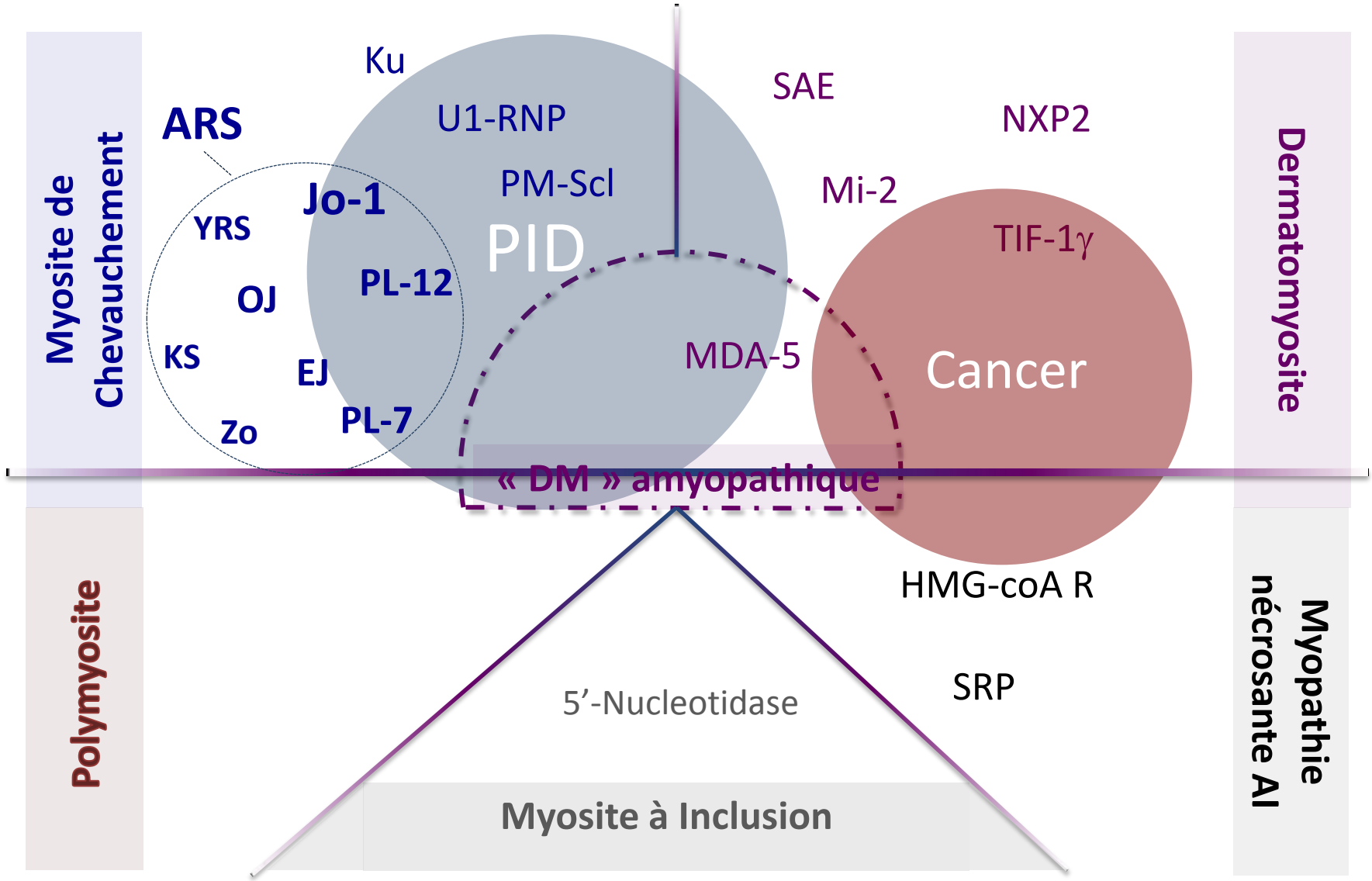
**Prévalence // avec certains AC ++**

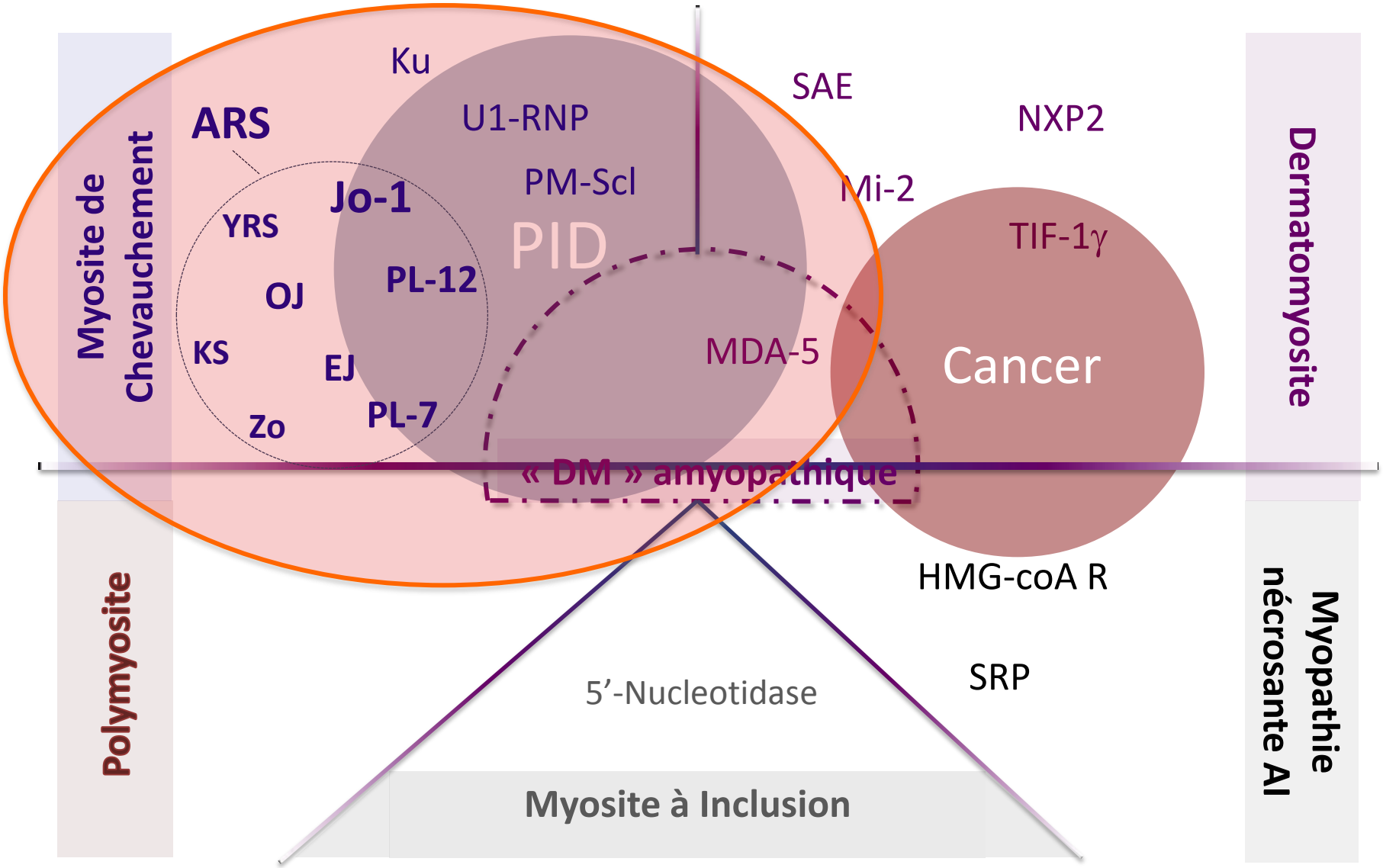
*Yoshida S. AR 83; Bernstein RM Br Med J 84*

*Hochberg MC J Rheum 84*

*Sato S, A&R 09; Nakashima, Rheum 2010*

# Pneumopathie Interstitielle Diffuse


Myosite de Chevauchement
Dermatomyosite
Polymyosite
Myopathie nécrosante AI
ARS
Jo-1
YRS
OJ
KS
EJ
Zo
PL-12
PL-7
Ku
U1-RNP
PM-Scl
PID
SAE
NXP2
Mi-2
TIF-1γ
MDA-5
Cancer
« DM » amyopathique
HMG-coA R
SRP
5'-Nucleotidase
Myosite à Inclusion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Cancer
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SRP
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Myosite à Inclusion

# Prévalence selon Ab

| Autoanticorps | | Prévalence | Références | *Remarques* |
|---|---|---|---|---|
| **SAS** | **Tous** | **77%** au diagnostic | Hervier B, Autoimmunity Rev 2012 | *83% dans le suivi* |
| | **SAS Jo-1** | **67%** | | |
| | **SAS non Jo-1** | **85%** | | |
| **MDA-5** | | **>90%** | Allenbach Y, Neurology (in revision) | |
| **Autres MSA** | | **10%** | | *rarement 1er plan* |
| **RNP*** | | **53%** | Szodoray P, Lupus 2012 | |
| **PM-Scl*** | | **15-25%** | D'aoust A&R 2014; De Lorenzo Neurology 2018 | |
| **Ku*** | | **35%** | Rigolet A, Medicine 2012 | |

** Toutes formes (pas limité à celles avec atteinte musculaire)*

# Un peu de Physiopathologie

**Anti-MDA-5**

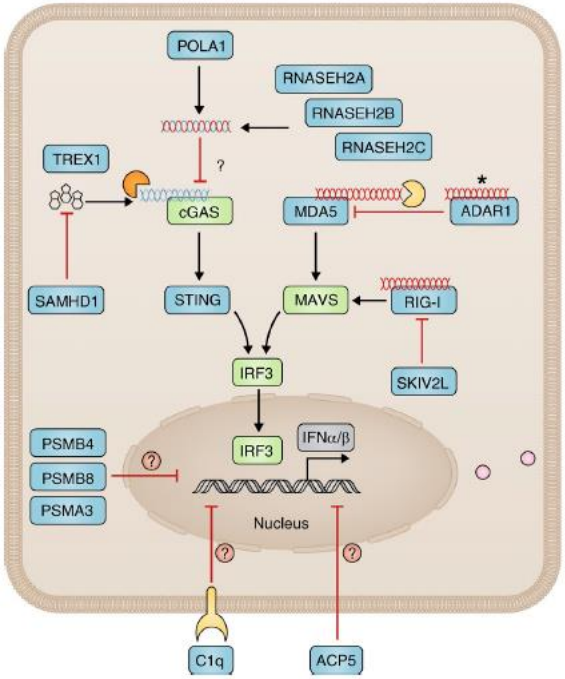
# Un peu de Physiopathologie

## Type I interferon–mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview

Mathieu P. Rodero[1] and Yanick J. Crow[1,2,3]

[1]INSERM UMR 1163, Laboratory of Neurogenetics and Neuroinflammation, 75015 Paris, France
[2]Paris Descartes University, Sorbonne-Paris-Cité, Institut Imagine, Hôpital Necker, 75015 Paris, France
[3]Faculty of Biology, Medicine, and Health, Division of Evolution and Genomic Sciences, School of Biological Sciences, University of Manchester, Manchester M13 9NT, England, UK

JEM 2016




**IFNα**
Allenbach Y, Am J Path 16

# Un peu de Physiopathologie

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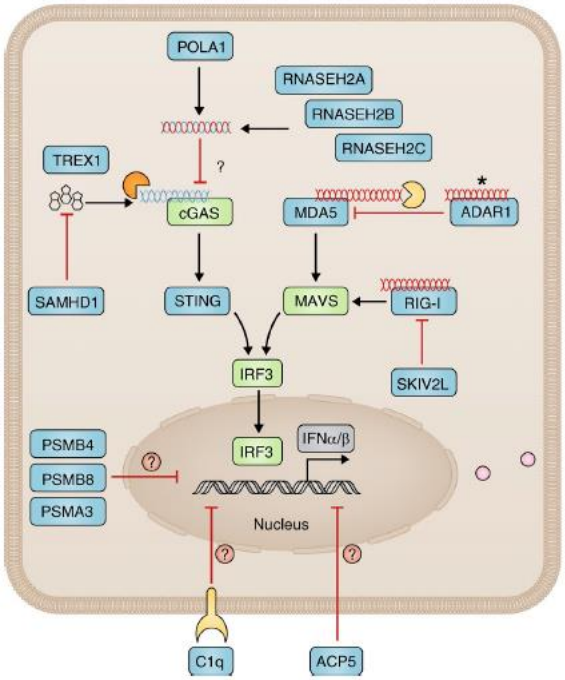
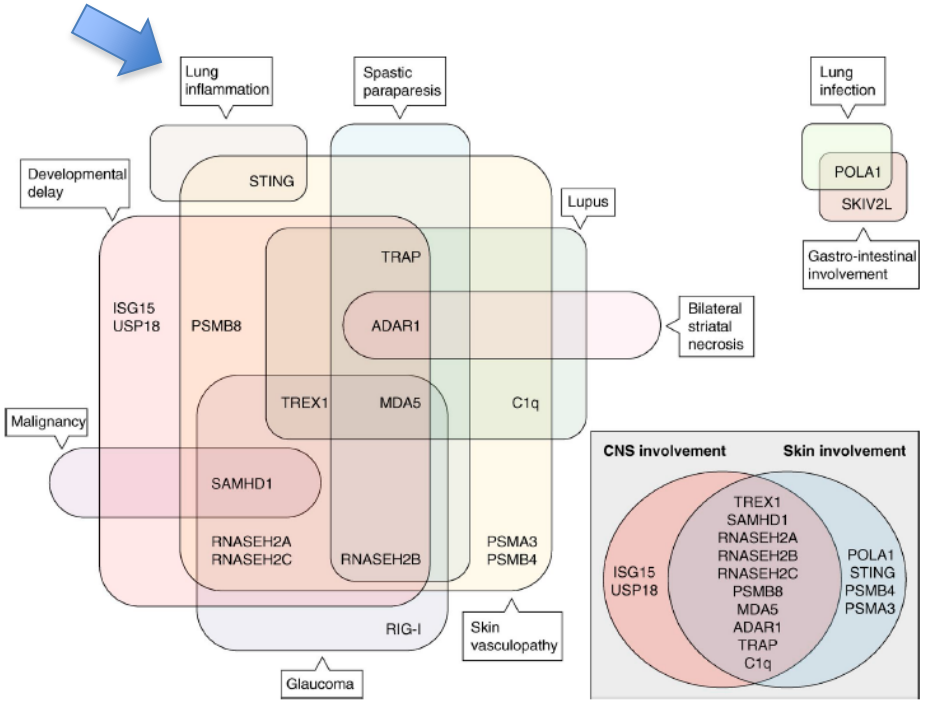
JEM 2016



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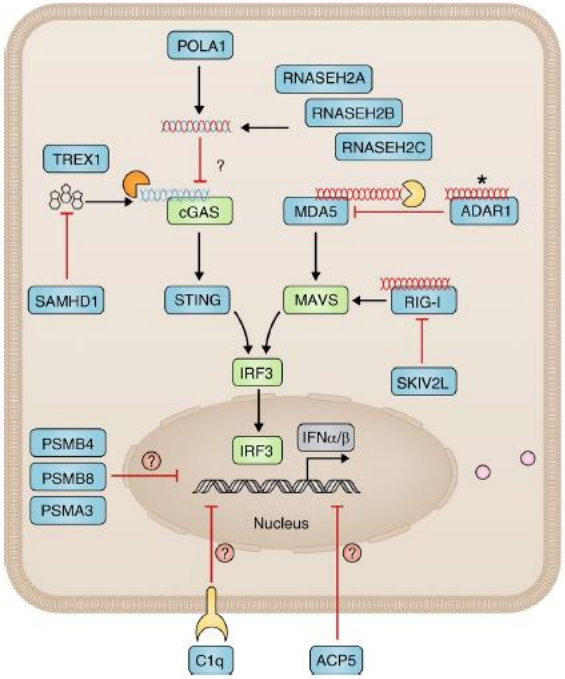



**IFNα**
Allenbach Y, Am J Path 16

Et après …
Rôle pathogènes des Ab ??
Macrophage alvéolaire ????

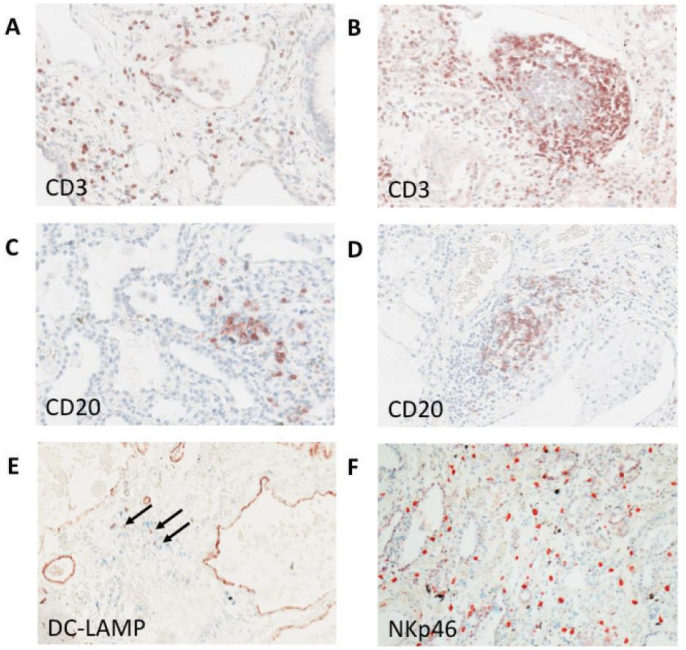
# Poumon SAS : Site Initiateur

Analogies avec PR*

Tabac-HLA *Chinoy H, ARD 12*

Poussières (WTC) *Webber MP, Mayo Clin Proc 14*

Structures lymphoïdes tertiaires *Malmström V, NRI 17*




*Gayed C, CRI 19*

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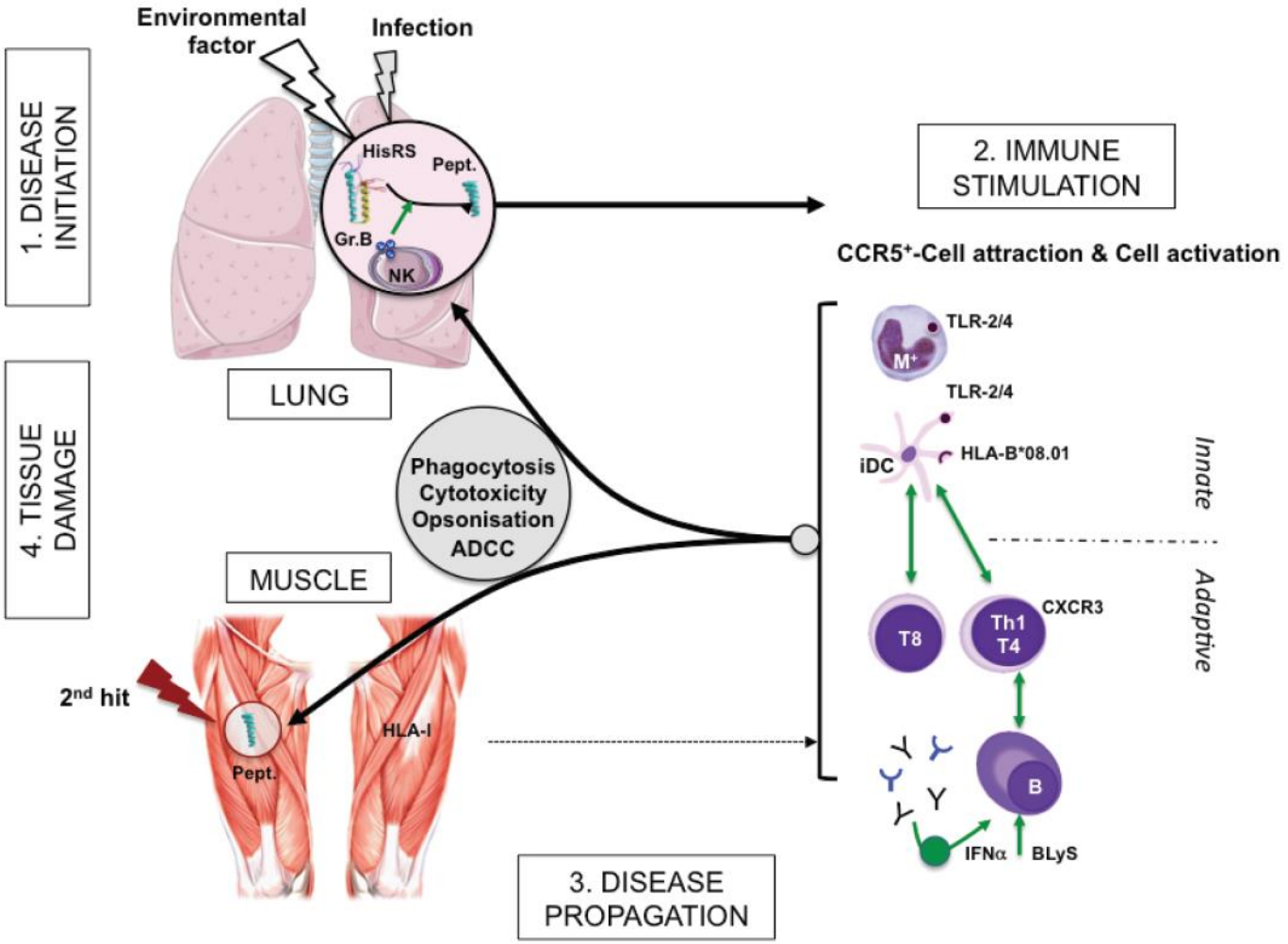
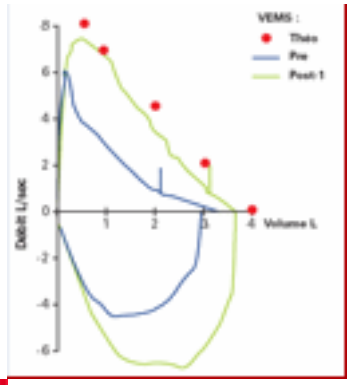



*Gayed C, CRI 19*

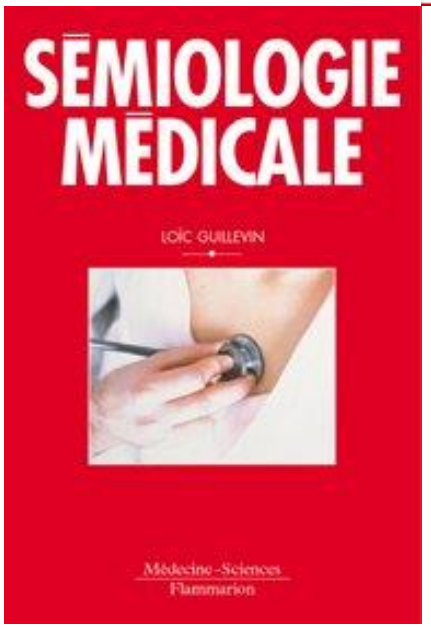
# Diagnostic, Evaluation

- Découverte fortuite (TDM/ EFR)

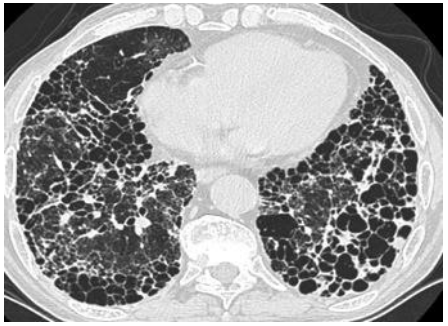
  Asymptomatique/Retardée




  - Fièvre (Aigües)
  - Dyspnée graduelle
  - Toux sèche
  - Crépitants

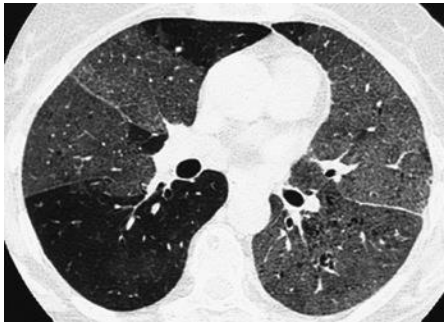


PIC



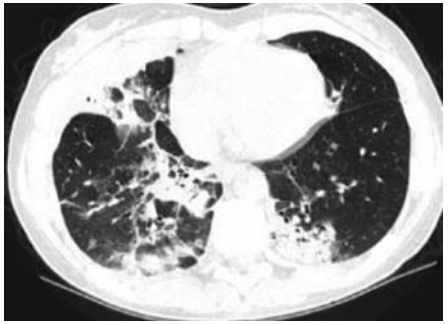
Rayon de Miel

PINS



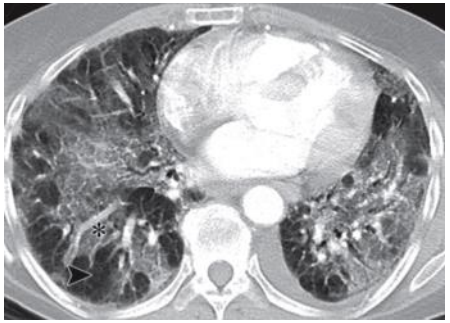
Verre dépoli
Opacités linéaires

PO



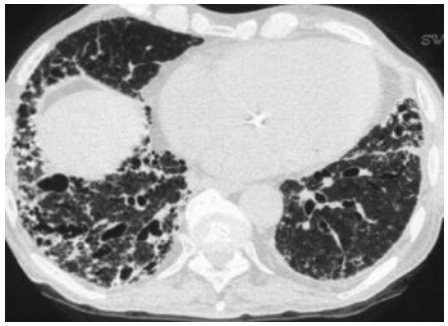
**Condensations Alvéolaires**

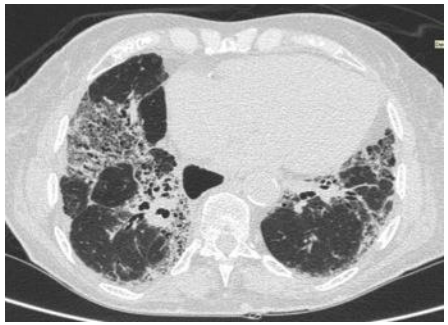
DAD



Associations étendues :
Condensations
+ Réticulations
+ V. dépoli

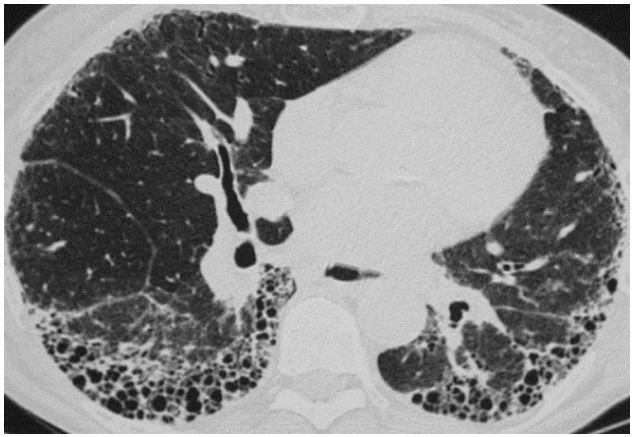
Bronchectasies par traction

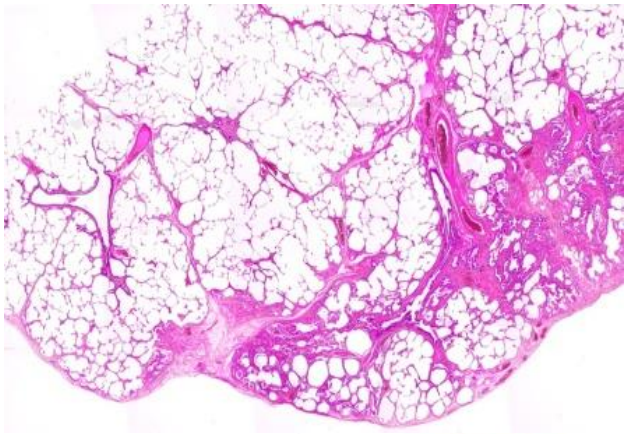




Opacités réticulaires

PIC





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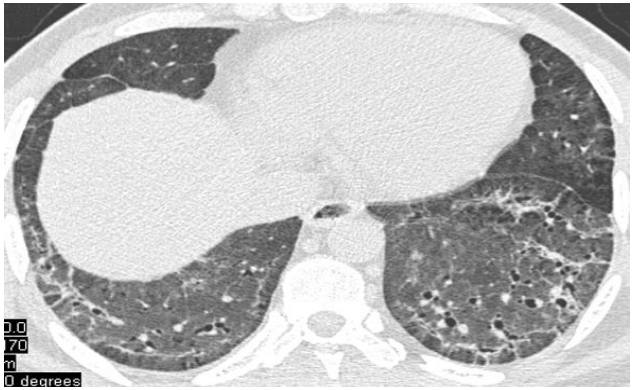
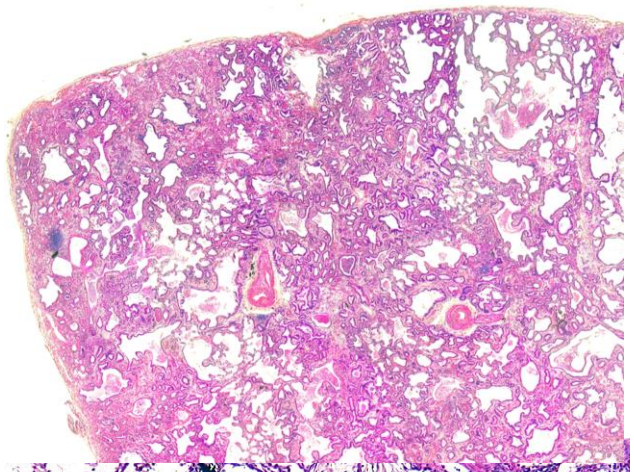
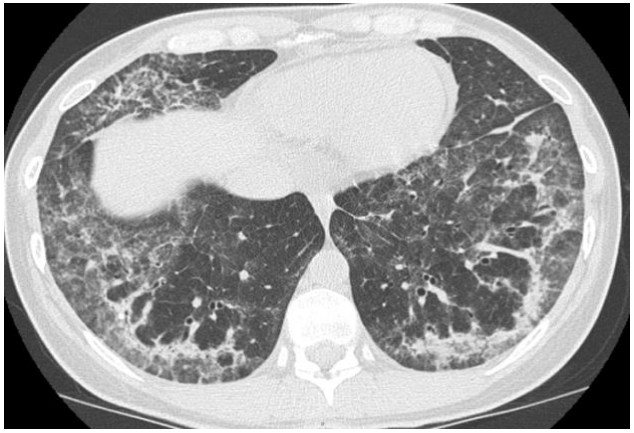


PO



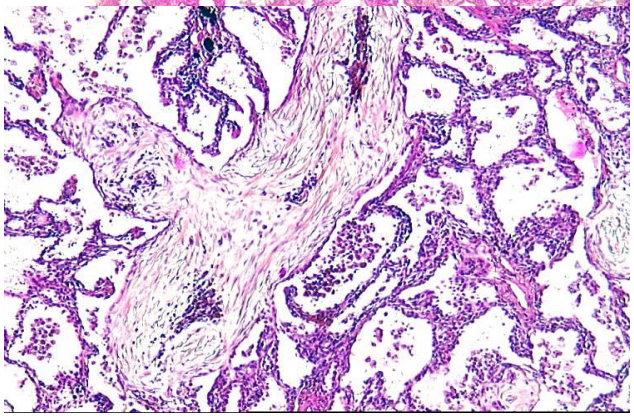


**Tableau S15-P01-C03-II** Données de la tomographie thoracique haute résolution au cours du syndrome des antisynthétases (SAS).

| Type d'atteinte interstitielle | Lésions pulmonaires | Fréquence au cours du syndrome des antisynthétases (%) |
|---|---|---|
| Pneumopathie interstitielle non Sspécifique (PINS) | Verre dépoli | > 45 |
| Pneumonie organisée (PO) | Condensation alvéolaire | 20 |
| PINS-PO | Association condensation et verre dépoli | 25 |
| Pneumopathie interstitielle commune (PIC) | Rayon de miel | 10 |
| Dommage alvéolaire diffus (DAD) | Association étendue des différentes lésions | < 5 |
| Adénopathies (minimes) | | 30 |
| Signes évocateurs de fibrose | Réticulations, Bronchectasies par traction | > 75 |

Hervier B, TDM 5e éd. 2019
*D'après* Debray MP, Eur J radiol 15

# Fréquence

| Pattern Histologique | Yousem et al. 2010 N=20 | Marie et al. 2013 N=22 | Obert et al. 2013 N=14 |
|---|---|---|---|
| Pneumopathie Organisée | 5% | 27% | 21% |
| PINS-OP | - | - | 14% |
| PINS | 20% | 50% | 50% |
| PIC | 50% | 23% | 0 |
| DAD | 25% | - | - |
| Autre | - | - | 14% |

13 BPC
3 Explants
4 Autopsies

Yousem et al. *Mod Pathol.* 2010
Marie et al. *Arthritis Care and Res.* 2013
Obert et al. *ERS* 2013

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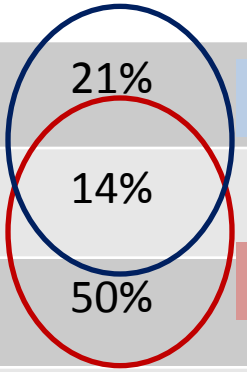



13 BPC
3 Explants
4 Autopsies

Yousem et al. *Mod Pathol.* 2010
Marie et al. *Arthritis Care and Res.* 2013
Obert et al. *ERS* 2013

# Facteurs pronostiques ?

Mode de Survenue

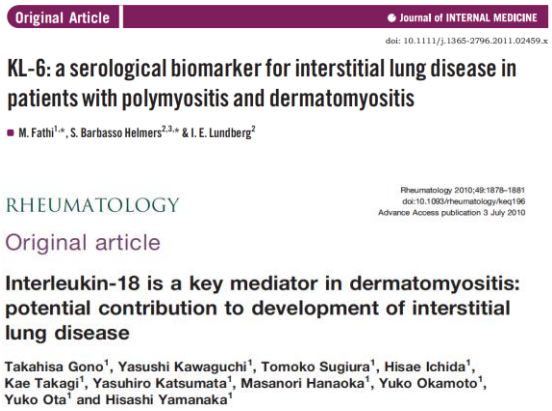
Autoanticorps spécifiques

PID elle-même (EFR, Pattern)

Pinal-Fernandez *et al*, *Rheumatology* 2017

Ethnie

Ferritine, KL-6, IL-18



Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2011.02459.x

KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis

M. Fathi[1,*], S. Barbasso Helmers[2,3,*] & I. E. Lundberg[2]

RHEUMATOLOGY

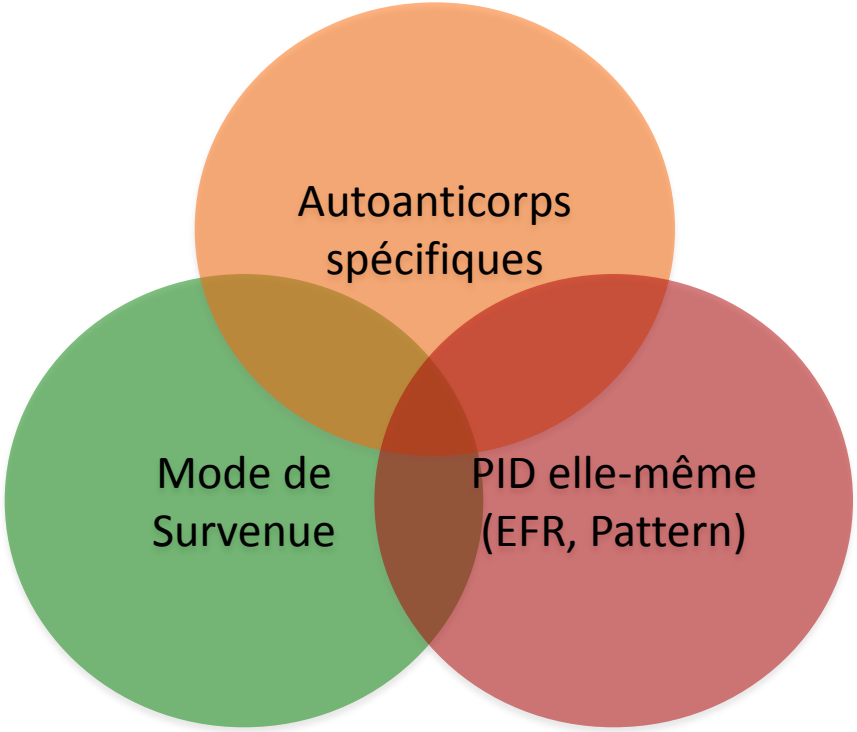
Rheumatology 2010;49:1878–1881
doi:10.1093/rheumatology/keq196
Advance Access publication 3 July 2010

Original article

Interleukin-18 is a key mediator in dermatomyositis: potential contribution to development of interstitial lung disease

Takahisa Gono[1], Yasushi Kawaguchi[1], Tomoko Sugiura[1], Hisae Ichida[1], Kae Takagi[1], Yasuhiro Katsumata[1], Masanori Hanaoka[1], Yuko Okamoto[1], Yuko Ota[1] and Hisashi Yamanaka[1]

# Facteurs pronostiques ?



RHEUMATOLOGY

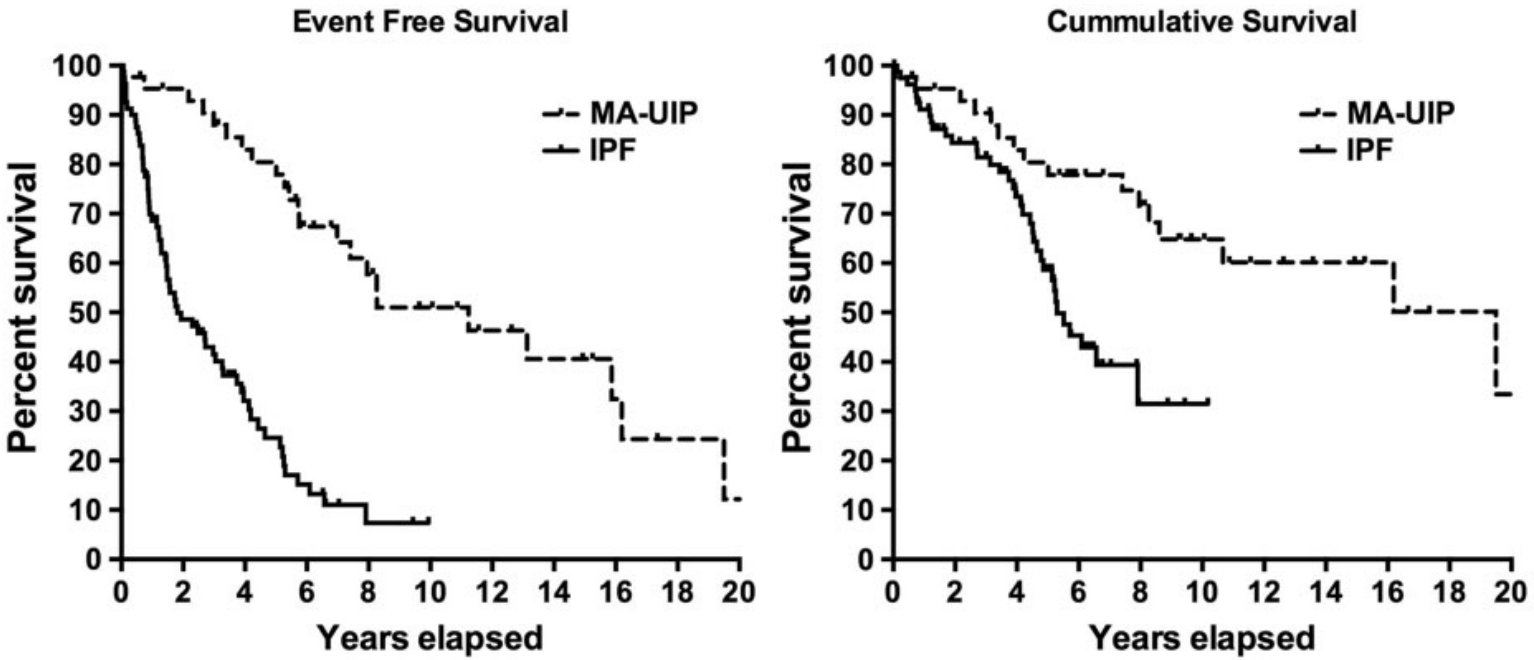
Rheumatology 2017;56:384–389
doi:10.1093/rheumatology/kew426
Advance Access publication 12 December 2016

Original article

# Myositis-associated usual interstitial pneumonia has a better survival than idiopathic pulmonary fibrosis

**Rohit Aggarwal[1], Christine McBurney[1], Frank Schneider[2], Samuel A. Yousem[2], Kevin F. Gibson[3], Kathleen Lindell[3], Carl R. Fuhrman[4] and Chester V. Oddis[1]**

| Clinical features | MA-UIP (n = 43) | IPF-UIP (n = 81) | P-value |
|---|---|---|---|
| Age at ILD diagnosis, mean (S.D.), years | 46 (11.0) | 63 (8.4) | <0.001 |
| Gender, male, % | 35 | 73 | <0.001 |
| Caucasian, % | 83 | 98 | 0.004 |
| Baseline FVC%, mean (S.D.) | 60 (19.6) | 65 (15.3) | 0.11 |
| Baseline DLCO%, mean (S.D.) | 47 (18.3) | 47 (17.3) | 1.0 |
| Death, n (%) | 16 (37) | 36 (44) | 0.43 |
| Age at death, mean (S.D.), years | 54 (11.7) | 68 (7.5) | <0.001 |
| Transplant, n (%) | 10 (23) | 45 (56) | 0.001 |
| Age of transplant, mean (S.D.), years | 54 (6.4) | 64 (8.8) | <0.001 |
| Pulmonary event (death or transplant), n (%) | 23 (53.5) | 63 (77.8) | 0.005 |
| Tobacco use (current or past), n (%) | 16 (40)[a] | 56 (69.1) | 0.002 |




IPF: idiopathic pulmonary fibrosis; MA-UIP: myositis-associated usual interstitial pneumonia; Event: Death or Lung Transplant.

# Aigu/Subaigu *vs.* Progressif

## Prognostic Factors for Myositis-Associated Interstitial Lung Disease

2014

**Tomoyuki Fujisawa[1]*, Hironao Hozumi[1], Masato Kono[1], Noriyuki Enomoto[1], Dai Hashimoto[1], Yutaro Nakamura[1], Naoki Inui[2], Koshi Yokomura[3], Naoki Koshimizu[4], Mikio Toyoshima[5], Toshihiro Shirai[6], Kazumasa Yasuda[7], Hiroshi Hayakawa[8], Takafumi Suda[1]**

**1** Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan, **2** Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan, **3** Department of Respiratory Medicine, Seirei Mikatahara General Hospital, Hamamatsu, Japan, **4** Department of Respiratory Medicine, Fujieda Municipal General Hospital, Fujieda, Japan, **5** Department of Respiratory Medicine, Hamamatsu Rosai Hospital, Hamamatsu, Japan, **6** Department of Respiratory Medicine, Shizuoka General Hospital, Shizuoka, Japan, **7** Department of Respiratory Medicine, Iwata City Hospital, Iwata, Japan, **8** Department of Respiratory Medicine, Tenryu Hospital, National Hospital Organization, Hamamatsu, Japan

114 PM/DM/CADM

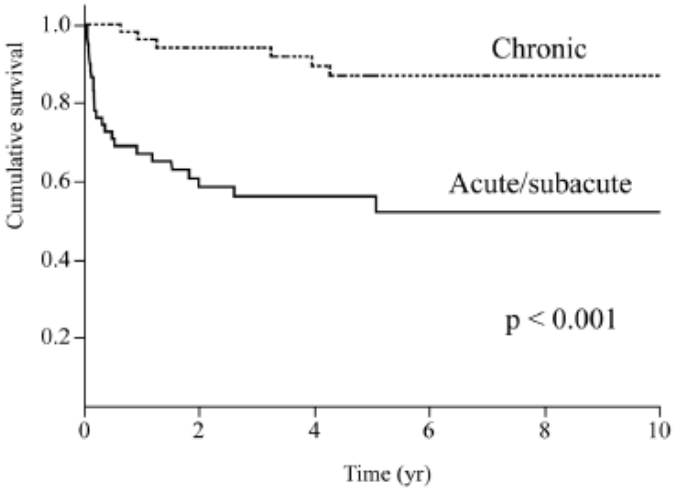



**Figure 1. Survival curves for the acute/subacute and chronic forms of ILD in patients with PM/DM/CADM.** Patients with the acute/subacute form have a significantly lower survival rate than those with the chronic form (log-rank, $p<0.0001$).
doi:10.1371/journal.pone.0098824.g001

# Aigu/Subaigu *vs.* Progressif

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**Tomoyuki Fujisawa[1]*, Hironao Hozumi[1], Masato Kono[1], Noriyuki Enomoto[1], Dai Hashimoto[1], Yutaro Nakamura[1], Naoki Inui[2], Koshi Yokomura[3], Naoki Koshimizu[4], Mikio Toyoshima[5], Toshihiro Shirai[6], Kazumasa Yasuda[7], Hiroshi Hayakawa[8], Takafumi Suda[1]**

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114 PM/DM/CADM

**RP-ILD**
**Séries Françaises: MDA-5 1/3; SAS 1/6**

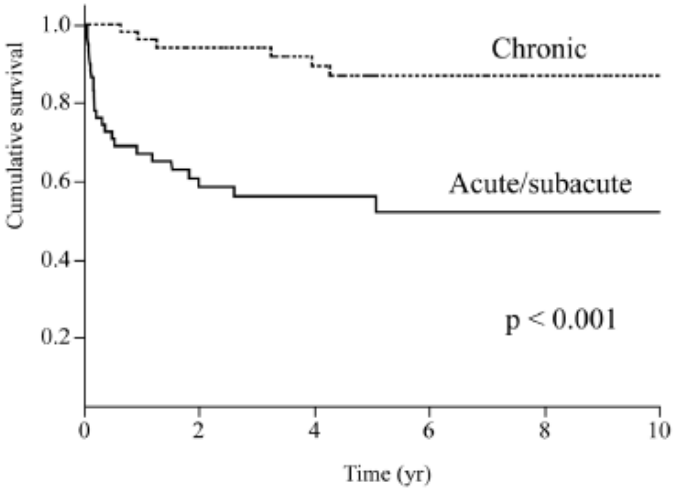
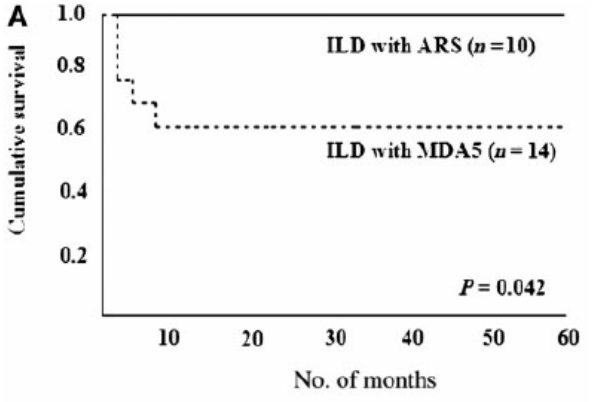



**Figure 1. Survival curves for the acute/subacute and chronic forms of ILD in patients with PM/DM/CADM.** Patients with the acute/subacute form have a significantly lower survival rate than those with the chronic form (log-rank, $p<0.0001$).
doi:10.1371/journal.pone.0098824.g001

# Anticorps anti-MDA5

FIG. 2 The cumulative 60-month survival rates in each group (**A**), the <500 and ⩾500 ng/ml serum ferritin subsets of ILD with anti-MDA5 antibody (**B**), and the <1600 and ⩾1600 ng/ml serum ferritin subsets of ILD with anti-MDA5 antibody (**C**). The 60-month cumulative survival rates were calculated using the Kaplan–Meier test. The log-rank test was also used to compare survival rates.




*Gono T, Rheumatol 10*

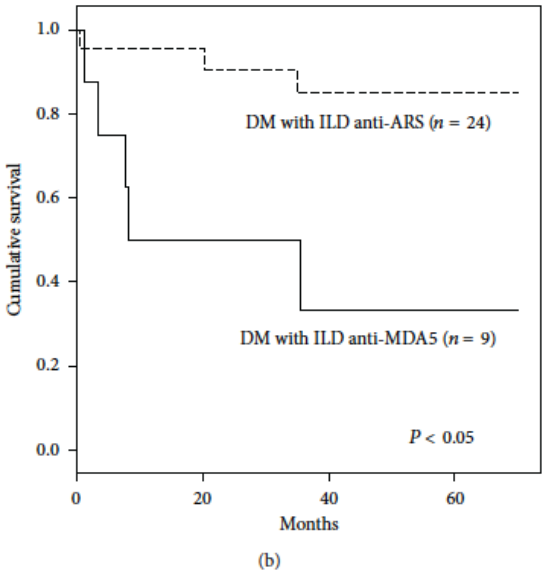


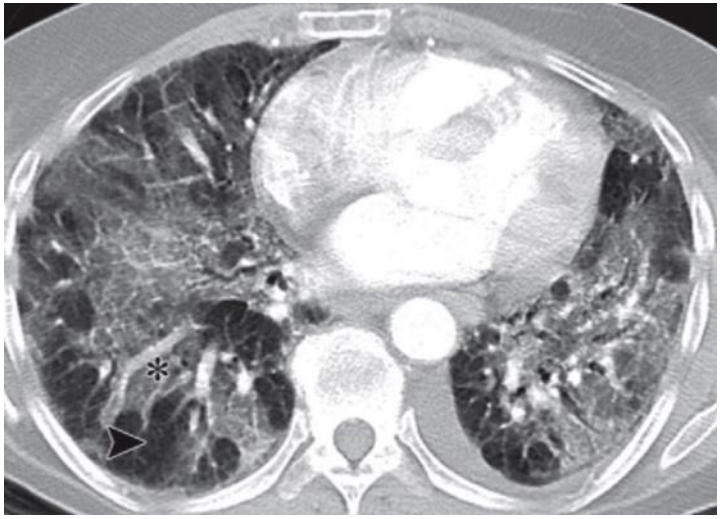

FIGURE 3: Cumulative 70-month survival rates for DM patients with and without anti-MDA5 antibody (a) and for DM patients with ILD associated with anti-ARS or anti-MDA5 (b). The 70-month cumulative survival rates were calculated using the Kaplan-Meier test. The log-rank test was also used to compare survival rates. ARS: aminoacyl-tRNA synthetase; DM: dermatomyositis; ILD: interstitial lung disease.

*Labrador-Horillo M, JIR 14*

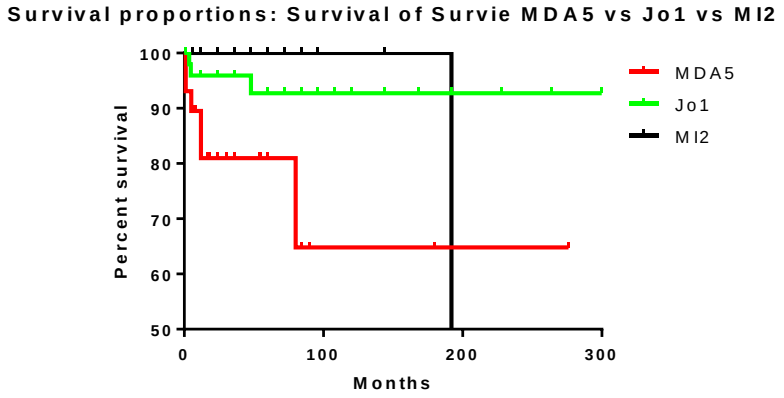
# Avec anticorps anti-MDA5

(anti-CADM-140) *melanoma differenciation-associated gene 5*

**PID AIGUE: 57% - 79% et sévère (DAD): 29%**



*Hoshino K, Rheumatology 10;*
*Labrador-Horillo M, J Imm Res, 14;*
*Hamaguchi Y. Arch Dermatol 11.*



# Syndrome des antisynthétases



## Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset

I Tillie-Leblond,[1,8] M Wislez,[1] D Valeyre,[2] B Crestani,[3] A Rabbat,[4] D Israel-Biet,[5] M Humbert,[6] L J Couderc,[7] B Wallaert,[8] J Cadranel[1]

Thorax 2008;63:53-9

**AIGUE**

Fièvre

\+ Sévère (*Dyspnée NYHA, EFR*)

Insuffisance respi: 47%

Myosite + rare (31%)

Association AC impossible

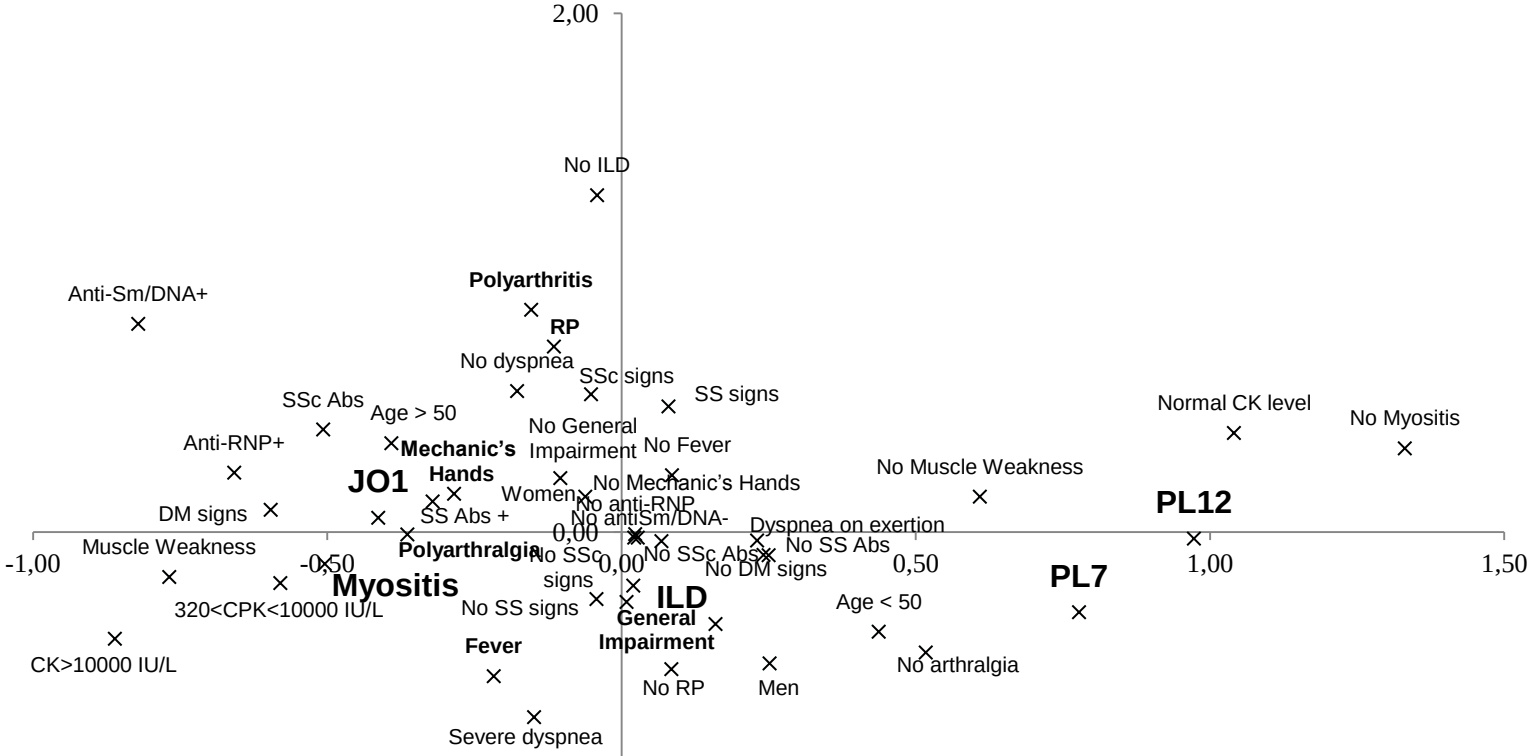
Amélioration initiale

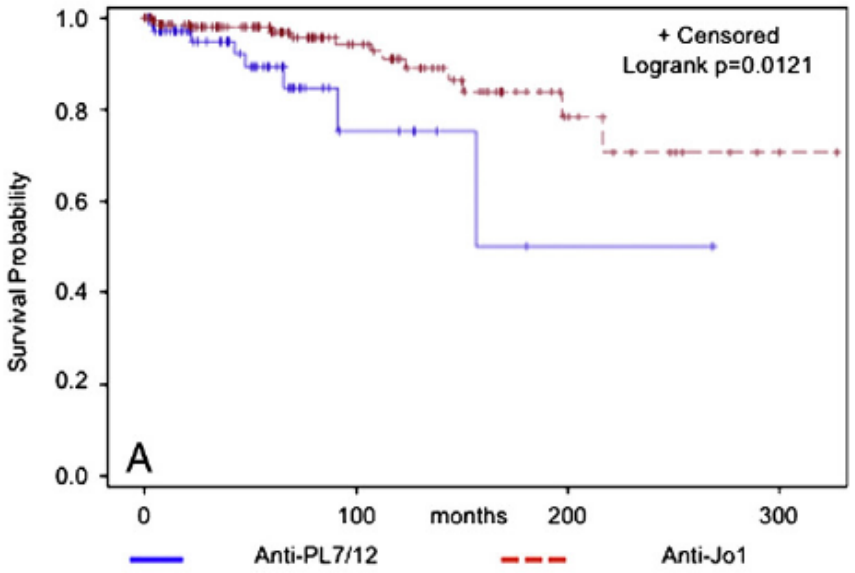
MAIS

Progression/Décès > à 1 an:

38% *vs.* 12% ($p$<0,05)

Tillie-Leblond I, Thx 2008;63:53-9




PL7-PL12 < Jo-1

*Hervier B, Autoimmunity Rev 12*

# Autres Facteurs pronostiques (*f. chroniques*) ?

**Pattern TDM: PIC**

-corrélé à la progression PID

*Marie I. Arthr Care R. 12*

-non corrélé à la mortalité

*Hervier B. Autoimmunity Rev 12*

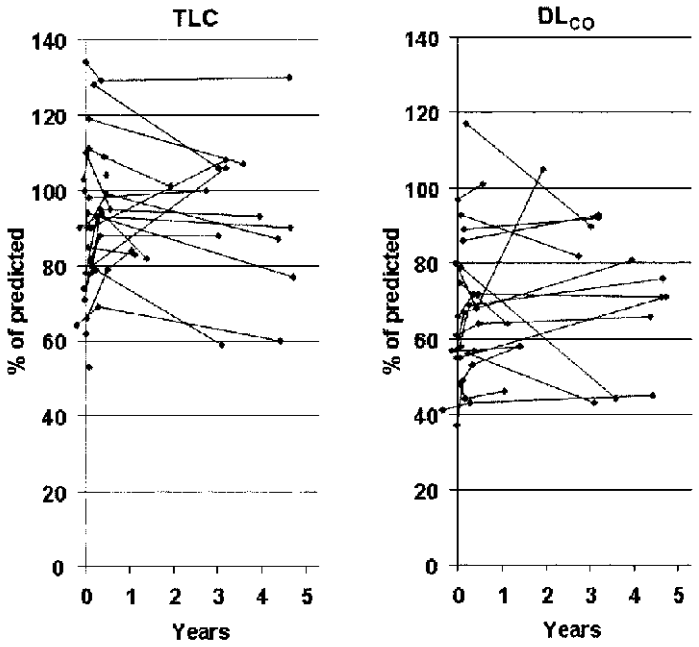
**Extension TDM ?**

-A la différence SSc

*Goh NS, AJRCCM 08*

-PINS corrélé aux modifications de traitement

*Stanciu R. J Rheum 12*




**EFR: Travaux rétrospectifs contradictoires**

**1 seul travail prospectif (**23 p**)**

*« L'évolution de la PID ne peut être prédite au Diagnostic ! Muscle ++ ? »*

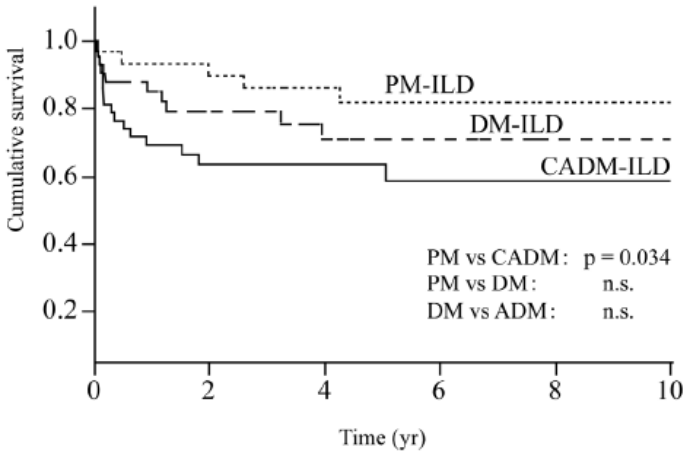
*Fathi M. Arthr Care Res 08*

**Formes progressives :**

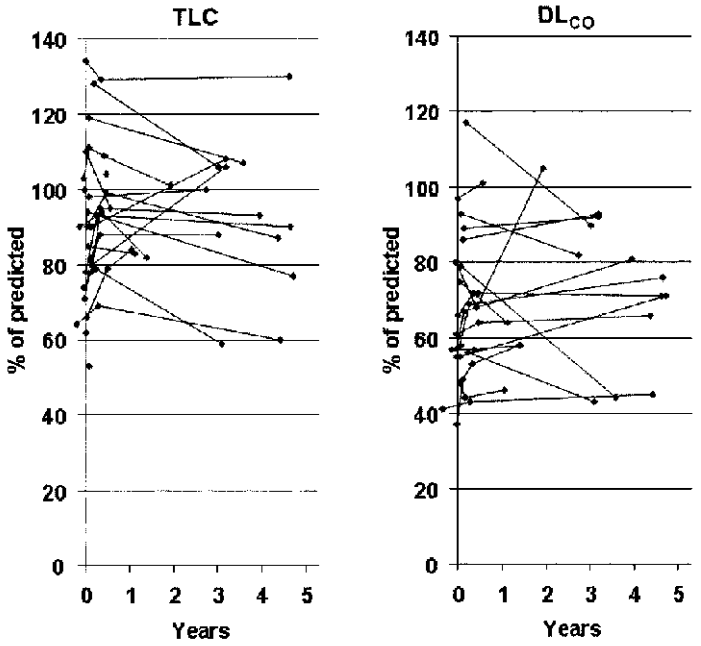
Cinétique > 1e Exploration

# Autres Facteurs pronostiques (*f. chroniques*) ?

N=114 (30 PM, 41 DM, 43 CADM)




Fujisawa et al. *Plos One* 2014




**EFR: Travaux rétrospectifs contradictoires**

**1 seul travail prospectif (**23 p**)**

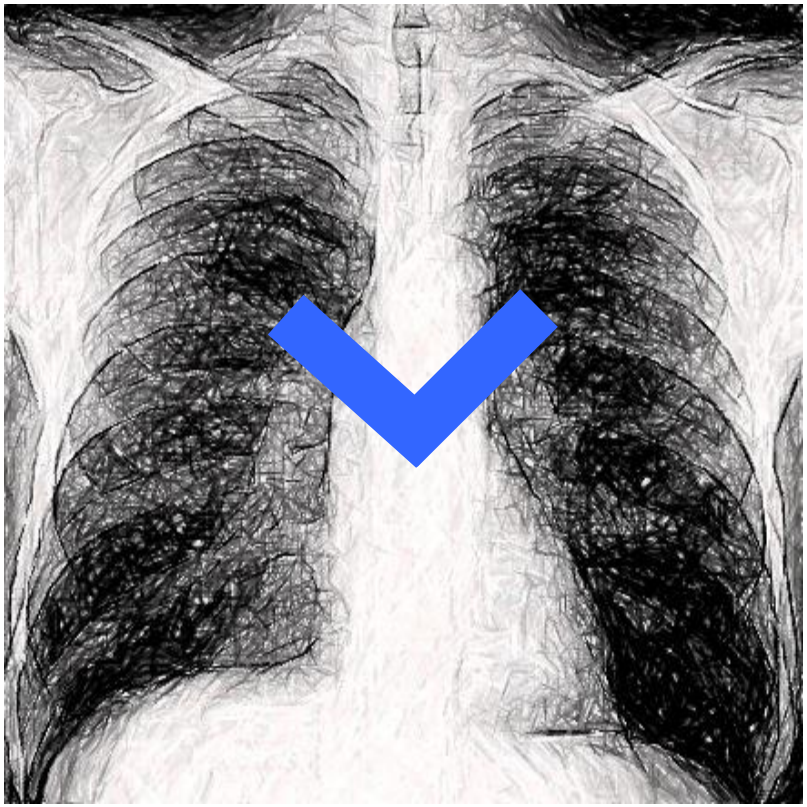
*« L'évolution de la PID ne peut être prédite au Diagnostic ! Muscle ++ ? »*

*Fathi M. Arthr Care Res 08*

**Formes progressives :**

Cinétique > 1e Exploration

# Complications PID associée aux MI



**Complication tardive**

*vs* PAH (Gpe 1) des MCTD

**8% au cours SAS, Tardif**

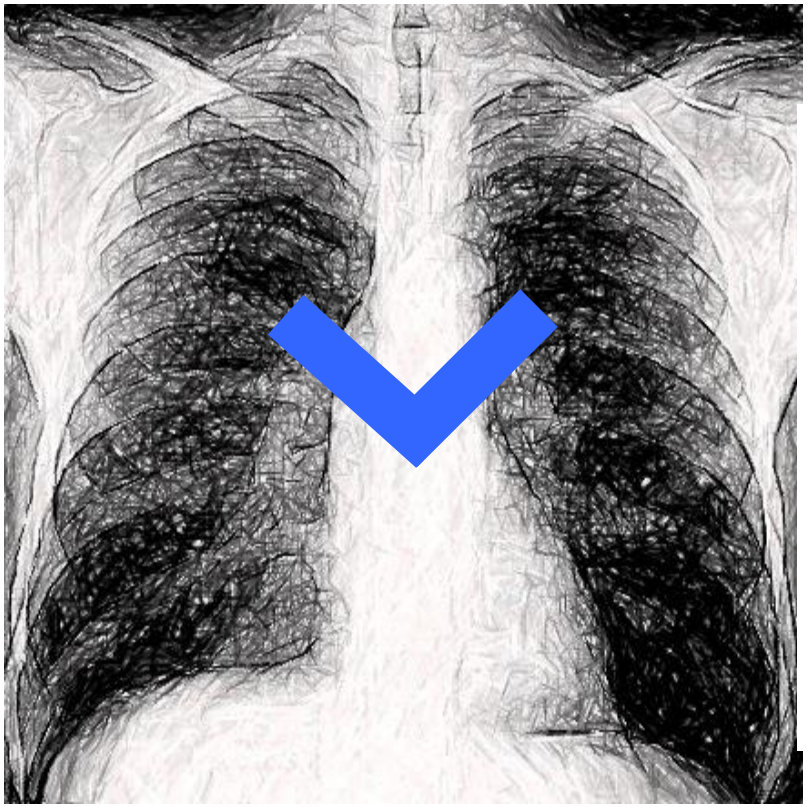
*Hervier B. Eur Respir J 14*

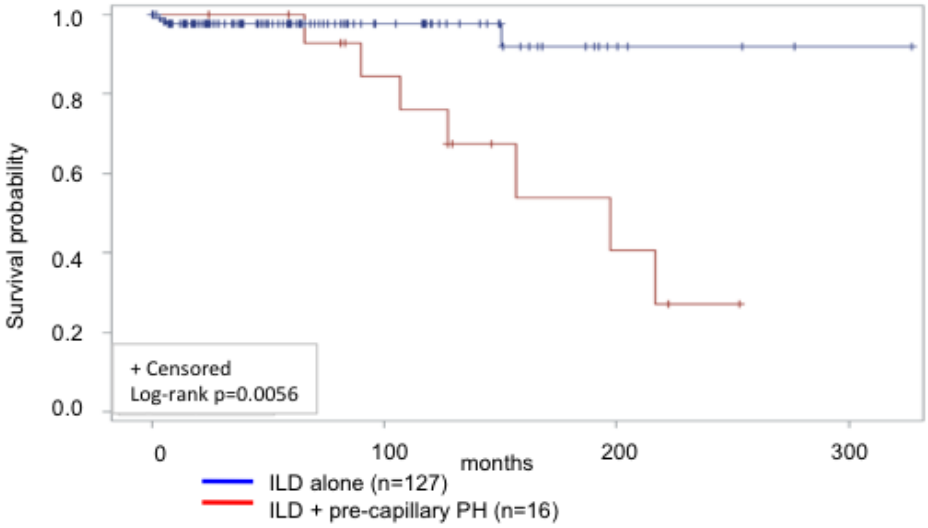
**PH-ILD (Gpe 3)** Sévère ->
Facteur vasculaire ?

**Pas de traitement recommandé**
**Mortalité +++**

**ETT KT**

# Hypertension Pulmonaire






*Hervier B. ERJ 14*

# Hypertension Pulmonaire

**Etude histo-clinique**
**(12 explants)**
Pr D. Montani, KB, APHP

# Observation, Thanks to Dr Y. Uzunhan, Avicenne, APHP

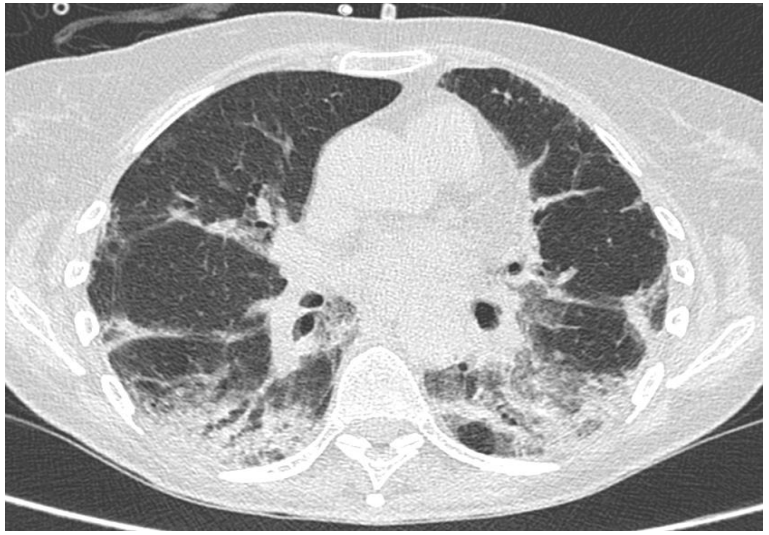
Femme, 63 ans, sans Tabac

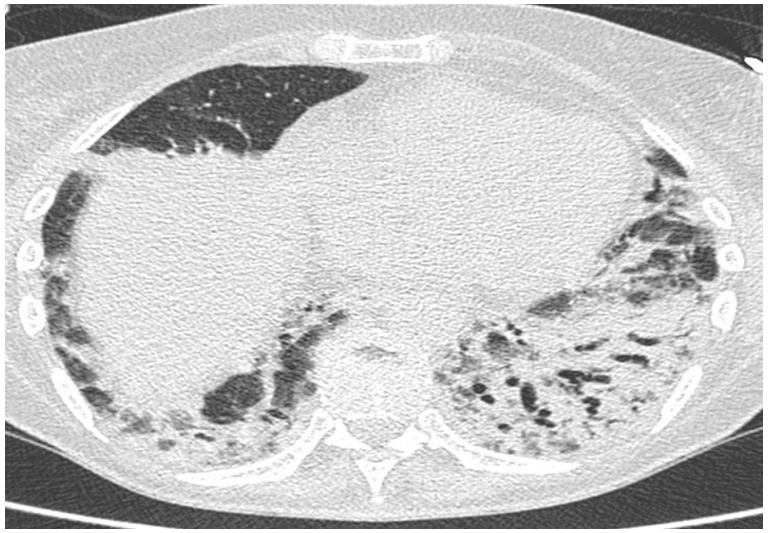
Lésions cutanées mains
Arthralgies
Dyspnée d'effort d'installation subaigue
Myalgies +
Fièvre 38° C

DLCO 57 % CVF 65 %
GDS AA 67mmHg / 38mmHg
**TDM**

CRP 70mg/L
CPK 210, EMG Normal

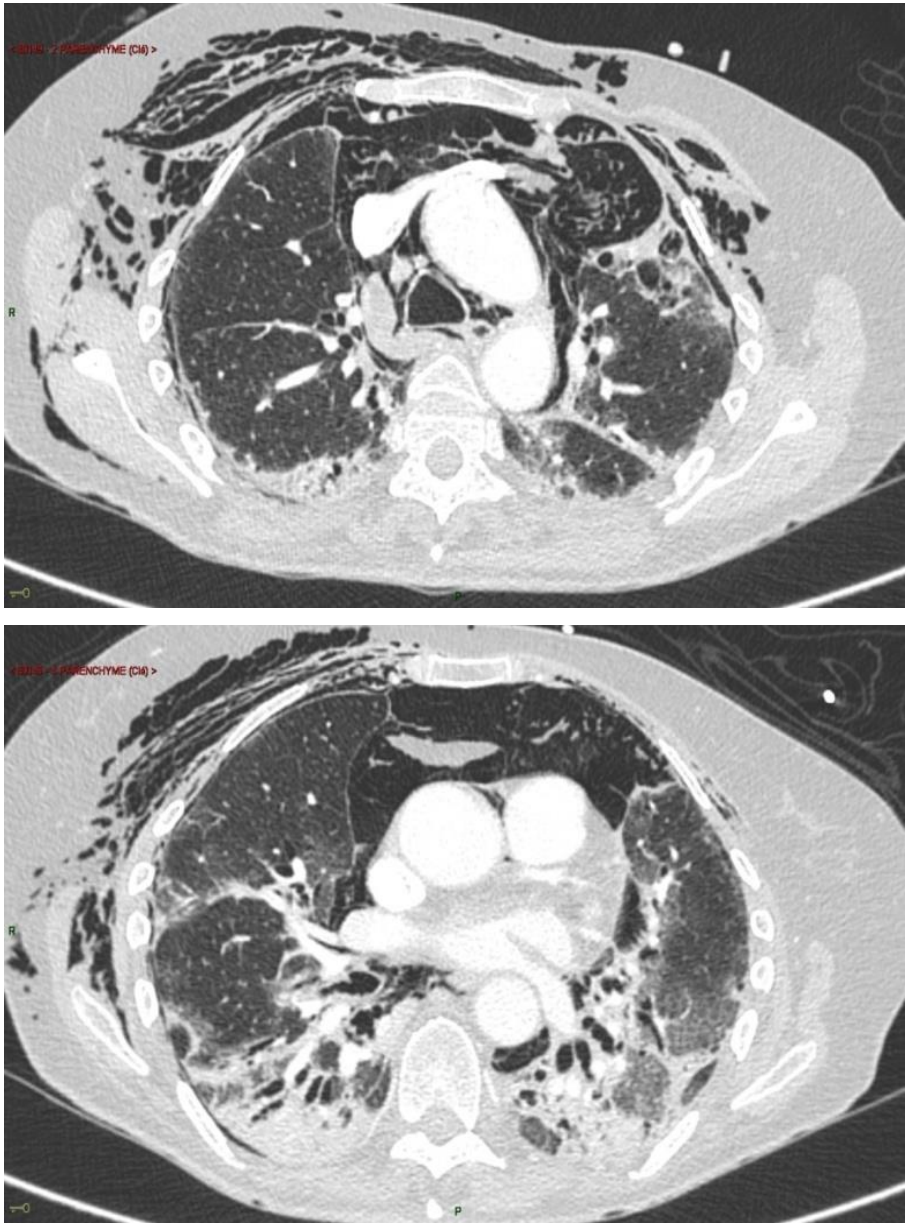
Dégradation clinique respiratoire J5

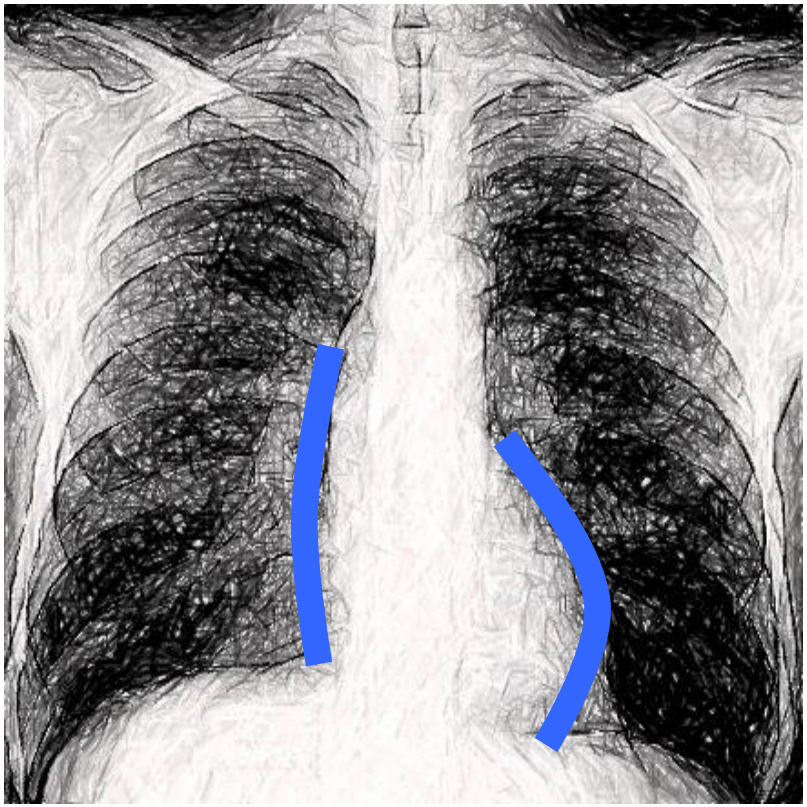




AAN 1/160 Moucheté
Fluorescence cytoplasmique atypique

Anti-MDA5+





Pneumothorax

**Pneumomédiastin**

**Complication Rare mais Grave**

**2- 8% des MI**

*Kono H. ARD 00* **(48 p)**
*Ye S. Clin Rheum 07* **(70p ILD+)**
*Le Goff B. Arthr Care Res 09* **(≈500 p)**

**Délai médian 8 mois (3-26mois)**
**Rechercher Pneumothorax 40%**

Clin Rheumatol
DOI 10.1007/s10067-015-3001-3

BRIEF REPORT

# Clinical and serological features of patients with dermatomyositis complicated by spontaneous pneumomediastinum

Xiaolei Ma[1] · Zhiyong Chen[2] · Wei Hu[3] · Ziwei Guo[2] · Yan Wang[1] · Masataka Kuwana[4] · Lingyun Sun[1]

Received: 20 February 2015 / Revised: 22 June 2015 / Accepted: 28 June 2015

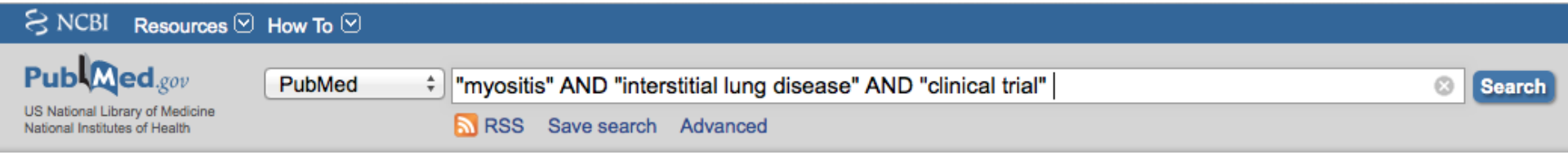

| | Patients with PNM ($n$=11) | Patients without PNM ($n$=82) | $P$ |
|---|---|---|---|
| Sex, M/F | 7/4 | 32/50 | NS |
| Age at the onset of DM, years | 49 (42–58) | 43 (40–56) | NS |
| Cutaneous ulcer, no. (%) | 4 (36.4 %) | 9 (11.0 %) | 0.04 |
| Rapidly progressive ILD, no. (%) | 7 (63.6 %) | 20 (24.4 %) | 0.01 |
| CK, units/l | 58.5 (30.5–394.3) | 284 (73.0–917.0) | 0.04 |
| Serum ferritin, ng/ml | 1125 (362.4–2303.0) | 1028 (322–1500) | NS |
| CRP, mg/l | 15.3 (2.6–52.5) | 0.2 (0.2–25.9) | NS |
| Anti-MDA5 positive, no. (%) | 10 (90.9 %) | 43 (52.4 %) | 0.02 |
| Diagnosis of CADM, no. (%) | 7 (63.6 %) | 18 (22.0 %) | 0.007 |

*PNM* pneumomediastinum, *ILD* interstitial lung disease, *DM* dermatomyositis, *CK* creatine kinase, *CRP* C reactive protein, *Anti-MDA5* anti-melanoma differentiation-associated gene 5, *CADM* clinically amyopathic DM

**Mécanisme ?**

# II. Traitements PID

*G. Richter 1965*


NCBI
Resources
How To
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
"myositis" AND "interstitial lung disease" AND "clinical trial"
Search
RSS
Save search
Advanced

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed "myositis" AND "interstitial lung disease" AND "clinical trial" Search

RSS Save search Advanced

No items found.

**Search details**

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"myositis"[All Fields] AND
"interstitial lung disease"[All
Fields] AND "clinical trial"[All
Fields]
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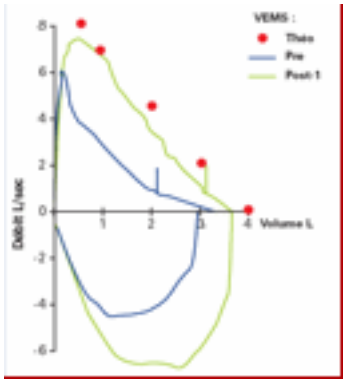
Search See more...

**Recent Activity**

Turn Off Clear

"myositis" AND "interstitial lung disease" AND "clinical trial" A... (0) PubMed

# Mises en garde



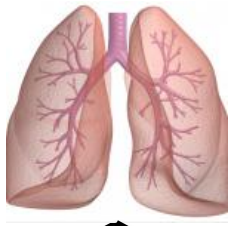
Ne pas regarder que la CVF !

~~TM-6'~~

Crièteres de Jugement...

*Raghu G, AJRCCM 2012*

Difficultés: Evolutivité, Facteurs prédictifs, Sévérité; Muscle



Rapidement progressif (Réanimation)

« Sévère/Symptomatique »*

Pauci-symptomatique

2è ligne

*Vaccinations*
*Réhabilitation pulmonaire*

Rapidement progressif (Réanimation)

Corticothérapie IV - orale

CYC ou Anticalcineurines

Echanges Plasmatiques

IV-Ig (Muscle)

« Sévère/Symptomatique »*

Pauci-symptomatique

2è ligne

* CVF < 70%, $DL_{CO}$ < 60%

Rapidement progressif (Réanimati

« Sévère/Symptomatique »*

Corticothérapi

CY

smatiques

IV-Ig (Muscle)

**Faible niveau de preuve: aucun essai, aucune donnée rétrospective**

Pauci-symptomatique

2è ligne

* CVF < 70%, $DL_{CO}$ < 60%

Rapidement progressif (Réanimation)

Corticothérapie IV - orale

CYC ou Anticalcineurines

Echanges Plasmatiques

IV-Ig (Muscle)

« Sévère/Symptomatique »*

Corticothérapie IV - orale

Anticalcineurines ou CYC–relais IS oral

Pauci-symptomatique

Corticothérapie orale

IS oral

2è ligne

* CVF < 70%, $DL_{CO}$ < 60%

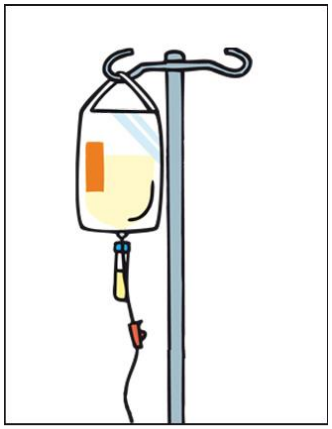
# Corticoïdes

- Admis de tous...

- IV: Pas de données

→ dès que symptomatique

Doses ???




- « **Toujours** » en association à un IS (>3/4)

*Fujisawa T, PLOSone 14*

*Hervier B, Autoimmunity Rev 12*

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, Corticoïdes
Suivi moyen 32 mois
**Taux* de réponse 70%**

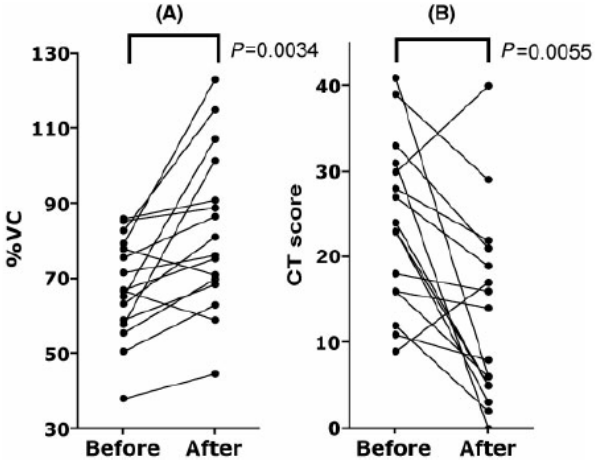



FIG. 1. Percent VC (A) and CT score (B) before and after IVCYC. The VC% improved significantly ($P=0.0034$ by Wilcoxon signed-rank test) after the IVCYC therapy. The CT score improved in 14/16 patients after the IVCYC therapy ($P=0.0055$ by Wilcoxon signed-rank test).

* Consensus FPI: Raghu G, AJRCCM 11

# METHOTREXATE/AZATHIOPRINE

Utilisation rapportée

*Cottin V, ERJ 03; Douglas WW, AJRCCM 01, Marie I ART 13*

Mais pas d'étude dédiée...

MTX: Ne pas être effrayé !

*Eviter chez les patients sévères*

1/100 PA, 1e année
Diagnostic: 6/9 parmi
- Dyspnée rapide
- Fièvre > 38° C
- Tachypnée > 28 et Toux sèche
- Infiltrat interstitiel ou alvéolaire
- Leucocytes > 15000
- LBA et Hc stériles
- Diminution CVF et DLCO
- PaO2 < 50 mmHg
- Histopathologie

Bonne évolution 90% des cas

*Searles G, JR 87*

*J Rheumatol.* 2013 May ; 40(5): 640–646. doi:10.3899/jrheum.121043.

# Mycophenolate Mofetil Improves Lung Function in Connective Tissue Disease-associated Interstitial Lung Disease

**Dr. Aryeh Fischer, MD, Kevin K. Brown, MD, Roland M. Du Bois, MD, Stephen K. Frankel, MD, Gregory P. Cosgrove, MD, Evans R. Fernandez-Perez, MD, Tristan J. Huie, MD, Mahalakshmi Krishnamoorthy, MD, Richard T. Meehan, MD, Amy L. Olson, MD, Joshua J. Solomon, MD**, and **Jeffrey J. Swigris, DO**
Autoimmune and Interstitial Lung Disease Program, National Jewish Health, Denver, Colorado, USA; and the Imperial College, London, UK

dont 32 PM/DM
Suivi moyen 2 ans ½
Amélioration significative mais...

Epargne cortisonée mais...

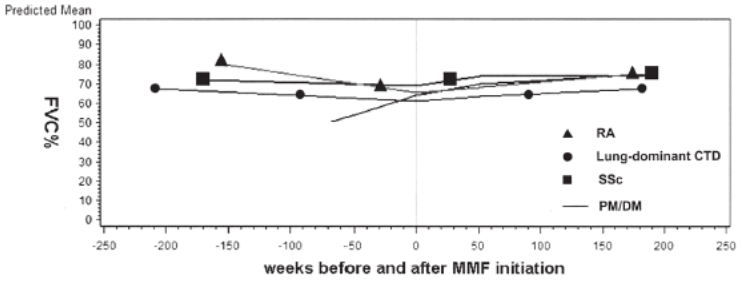



**Figure 4.**
Mixed-effects model estimates for percentage of predicted forced vital capacity (FVC%) in subjects with rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/ dermatomyositis (PM/DM), or lung-dominant connective tissue disease (CTD). MMF: mycophenolate mofetil.

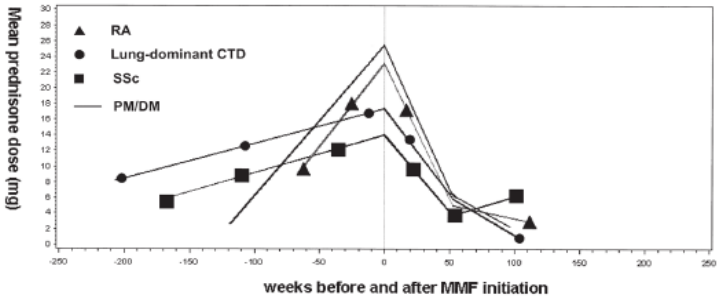



**Figure 2.**
Mean prednisone dose over time in subjects with rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), or lung-dominant connective tissue disease (CTD). MMF: myco-phenolate mofetil.

**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

Efficacité équivalente
Effets secondaires : idem

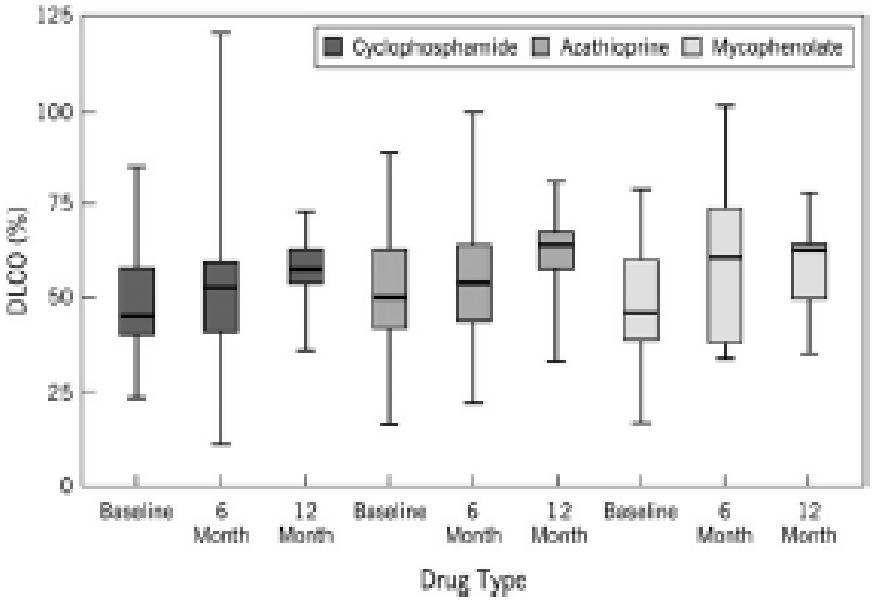



**Figure 2** Percentage DLCO after 6 and 12 months of treatment.

# Anticalcineurines

- Ciclosporine

  Petites séries rétrospectives, En association avec les corticoïdes,

  1e ligne > 2nd ligne, Taux de réponse > 85%. Effets secondaires (1/3)

  *Labirua-Iturburu A,Clin Exp Rheumatol 13 (15p); Cavagna L, JR 13 (17p)*

- Tacrolimus

N=13, Suivi moyen 28 mois.
Taux de réponse:
100% MAIS *77%
Epargne cortisonée

N=54, Taux de réponse: 94%
Patients réfractaires,
Critères ?

ARTHRITIS & RHEUMATISM
Vol. 52, No. 8, August 2005, pp 2439–2446
DOI 10.1002/art.21240


Treatment of Antisynthetase-Associated Interstitial Lung Disease With Tacrolimus

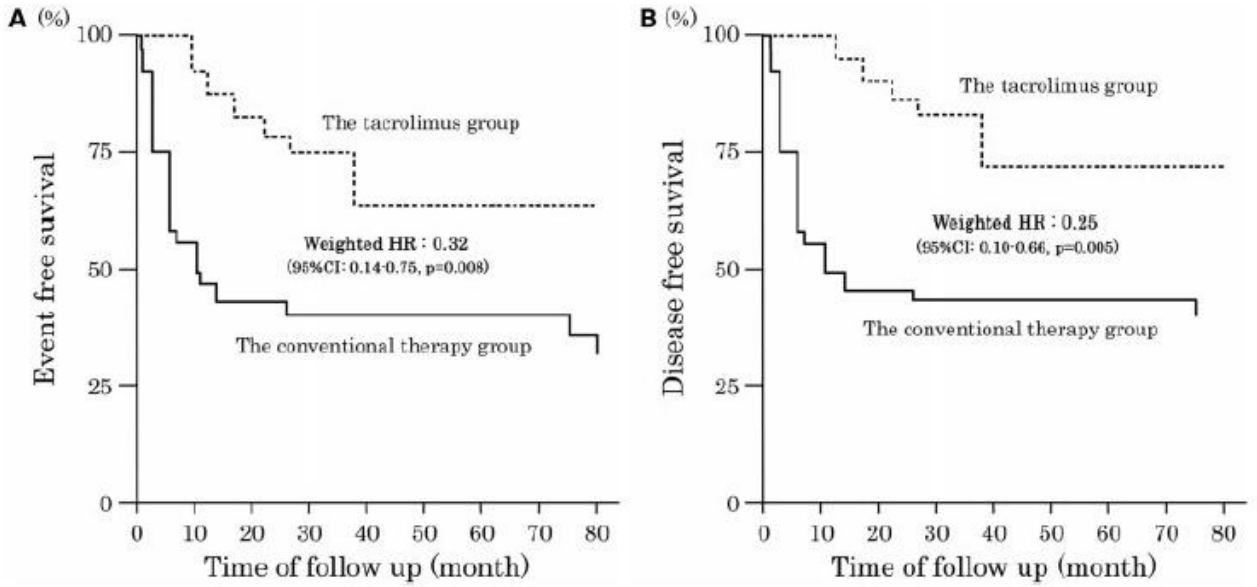
Margaret R. Wilkes, Susan M. Sereika, Noreen Fertig, Mary R. Lucas, and Chester V. Oddis

Myositis-associated Interstitial Lung Disease: Predictors of Failure of Conventional Treatment and Response to Tacrolimus in a US Cohort

Niharika Sharma, Michael S. Putman, Rekha Vij, Mary E. Strek, and Anisha Dua *JR 2017*

# Combinaison ?

FIG. 1 Adjusted survival curves of the tacrolimus group and the conventional therapy group




(**A**) Adjusted event-free survival curves. The tacrolimus group had significantly longer event-free survival compared with the conventional therapy group. (**B**) Adjusted disease-free survival curves. The tacrolimus group had significantly longer disease-free survival compared with conventional therapy group.

*Kurita T, Rheum 2014*

N=49. 1e ligne de traitement, « Add on therapy »,
Suivi moyen 25 mois. 38% rapidement progressif.
MAIS Groupe Tacrolimus 36% CYC vs 8% !

Rapidement progressif (Réanimation)

Corticothérapie IV - orale

CYC ou Anticalcineurines

Echanges Plasmatiques

IV-Ig (Muscle)

« Sévère/Symptomatique »*

Corticothérapie IV - orale

Anticalcineurines ou CYC–relais IS oral

Pauci-symptomatique

Corticothérapie orale

IS oral

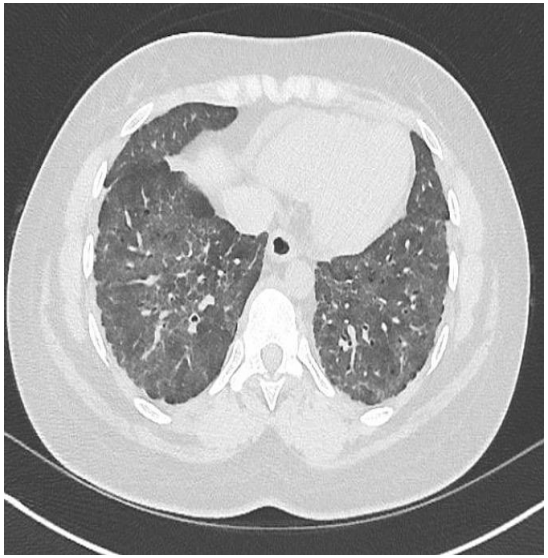
2è ligne

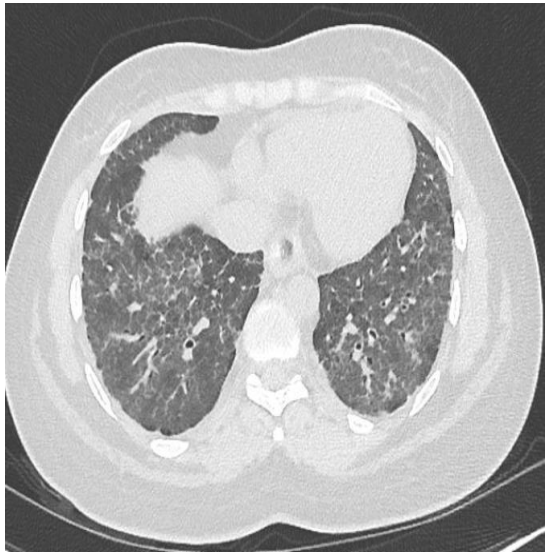
+ Thérapie ciblée (anti-CD20 ++)*

* CVF < 70%, $DL_{CO}$ < 60%

Patiente 1

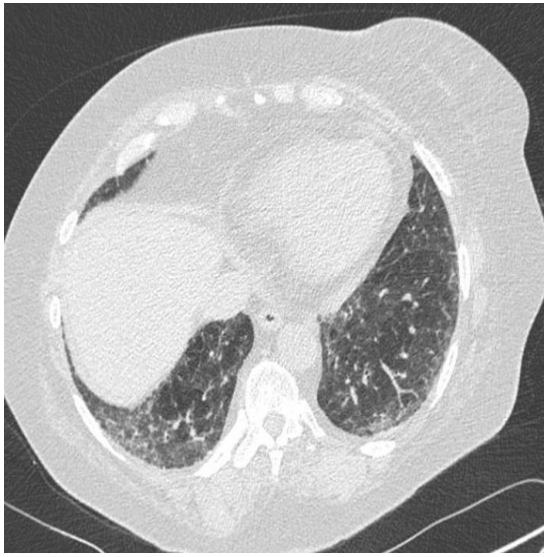
Bolus Cortico, 1MKJ CYC n° 2

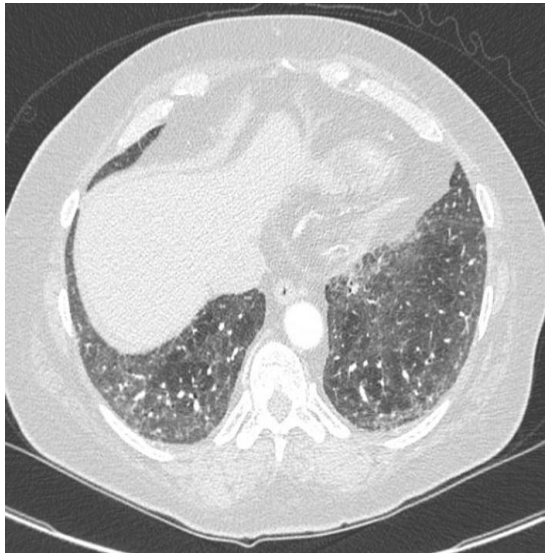




Patiente 2

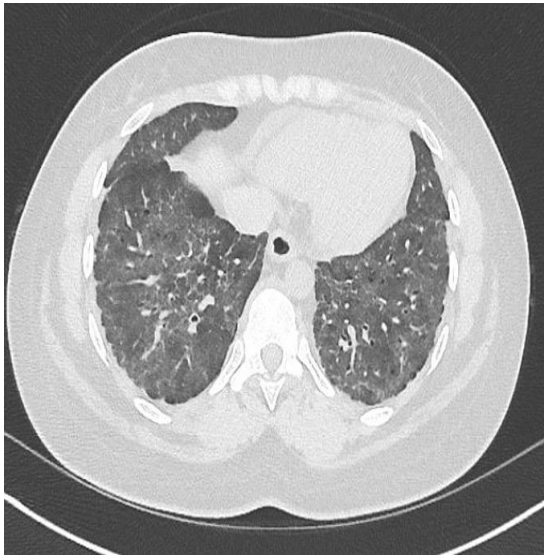
Bolus Cortico, 1MKJ, CYC n° 4

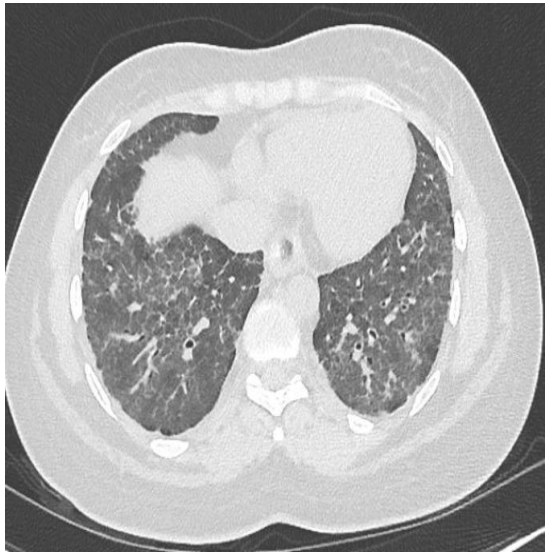


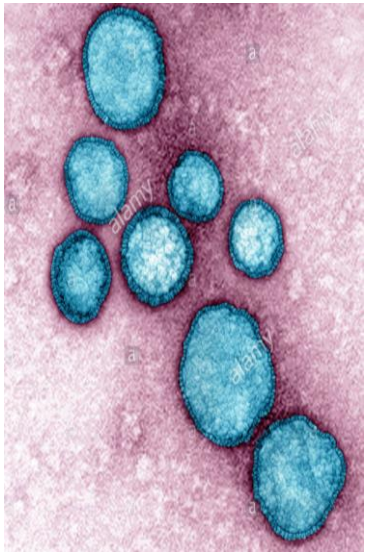


Patiente 1

Bolus Cortico, 1MKJ CYC n° 2







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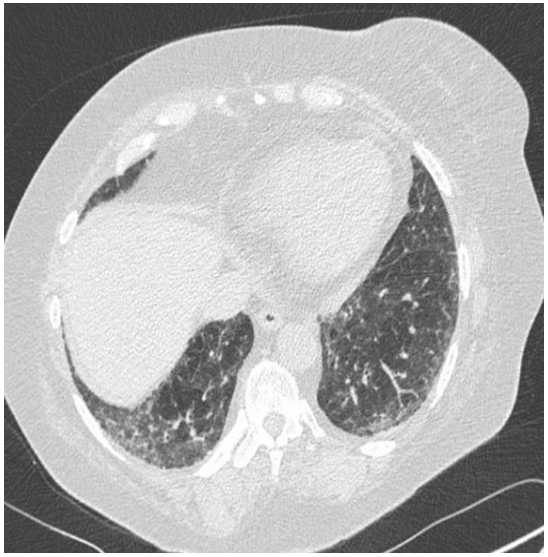
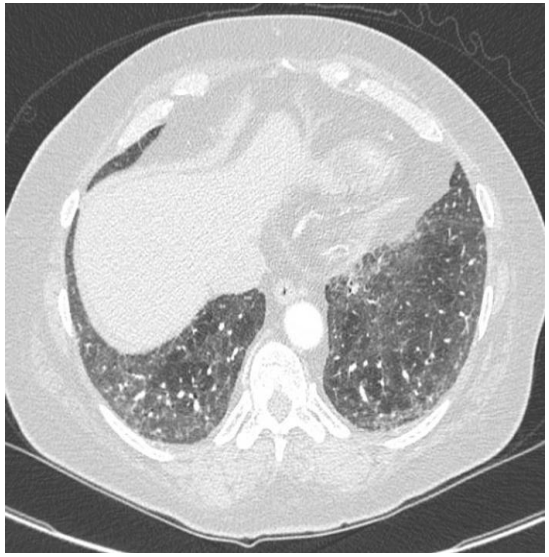
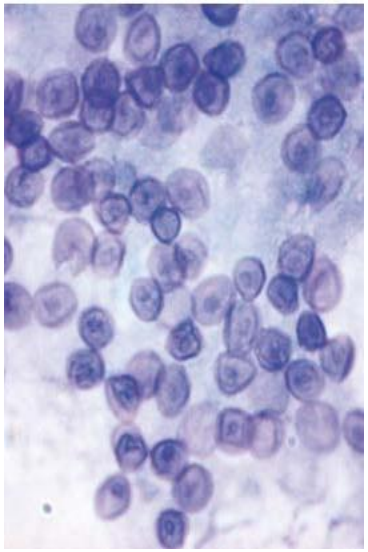







Pr B. Crestani, Bichat, APHP

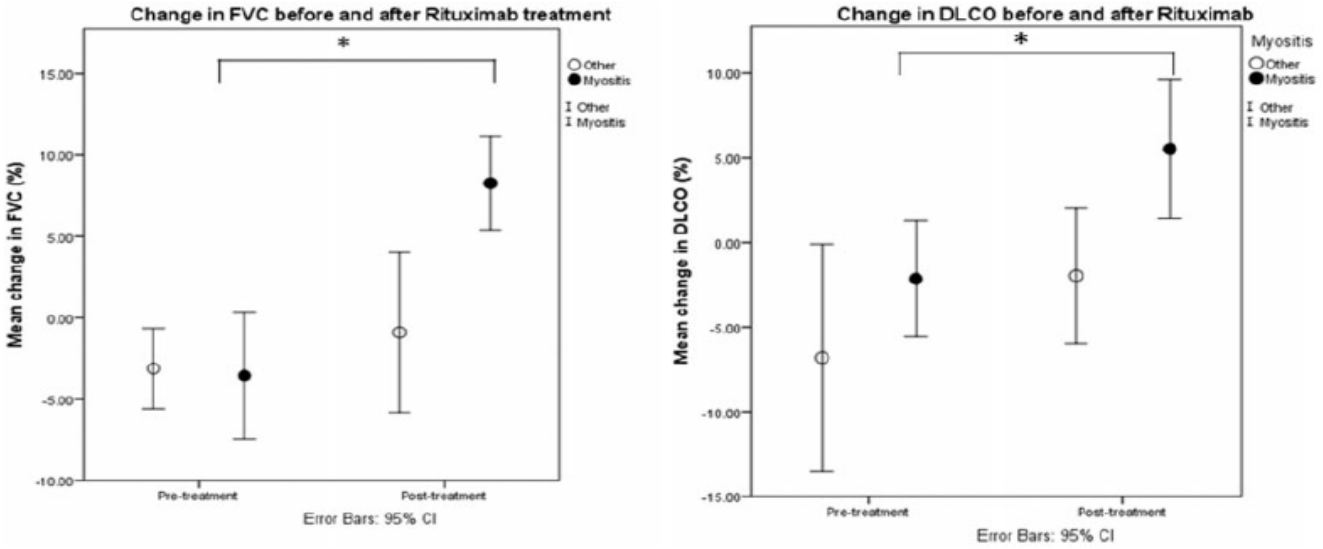
Pr O. Benveniste, Pitié, APHP


Pr B. Crestani, Bichat, APHP

Pr O. Benveniste, Pitié, APHP

Pr. J. Cadranel, Tenon, APHP: « aux malades sévères »

FIG. 2 Comparison of myositis subgroup and other patients' response to treatment




*Sharp C. Rheumatology 2016* (n=13)

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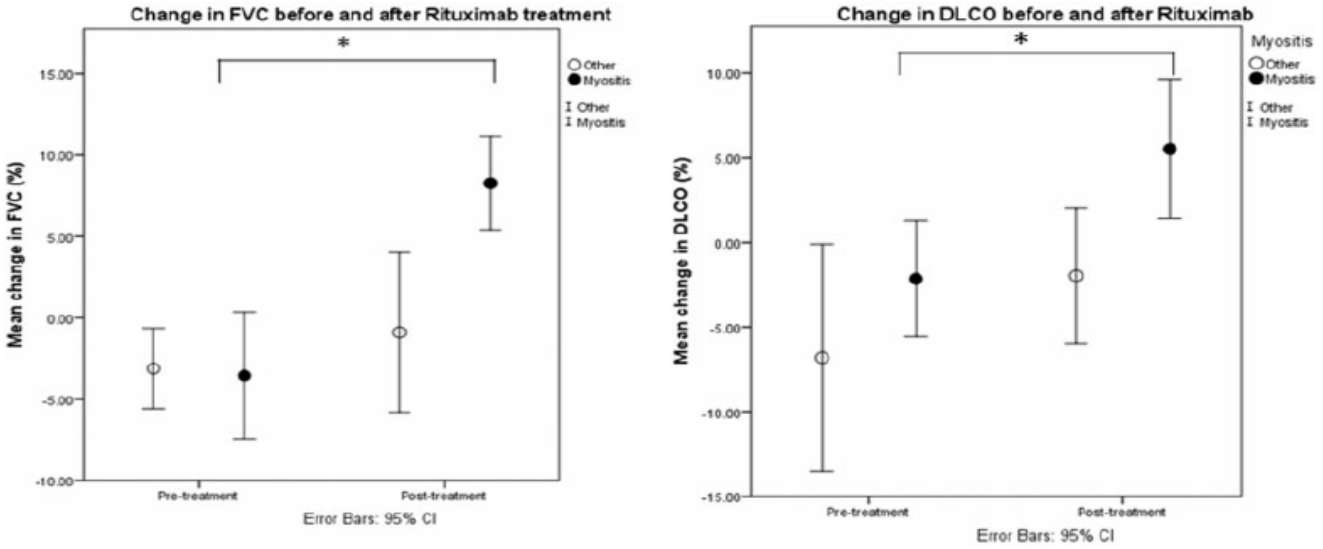


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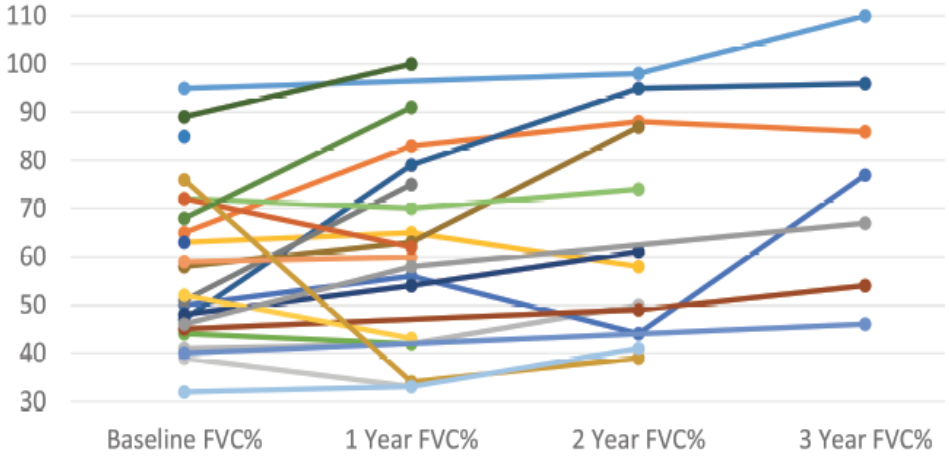
B

% FVC : 56-64%




*Doyle TJ. JRheum2018* (n=25)

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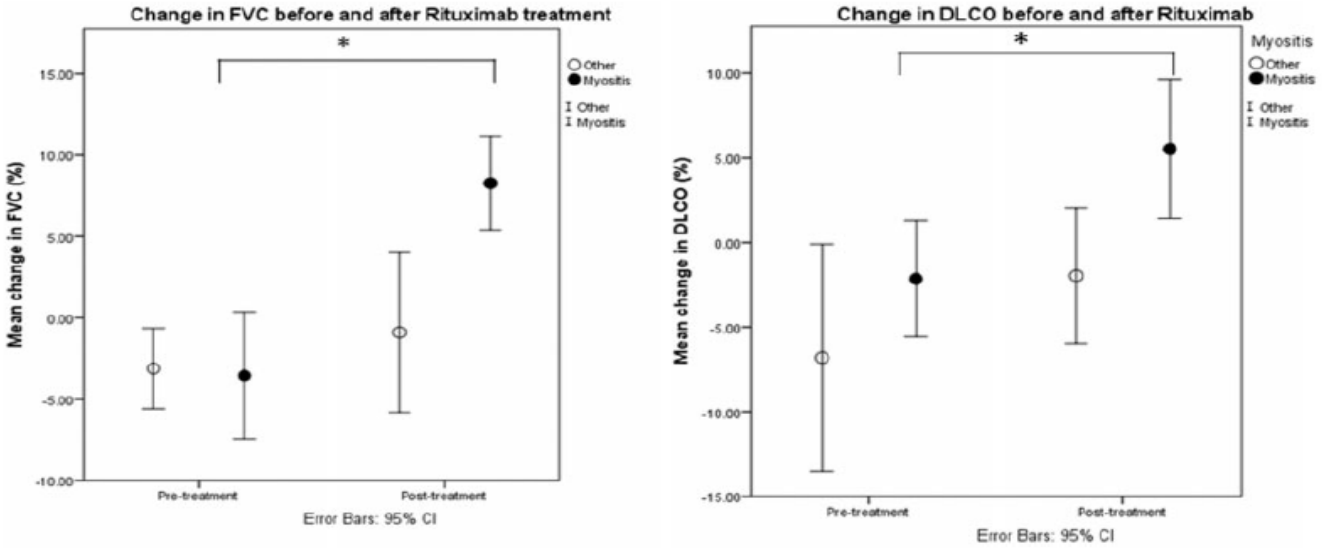


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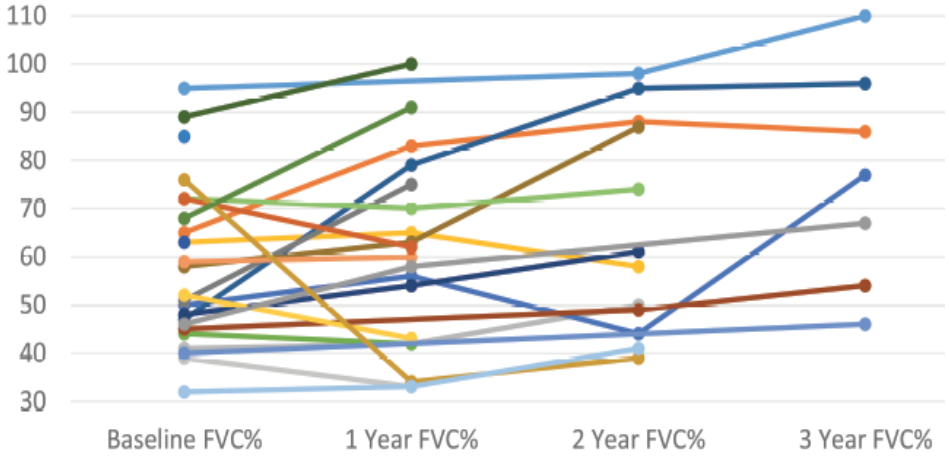
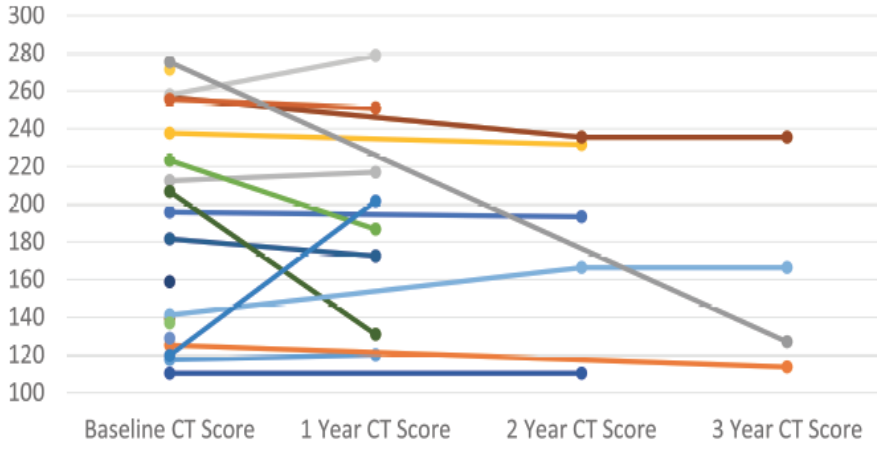



A

CT-Score ...




*Doyle TJ. JRheum2018* (n=25)

RHEUMATOLOGY 270, 299

Original article doi:10.1093/rheumatology/kev004

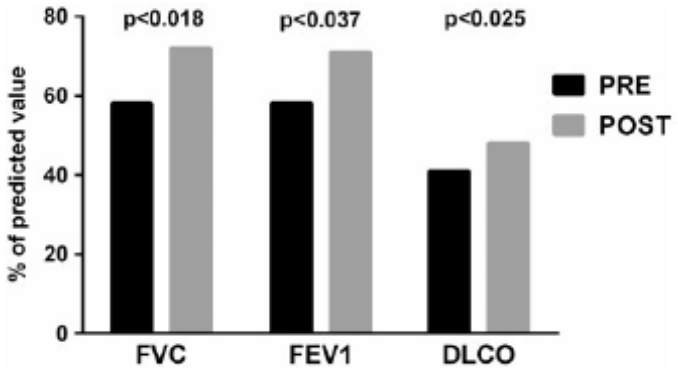
**Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease**

Helena Andersson[1,2], Marthe Sem[2], May Brit Lund[3], Trond Mogens Aaløkken[4], Anne Günther[4], Ragnhild Walle-Hansen[5], Torhild Garen[2] and Øyvind Molberg[1,2]

30 patients, rétrospectif, > 52 semaines, 1-11 cures (2.7)
Rapidement progressif: 50%
En association à
- CTT (97%)
- IS (83%)
En première ligne: 30% !!

Meilleure évolution si 1e année et rapidement progressif

FIG. 1 Pulmonary function tests




Median changes in pulmonary function measured as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and unadjusted diffusing capacity of the lungs for carbon monoxide (DLCO), pre- and post-Rtx treatment for 24 ASS patients with a median follow-up time of 52 months. Details of pulmonary function tests on individual patients are available in Fig. 2.

Mais Consensus FPI = 14/24 = 58%
Score radiologique = 17/23 = 74%

En 2018, 17 séries > 5p, Toujours en 2e ligne

*Hervier B, RMI 15*

RHEUMATOLOGY 270, 299

Original article doi:10.1093/rheumatology/kev004

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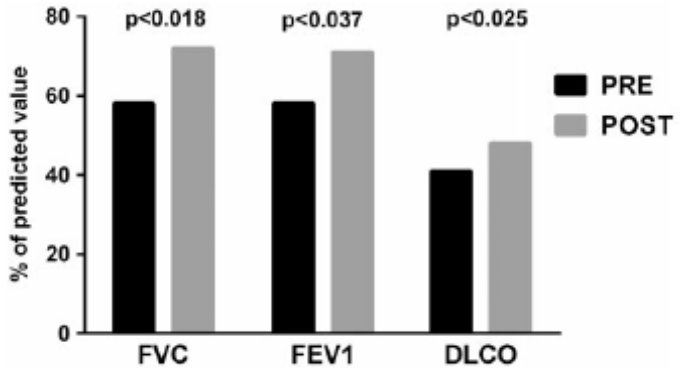


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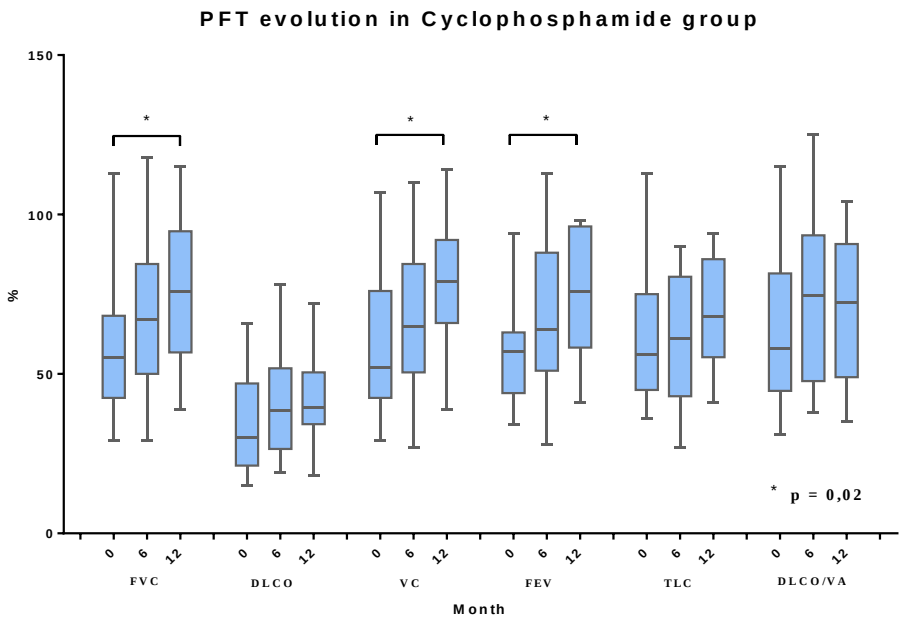
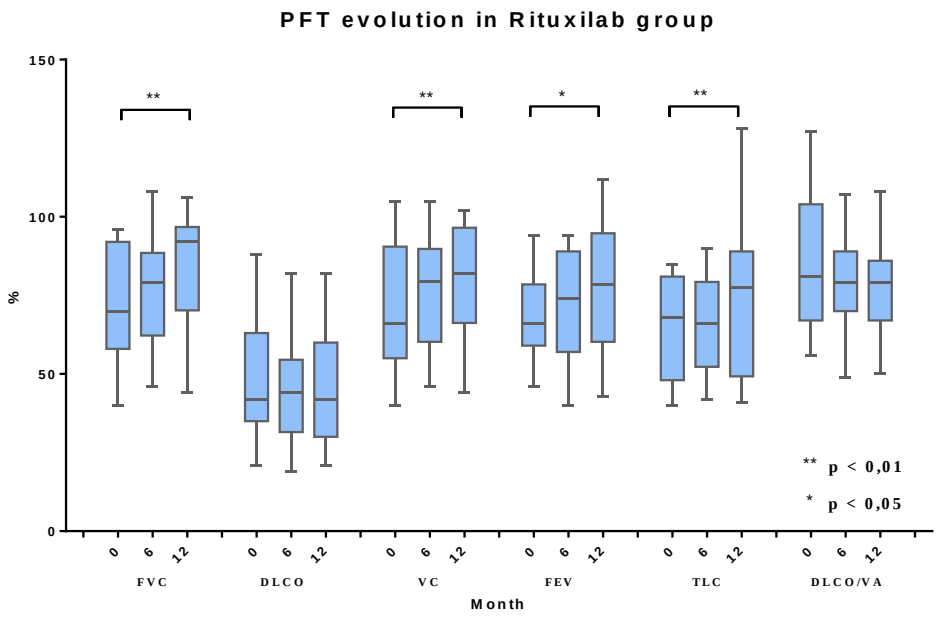
Nombre décès idem patients non-Ritux, mais 7/30= 23% (infections)

# Endoxan *vs* Rituximab (ASyS-ILD)

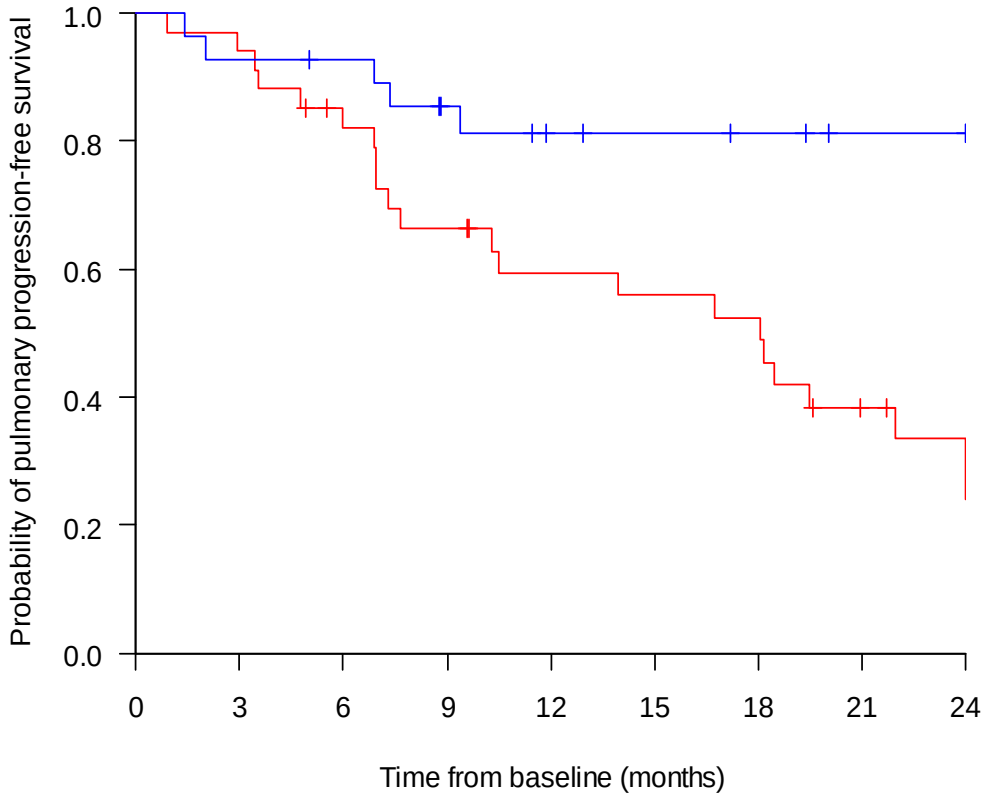



V. Langlois (submitted)

# Endoxan *vs* Rituximab (ASyS-ILD)

**Survie sans progression pulmonaire**




V. Langlois (submitted)

# RTX données prospectives …

PLOS ONE

RESEARCH ARTICLE

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

**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]**

Objectif secondaire.

50% de réponse… sur la CVF

# RTX données prospectives …

- **Ever-ILD** *PHRC Besançon/Dijon*

  *122 CTD-ILD, réfractaires*

  *RTX + MMF vs MMF seul*

- ***RECITAL*** *London*

  *116 CTD-ILD, réfractaires ou non*

  *RTX vs CYC*

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

# Autres thérapies ciblées

## 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

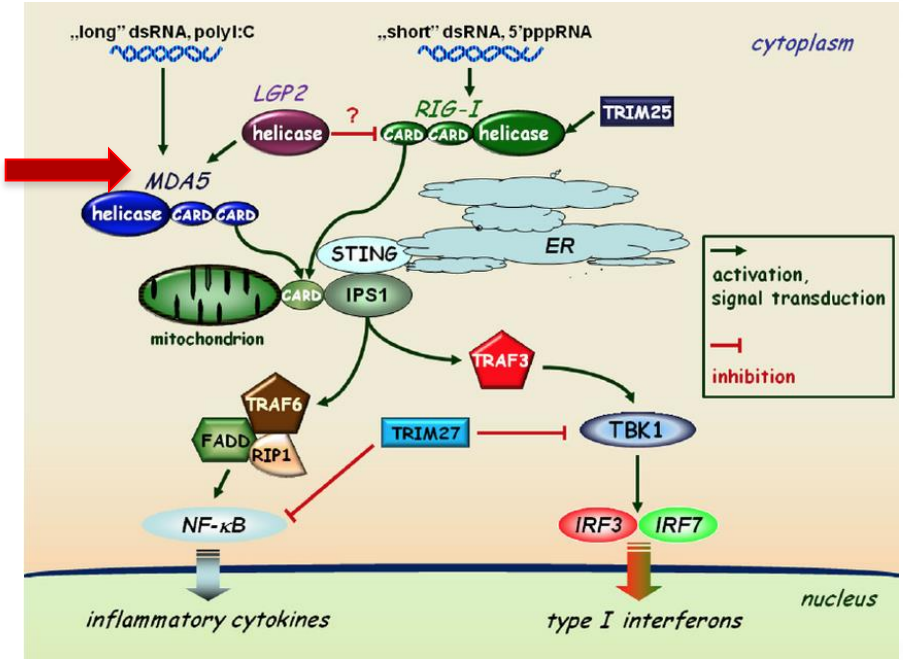
*Letter, ARD 2014, n=4*

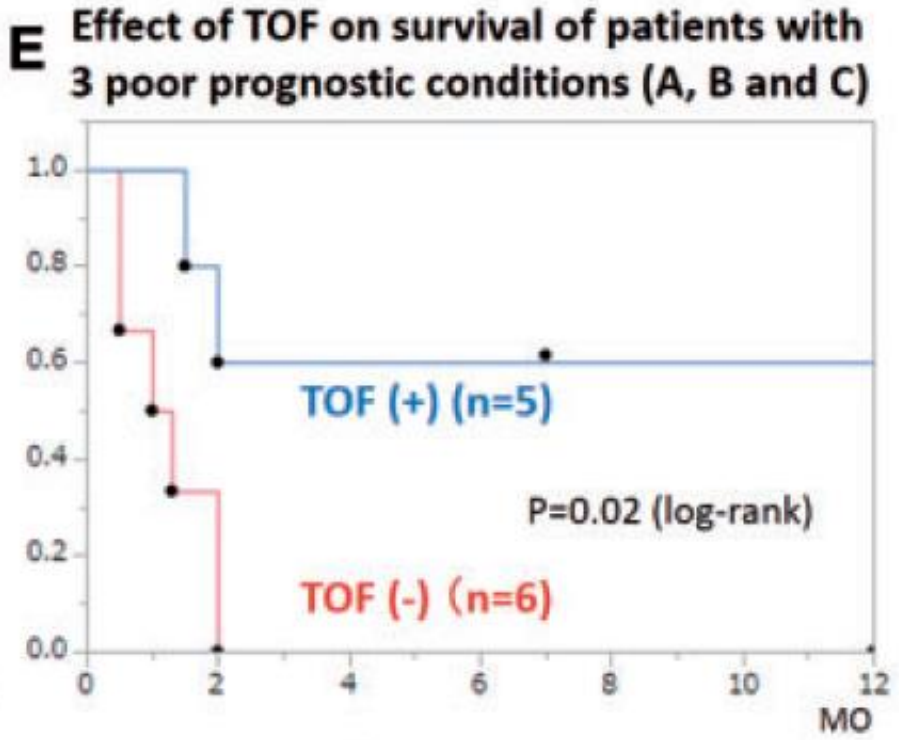
RHEUMATOLOGY

Rheumatology 2018;57:2114–2119
doi:10.1093/rheumatology/key188
Advance Access publication 27 July 2018

# Tofacitinib for refractory interstitial lung diseases in anti-melanoma differentiation-associated 5 gene antibody-positive dermatomyositis

Kazuhiro Kurasawa[1], Satoko Arai[1], Yumeko Namiki[1], Ayae Tanaka[1], Yuta Takamura[1], Takayoshi Owada[1], Masafumi Arima[1] and Reika Maezawa[1]



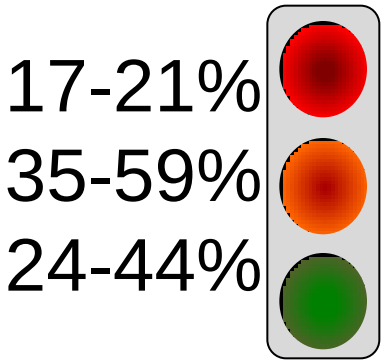



# Evolution

Chronique

Suivi & traitement **prolongés**

Arrêt ???




Non réponse/
Déclin progressif

Rechutes/
Exacerbation

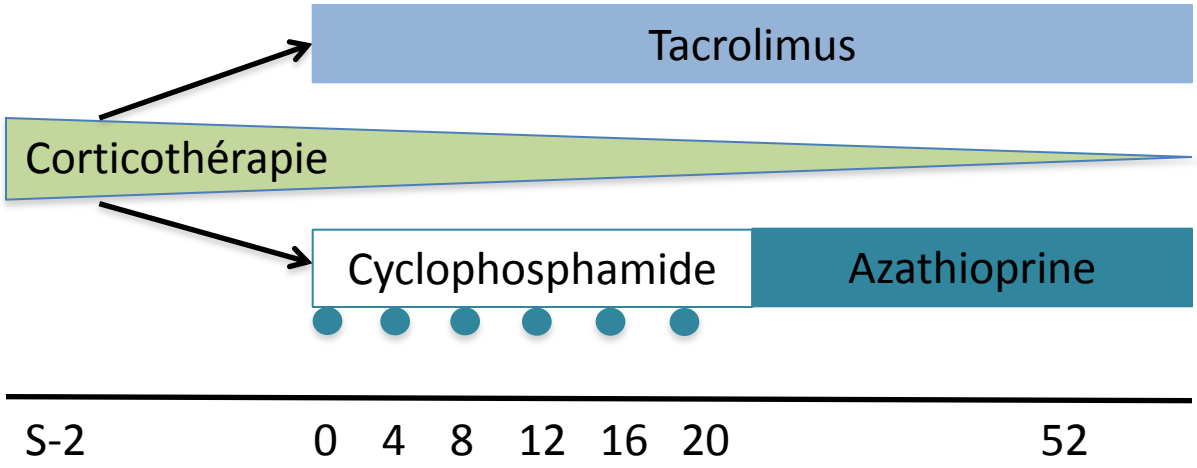
*Marie I. Arthr care Res 12*
*Obert J, Rheum Int 16*

**Hors MDA-5 75% à 8 ans**

**Mortalité x 3** *Cottin V ERJ 03*

# CATR.PAT Study, PHRC National

- PID antisynthétase non réanimatoire, de novo ou en rechute
- Survie sans événement à S52



**A. Selon vous quelles affirmations concernant les PID associées aux MI sont exactes ?**

1. Il s'agit du principal facteur de morbi-mortalité
2. On les rencontre au cours de toutes les MI
3. La PIC est la forme la plus fréquente
4. Nécessite une confirmation histologique
5. La PID conditionne les traitements

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**B. Vous recevez un patient déficitaire (myogène) et dyspnéique (PID). Parmi ceux-ci quels sont les éléments pronostiques péjoratifs ?**

1. Le type d'auto-Ab spécifique de la myosite
2. La rapidité de survenue de la PID
3. La mesure de la CV aux EFR
4. Le pattern radiologique
5. Hypertension pulmonaire

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**C. Mr John P, présente une PID associée à une myosite de chevauchement, NYHA III, CV 55%, DLCO 51%. Votre traitement de choix est:**

1. Bolus corticoïdes puis oraux, en monothérapie
2. Corticothérapie et Immunosuppresseurs
3. Vaccinations à jour, PnC, HI, Grippe annuelle
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