Pneumopathies interstitielles: qu'attendre des investigations immunologiques ?

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Introduction

Intérêt pronostique

How can autoantibodies predict the long-term outcome of patients with interstitial lung disease? Results from a retrospective cohort study

Christos F. Kampolis[a,*], Aliki I. Venetsanopoulou[a], Foteini Karakontaki[b], Vlasis Polychronopoulos[b], Panayiotis Vlachoyiannopoulos[a], Athanasios G. Tzioufas[a]

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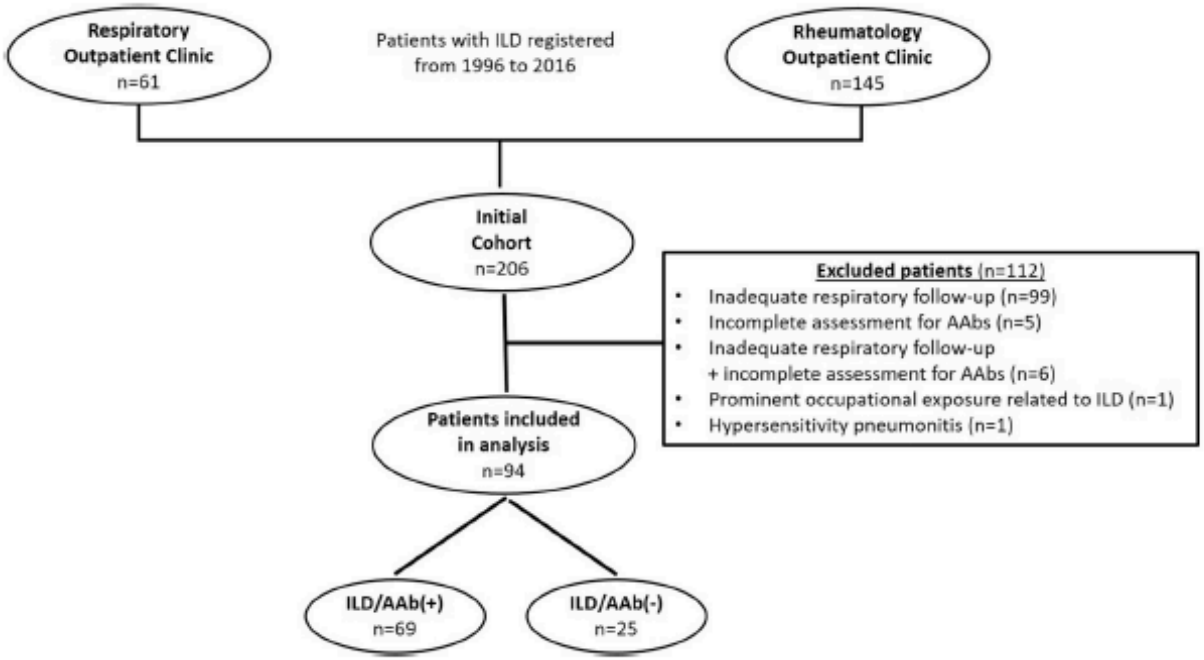
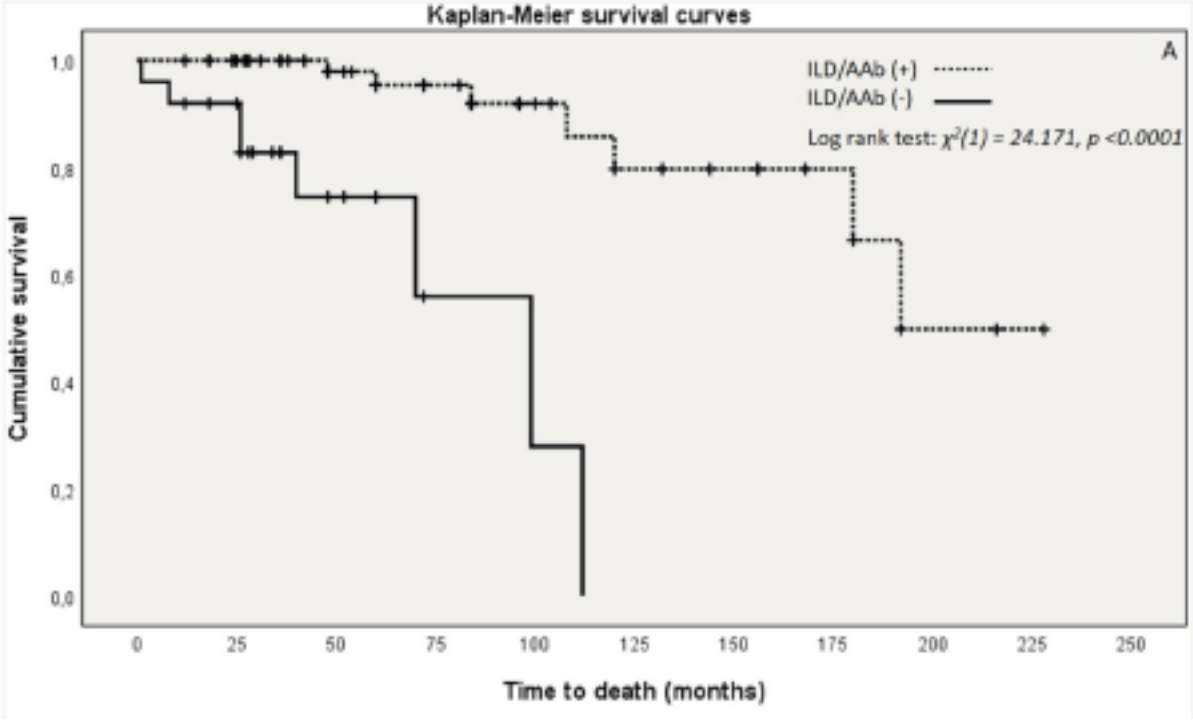
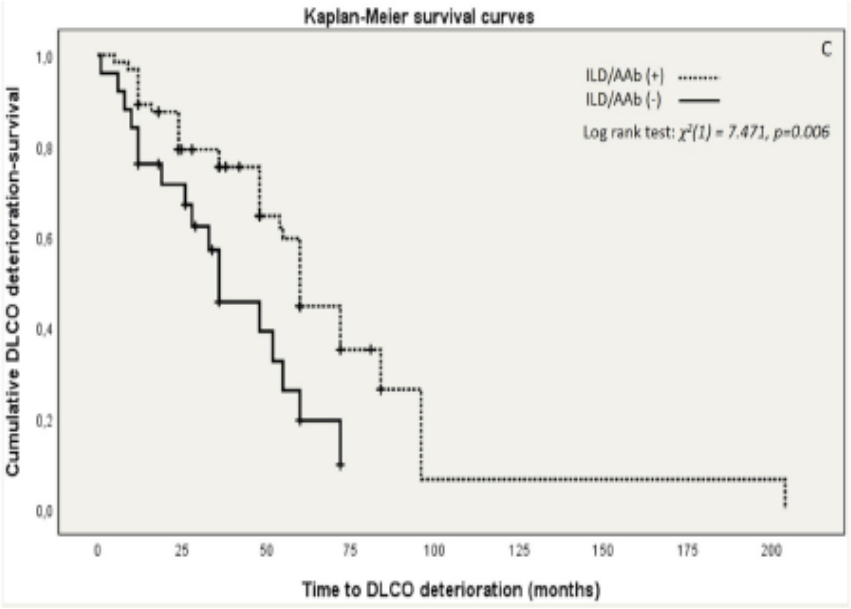
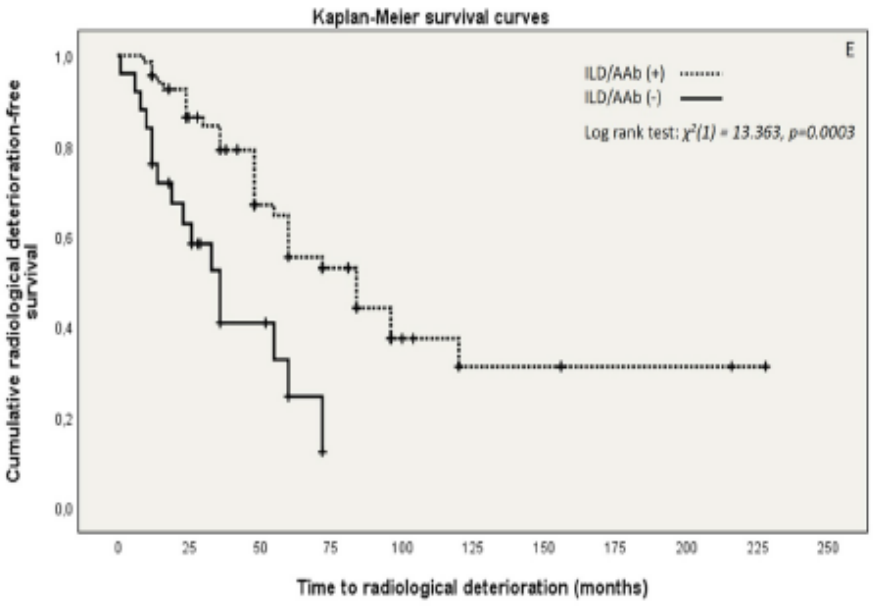


Kampolis et al. Autoimmunity Reviews 2018


Kaplan-Meier survival curves
A
ILD/AAb (+)
ILD/AAb (-)
Log rank test: $\chi^2(1) = 24.171$, $p < 0.0001$
Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
150
175
200
225
250
Time to death (months)


Kaplan-Meier survival curves
C
ILD/AAb (+)
ILD/AAb (-)
Log rank test: $\chi^2(1) = 7.471$, $p=0.006$
Cumulative DLCO deterioration-survival
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
150
175
200
Time to DLCO deterioration (months)


Kaplan-Meier survival curves
E
ILD/AAb (+)
ILD/AAb (-)
Log rank test: $\chi^2(1) = 13.363$, $p=0.0003$
Cumulative radiological deterioration-free survival
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
150
175
200
225
250
Time to radiological deterioration (months)

Intérêt thérapeutique

Saunders et al. Trials (2017) 18:275
DOI 10.1186/s13063-017-2016-2

Trials

STUDY PROTOCOL Open Access

Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial

Peter Saunders[1], Vicky Tsipouri[1], Gregory J. Keir[2], Deborah Ashby[3], Marcus D. Flather[4], Helen Parfrey[5], Daphne Babalis[3], Elisabetta A. Renzoni[1,6], Christopher P. Denton[7], Athol U. Wells[1,6] and Toby M. Maher[1,6*]

Methods/design: RECITAL is a UK, multicentre, prospective, randomised, double-blind, double-dummy, controlled trial funded by the Efficacy and Mechanism Evaluation Programme of the Medical Research Council and National Institute for Health Research. The trial will compare rituximab 1 g given intravenously, twice at an interval of 2 weeks, with intravenously administered cyclophosphamide given monthly at a dose of 600 mg/m^2 body surface area in individuals with ILD due to systemic sclerosis, idiopathic inflammatory myositis (including anti-synthetase syndrome) or mixed connective tissue disease. A total of 116 individuals will be randomised 1:1 to each of the two treatment arms, with stratification based on underlying CTD, and will be followed for a total of 48 weeks from first dose. The primary endpoint for the study will be change in forced vital capacity (FVC) at 24 weeks. Key secondary endpoints include: safety, change in FVC at 48 weeks as well as survival, change in oxygen requirements, total 48-week corticosteroid exposure and utilisation of health care resources.

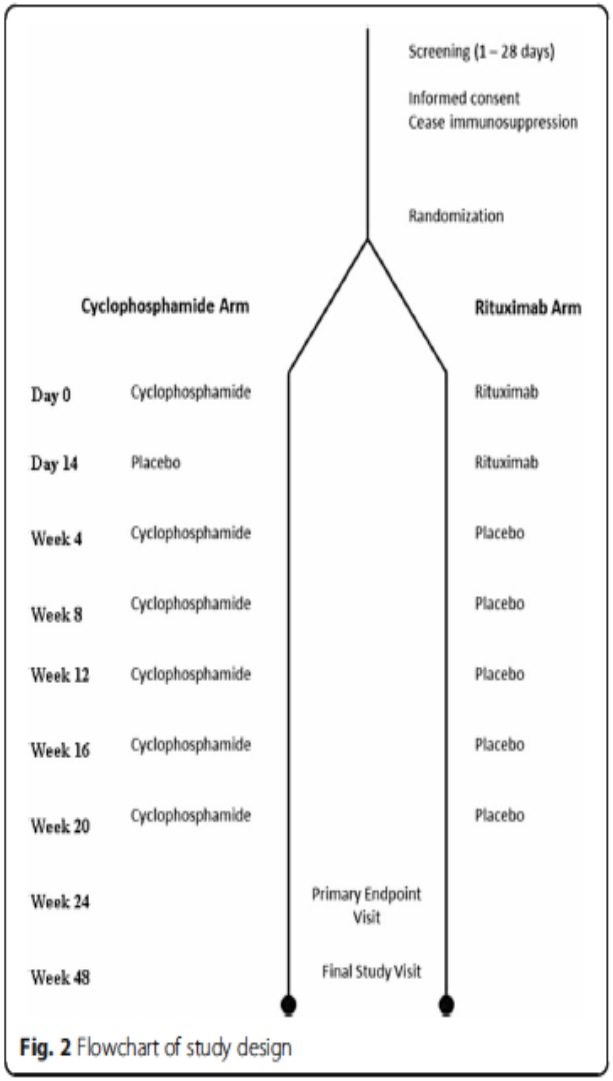


Fig. 2 Flowchart of study design

CTD-ILD and IPAF

Review

Role of Autoantibodies in the Diagnosis of Connective-Tissue Disease ILD (CTD-ILD) and Interstitial Pneumonia with Autoimmune Features (IPAF)

Adelle S. Jee [1,2], Stephen Adelstein [2,3,4], Jane Bleasel [2,5], Gregory J. Keir [6], MaiAnh Nguyen [2,4], Joanne Sahhar [7,8], Peter Youssef [2,5] and Tamera J. Corte [1,2,*]

J. Clin. Med. **2017**, *6*, 51

CTD-ILD

CTD	Prevalence of ILD	Radiological/Histopathological Pattern
SSc	40–75% with clinically significant disease (at least moderate impairment on pulmonary function) [11,31,32] Up to 70% with detectable interstitial changes on HRCT [31]	Most common: NSIP Other: UIP
RA	Detectable on HRCT: 30–60% Clinically evident 10–30% [33]	Most common: UIP Other: NSIP, OP, LIP
IIM	30–50% [34,35]	Most common: NSIP Other: UIP, OP, DAD
SLE	3–11% chronic diffuse interstitial disease [36] Up to 30% with detectable interstitial changes on HRCT Need to distinguish from acute pneumonitis (1–10%) and alveolar haemorrhage (rare)	Most common: NSIP Other: LIP, OP, UIP
SS	10–30% [31] Need to exclude pulmonary lymphoma	Most common: NSIP Other: LIP, OP, UIP
MCTD	20–85% [31]	Common: NSIP Other: UIP

IPAF

TABLE 1 Classification criteria of interstitial pneumonia with autoimmune features

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy), *and*
2. Exclusion of alternative aetiologies, *and*
3. Does not meet criteria of a defined connective tissue disease, *and*
4. At least one feature from at least two of these domains:
   A. clinical domain
   B. serological domain
   C. morphological domain

A. Clinical domain
1. Distal digital fissuring (*i.e.* "mechanic's hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

C. Morphological domain
1. Suggestive radiology patterns by HRCT:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

Gianluca Sambataro et al Eur Respir Rev 2018

IPAF

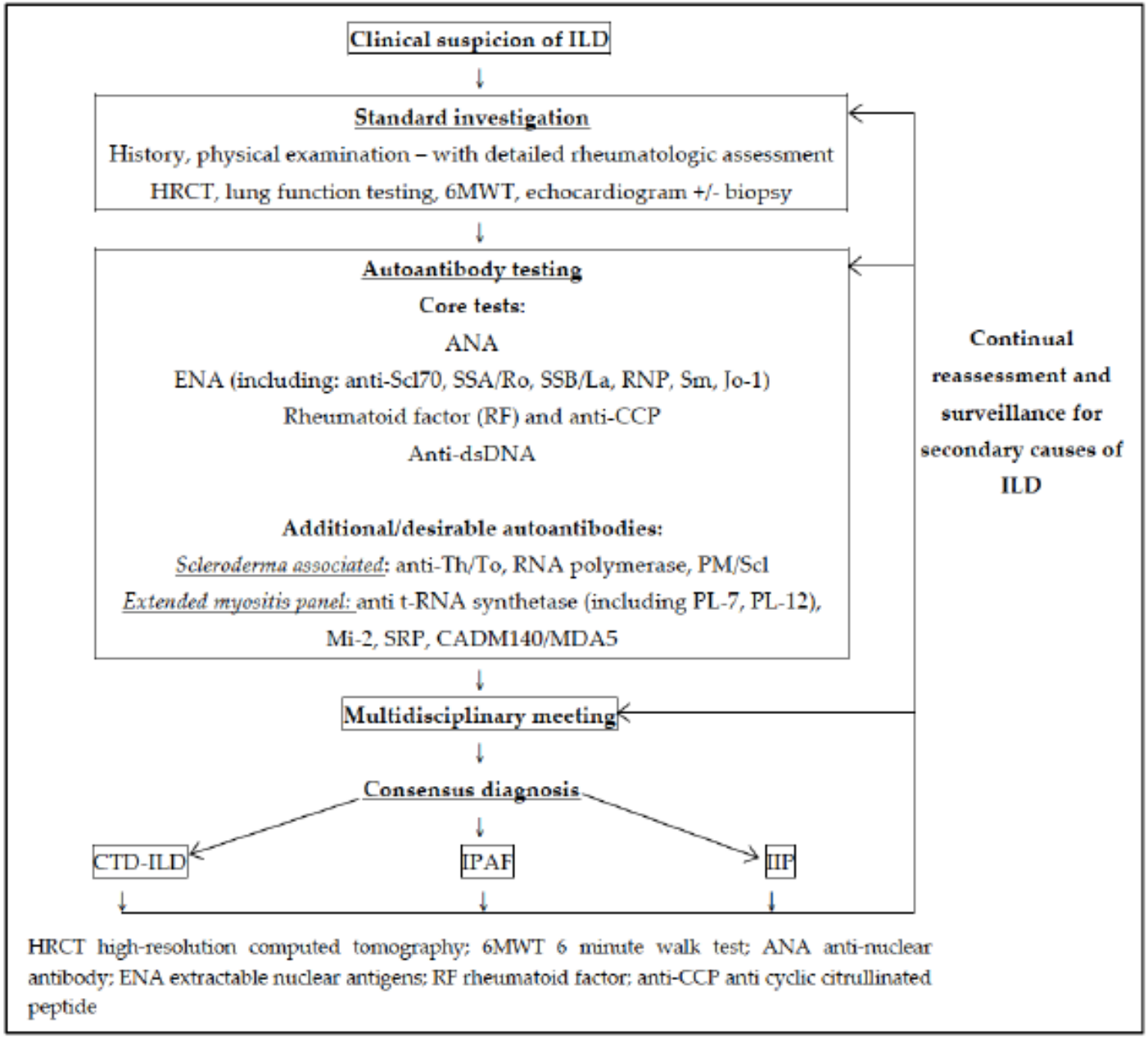
TABLE 1 Classification criteria of interstitial pneumonia with autoimmune features

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy), *and*
2. Exclusion of alternative aetiologies, *and*
3. Does not meet criteria of a defined connective tissue disease, *and*
4. At least one feature from at least two of these domains:
   A. clinical domain
   B. serological domain
   C. morphological domain

B. Serological domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or any titre for nuclear and centromere pattern
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, Pl-12, EJ, OJ, KS, Zo, tRS)
11. Anti-PM/Scl
12. Anti-MDA-5

Gianluca Sambataro et al Eur Respir Rev 2018



Jee A et al J Clin Med 2017

Eur Respir J. 2016 June ; 47(6): 1767–1775. doi:10.1183/13993003.01565-2015.

Characterisation of patients with interstitial pneumonia with autoimmune features

Justin M. Oldham[1,8], **Ayodeji Adegunsoye**[2,8], **Eleanor Valenzi**[3], **Cathryn Lee**[3], **Leah Witt**[2], **Lena Chen**[2], **Aliya N. Husain**[4], **Steven Montner**[5], **Jonathan H. Chung**[5], **Vincent Cottin**[6], **Aryeh Fischer**[7], **Imre Noth**[2], **Rekha Vij**[2,9], and **Mary E. Strek**[2,9]

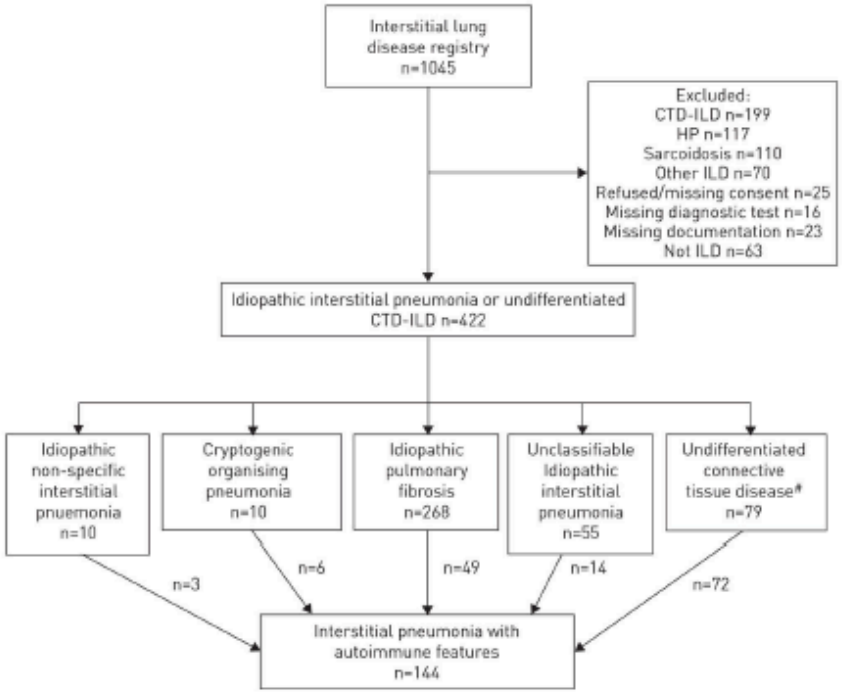
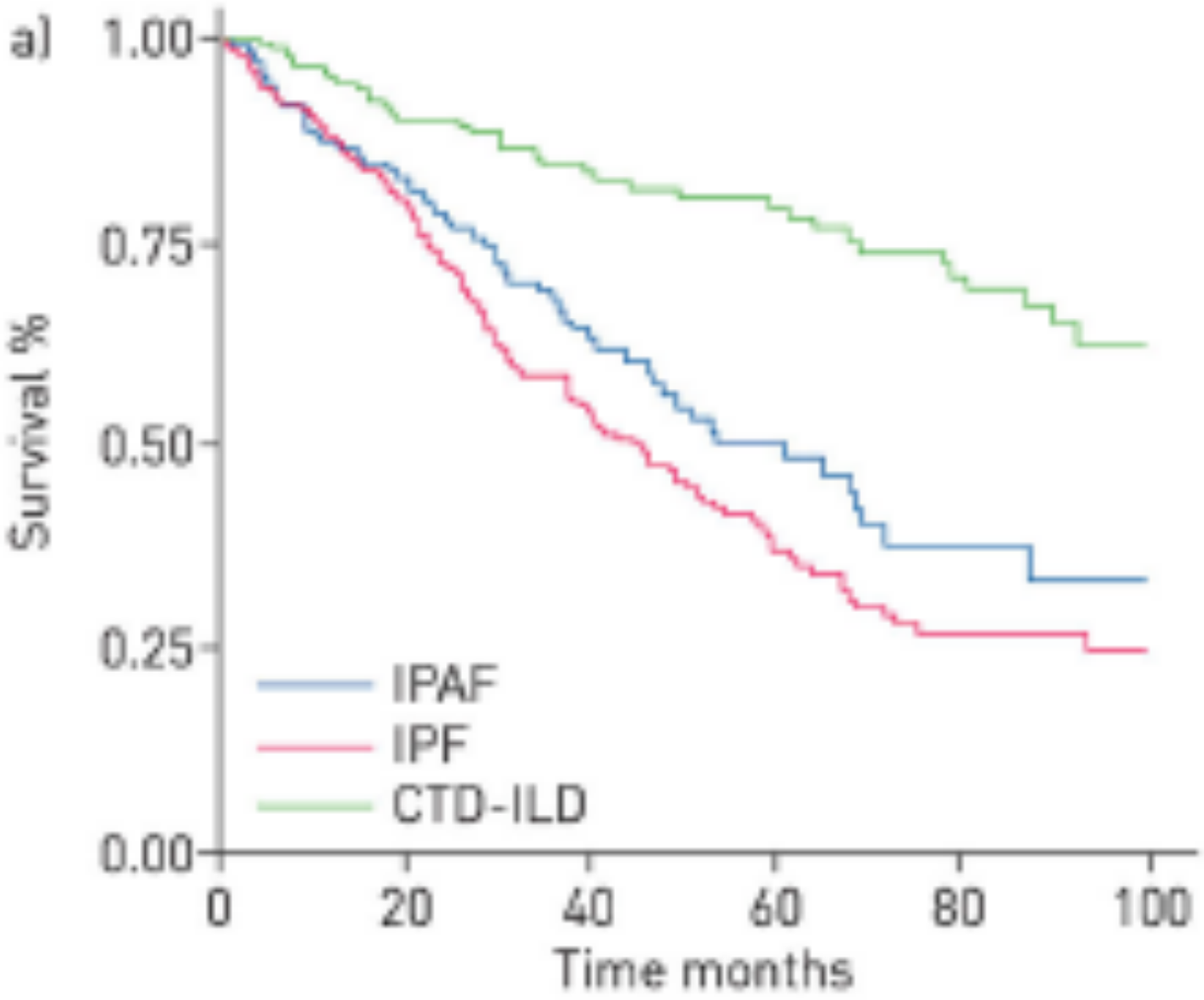


FIGURE 1.
Consort diagram. CTD: connective tissue disease; ILD: interstitial lung disease; HP: hypersensitivity pneumonitis; IIP: idiopathic interstitial pneumonia. #: based on narrow criteria as proposed by Corte *et al.* [3].


a)
1.00
0.75
0.50
0.25
0.00
Survival %
IPAF
IPF
CTD-ILD
0
20
40
60
80
100
Time months

Investigations

CTD-ILD – quelles maladies?

CTD	Prevalence of ILD	Radiological/Histopathological Pattern
SSc	40–75% with clinically significant disease (at least moderate impairment on pulmonary function) [11,31,32] Up to 70% with detectable interstitial changes on HRCT [31]	Most common: NSIP Other: UIP
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Quelles maladies systémiques rechercher ?

- Syndrome de Sjögren
- Sclérodermie systémique
- Syndrome SHARP/connectivites mixtes
- Lupus érythémateux systémique
- Myopathies inflammatoires
- Polyarthrite rhumatoïde

CTD-ILD –quels auto-anticorps ?

- Ac anti-nucléaires (F.A.N.)
- Ac anti-ADN natif double brin
- Ac anti-ECT
- DOT-Myosite
- Facteur rhumatoïde, anti-CCP
- ANCA (anti-MPO)

Anticorps anti-nucléaires

- **Titre: ≥ 1/160**
- **Répartition:**
  - **homogène**
  - **mouchetée**
  - **nucléolaire**
  - **centromérique**

➢ **Pas de corrélation entre le titre des AAN et la sévérité de la maladie (lupus érythémateux systémique)**

➢ **Les aspects en IFI manquent de spécificité, chavauchement entre les différents aspects de fluorescence**

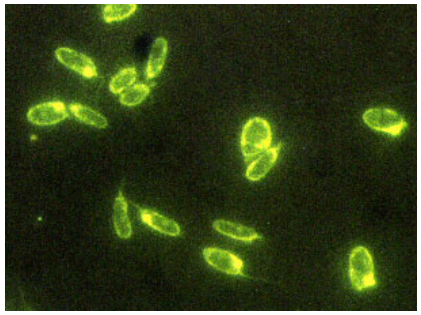
Sensibilité et spécificité des anticorps anti-nucléaires au cours de certaines connectivites

Table 1. Sensitivity and specificity of antinuclear antibody (ANA) tests in certain connective tissue diseases.[1]

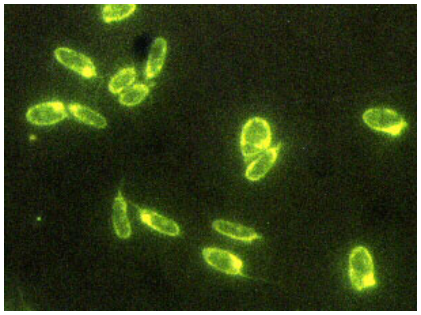
Disease	Sensitivity (%)	Specificity (%)
Polymyositis/dermatomyositis	61	63
Rheumatoid arthritis	41	56
Scleroderma	85	54
Secondary Raynaud	64	41
Sjögren's syndrome	48	52
Systemic lupus erythematosus	93	57

➢ **Faible spécificité des AAN au cours des connectivites**

Habash-Bseiso, Clin Med Res 2005



Anti-ADN natif



- Ne faire les anti-ADN et anti-ECT que lorsque les AAN sont positifs (sauf exception)
- Interprétation du résultat des anti-ADN en fonction de la technique et du contexte clinique (Chritidia luciliae, Test de Farr*, ELISA « maison »)
- Seules les IgG anti-ADN ont une valeur diagnostique
- Titre des anti-ADN: marqueur d'activité du LED
- L'absence d'anti-ADN n'élimine pas le diagnostic de LED (faible valeur prédictive négative).

Sensibilité et spécificité des anticorps anti-nucléaires

Antigen	Associated Condition	Sensitivity (%)	Specificity (%)
Anticentromere	Limited cutaneous systemic sclerosis	65	99.9
Anti-dsDNA antibody	Systemic lupus erythematosus	57	97
Anti-SSB/La antibody	Sjögren's, subacute cutaneous lupus erythematosus, neonatal lupus syndrome	16-40	94
Anti-SSA/Ro antibody	Sjögren's, subacute cutaneous lupus erythematosus, neonatal lupus syndrome	8-70	87
Anti-Smooth muscle antibody	Systemic lupus erythematosus	25-30	High*
Anti-U3-RNP antibody	Scleroderma	12	96
Scl-70	Systemic sclerosis	20	100

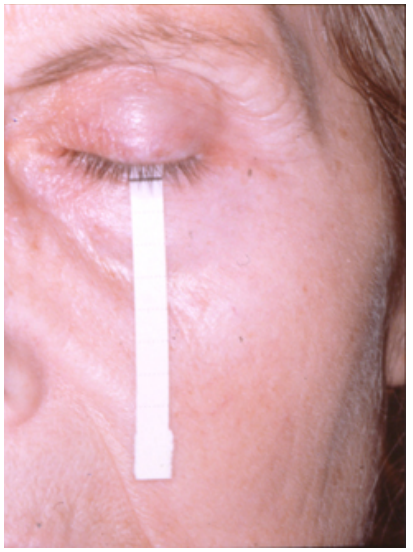
* Precise data not available.

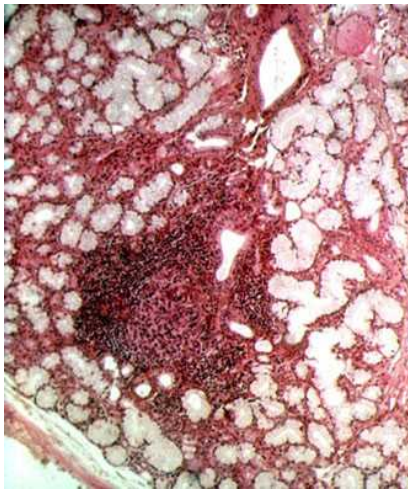
- **Anti-antigène nucléaire soluble: forte spécificité**

Habash-Bseiso, Clin Med Res 2005

Sjögren: critères diagnostiques (critères Européens)

1. Symptômes oculaires
2. Symptômes buccaux
3. Signes cliniques ophtalmologiques
4. Atteinte des glandes salivaires (flux, scinti)
5. BGSA
6. Anticorps anti-SSA ou anti-SSB





4/6 critères et au moins critère 5 ou 6 présents

Respiratory Medicine 137 (2018) 95–102

Contents lists available at ScienceDirect

Respiratory Medicine

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

Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjögren's syndrome

Tomoyuki Kakugawa[a,*], Noriho Sakamoto[a], Hiroshi Ishimoto[a], Toshimasa Shimizu[b], Hideki Nakamura[b], Aya Nawata[c,k], Chiyo Ito[d], Shuntaro Sato[e,f], Tetsuya Hanaka[d], Keishi Oda[d], Takashi Kido[d], Takuto Miyamura[a], Shota Nakashima[a], Takatoshi Aoki[g], Seiko Nakamichi[h], Yasushi Obase[a], Kazuyoshi Saito[i], Kazuhiro Yatera[d], Yuji Ishimatsu[j], Toshiyuki Nakayama[c], Yukunori Korogi[g], Atsushi Kawakami[b], Yoshiya Tanaka[k], Hiroshi Mukae[a]

Risk factors for interstitial lung diseases.

Characteristics	Unadjusted[a]		Adjusted[b]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, years	1.080 (1.035–1.127)	< 0.001	1.078 (1.032–1.127)	0.001
Sex, male	4.786 (0.829–27.643)	0.080	12.178 (1.121–132.307)	0.040
Smoking, s or ex	1.500 (0.444–5.064)	0.514		
Dry mouth, yes	1.308 (0.458–3.735)	0.616		
Dry eyes, yes	1.071 (0.452–2.541)	0.876		
ANA, positive	2.285 (0.602–8.670)	0.225		
RF, positive	0.961 (0.383–2.410)	0.932		
Anti-Ro/SS-A antibody, positive	2.113 (0.644–6.929)	0.217		
Anti-La/SS-B antibody, positive	1.434 (0.597–3.443)	0.420		
IgG, mg/dL	1.000 (1.000–1.001)	0.674		
Labial gland biopsy, focus score, ≥ 4	3.288 (1.363–7.961)	0.008	3.954 (1.423–10.987)	0.008

Scléodermie systémique: classification ACR/EULAR 2013

- Skin thickening of the fingers extending proximal to the metacarpophalangeal joints: SSc;
- If that is not present, 7 additive items apply:
  - skin thickening of the fingers,
  - fingertip lesions,
  - telangiectasia,
  - abnormal nailfold capillaries,
  - **interstitial lung disease** or pulmonary arterial hypertension,
  - Raynaud's phenomenon,
  - **SSc-related autoantibodies.**

Anti-centromere
Anti-topoisomerase I
Anti-RNA polymerase III

van den Hoogen F et al. Ann Rheum Dis 2013

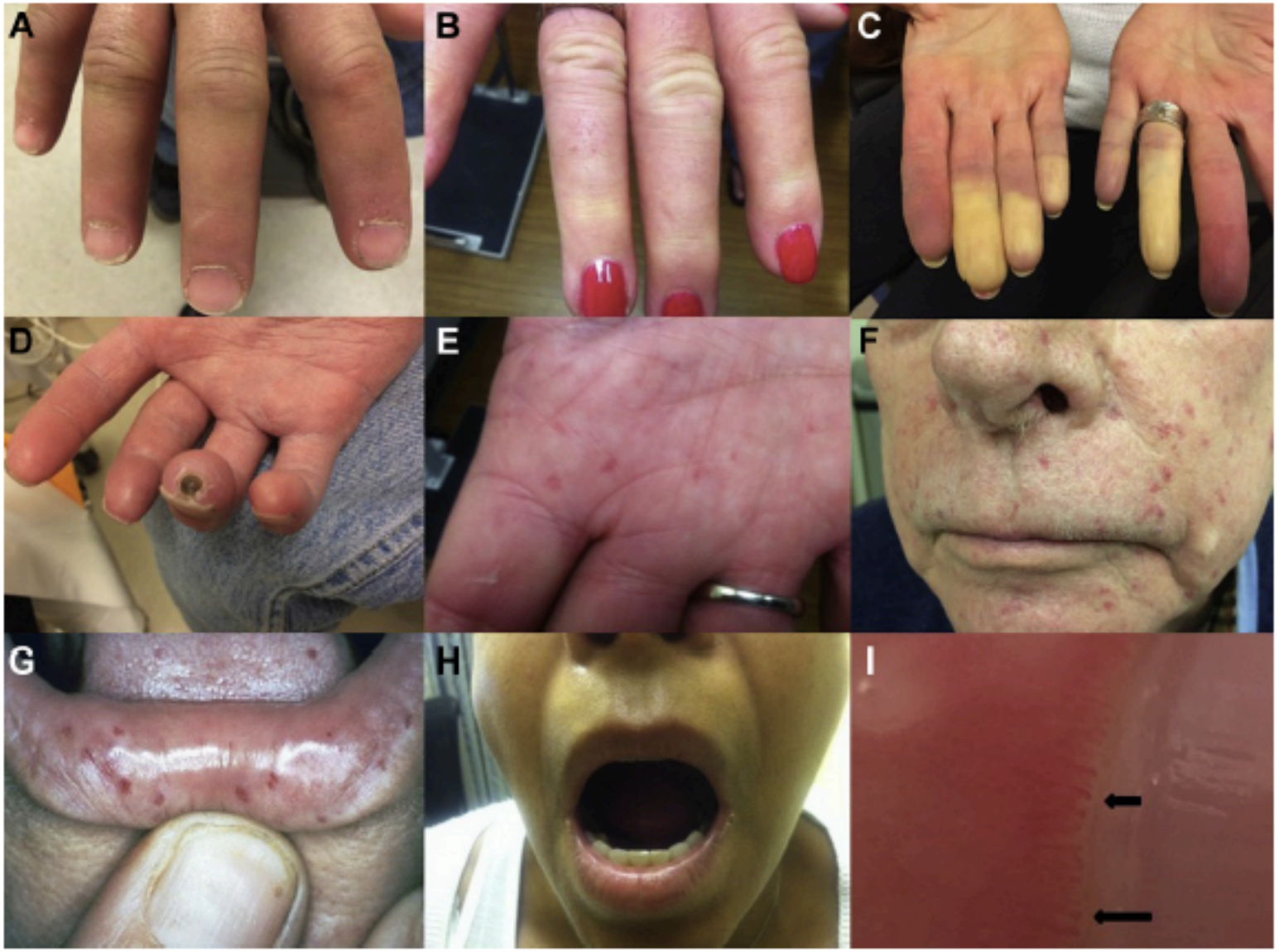
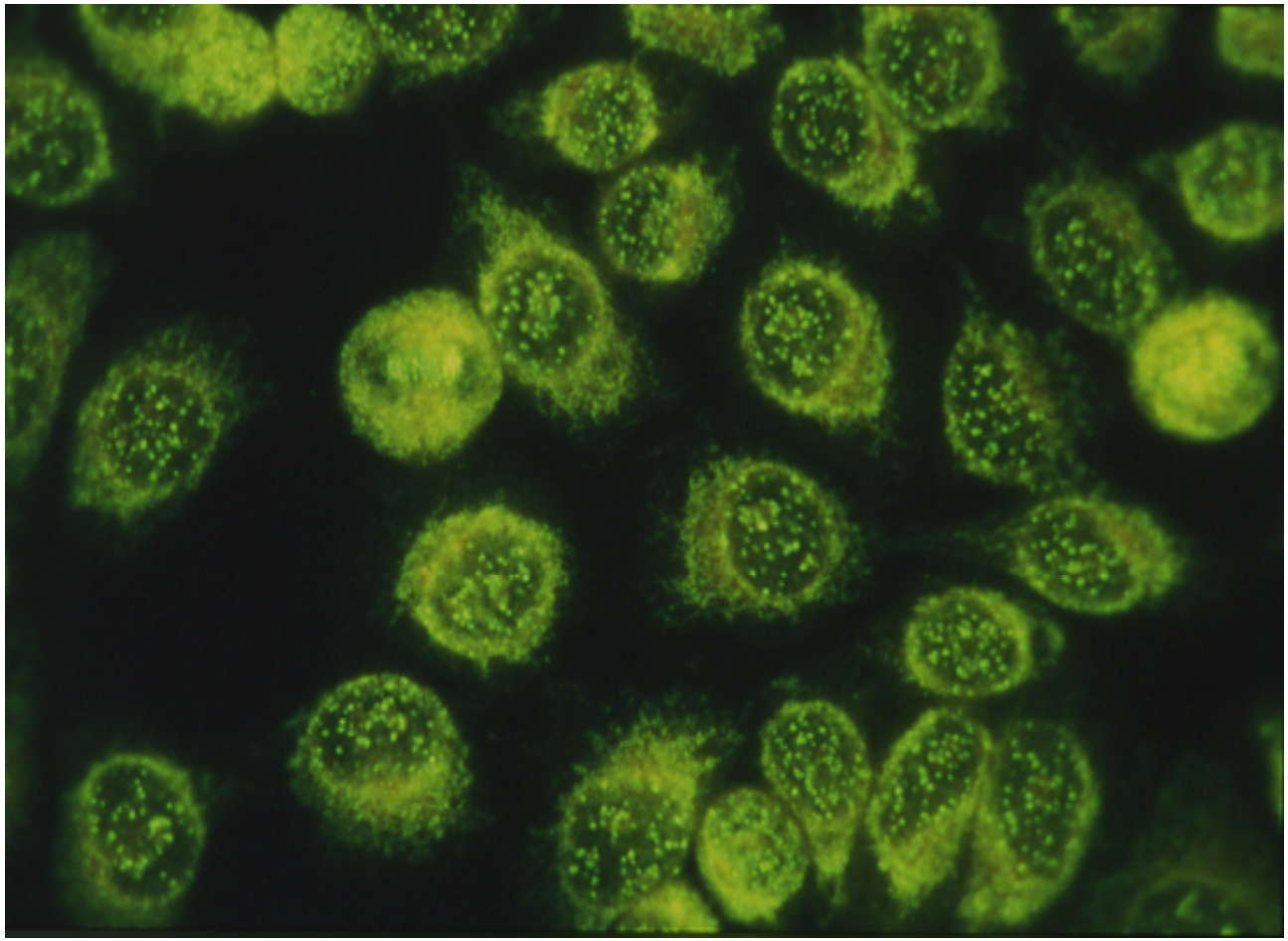


Figure 2 – *Clinical characteristics seen in systemic sclerosis/scleroderma. A, Sclerodactyly; note the lack of vertical skin creases on the extensor surfaces of the fingers from the proximal interphalangeal joint to the distal interphalangeal joint. B, Active Raynaud syndrome with sclerodactyly. C, Sharp demarcation in perfusion of the distal digits in a patient with active Raynaud syndrome. D, Ischemic ulceration in a patient with severe Raynaud syndrome. E, Palmar telangiectasia. F, Facial telangiectasia. G, Telangiectasia on the lip and tongue. H, Limited oral aperture. I, Dilated nail fold capillaries, which indicate a vasculopathy seen in scleroderma and other rheumatic syndromes.*

Doyle T et al. CHEST 2017

Ac anti-centromère

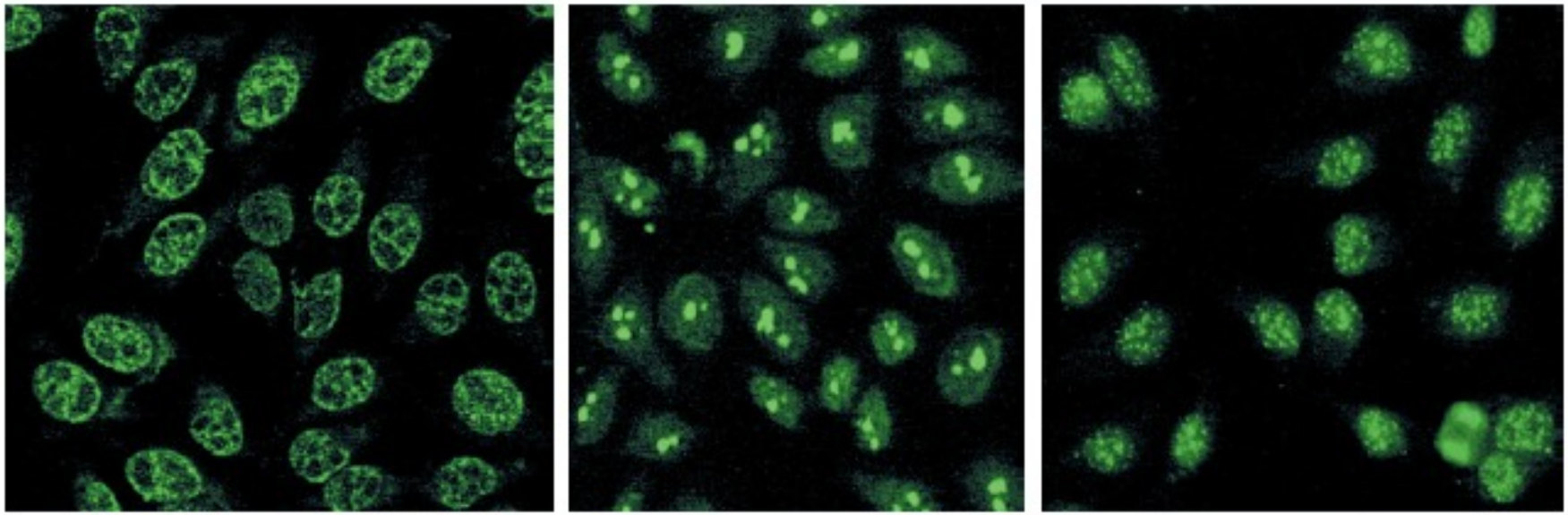


Antigen	Associated Condition	Sensitivity (%)	Specificity (%)
Anticentromere	Limited cutaneous systemic sclerosis	65	99.9

Habash-Bseiso, Clin Med Res 2005

Autoantibodies in scleroderma

A



B

Classic Autoantibodies	Clinical Features
Anti–topoisomerase I	Diffuse cutaneous scleroderma
Anticentromere proteins	Limited cutaneous scleroderma, pulmonary hypertension
Anti–RNA polymerase I/II	Diffuse cutaneous scleroderma, renal involvement
Antipolymyositis, sclerosis	Polymyositis, calcinosis
Antifibrillarin (U3RNP)	Diffuse cutaneous scleroderma, internal-organ involvement
Anti-Th/To	Limited cutaneous scleroderma, pulmonary fibrosis

New Autoantibodies	Role
Anti–endothelial cell	Induce apoptosis of endothelial cells
Anti–FBN 1	Activate normal human fibroblasts
Anti–MMP 1 and 3	Prevent degradation of ECM proteins
Anti-PDGFR	Stimulate normal human fibroblasts through Ha-Ras-ERK1/2-ROS
Anti–Nag-2	Induce endothelial-cell apoptosis

Gabrielli A et al. N Engl J Med 2009

Observational Study

Medicine®

OPEN

Single-specificity anti-Ku antibodies in an international cohort of 2140 systemic sclerosis subjects: clinical associations

S. Hoa, MD[a,b], M. Hudson, MD, MPH[a,b,c,*], Y. Troyanov, MD[d,e], S. Proudman, MBBS[f,g], J. Walker, MBBS, PhD[h], W. Stevens, MBBS, PhD[i], M. Nikpour, MBBS, PhD[i,j], S. Assassi, MD[k], M.D. Mayes, MD, MPH[k], M. Wang, MSc[b], M. Baron, MD[a,b,c], M.J. Fritzler, MD, PhD[l],

Abstract

Autoantibodies directed against the Ku autoantigen are present in systemic sclerosis (SSc) and have been associated with myositis overlap and interstitial lung disease (ILD). However, there is a paucity of data on the clinical correlates of anti-Ku antibodies in the absence of other SSc-specific antibodies. The aim of this study was to assess the clinical correlates of single-specificity anti-Ku in SSc.

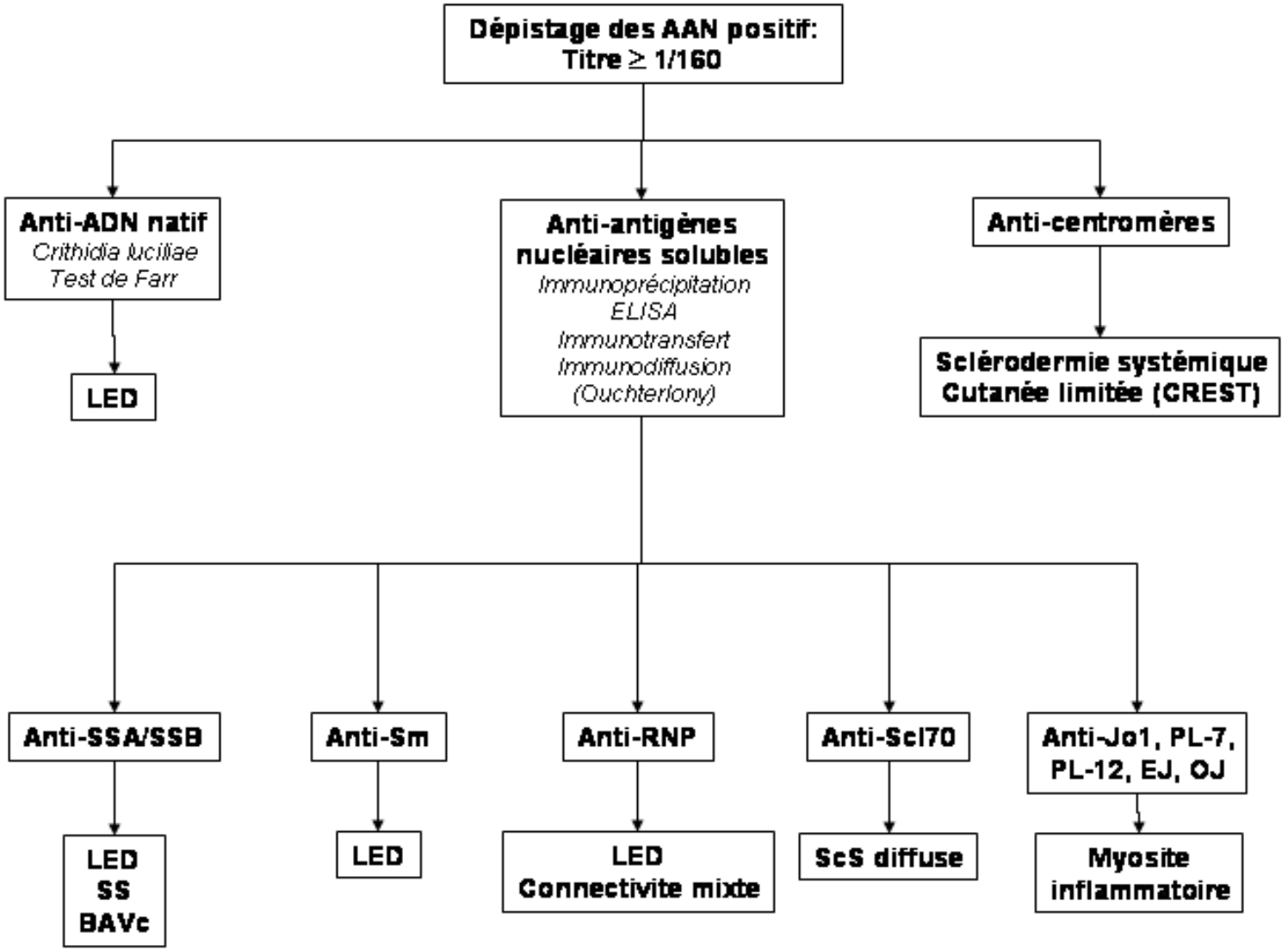
An international (Canada, Australia, USA, Mexico) cohort of 2140 SSc subjects was formed, demographic and clinical variables were harmonized, and sera were tested for anti-Ku using a line immunoassay. Associations between single-specificity anti-Ku antibodies (i.e., in isolation of other SSc-specific antibodies) and outcomes of interest, including myositis, ILD, and survival, were investigated.

Twenty-four (1.1%) subjects had antibodies against Ku, and 13 (0.6%) had single-specificity anti-Ku antibodies. Subjects with single-specificity anti-Ku antibodies were more likely to have ILD (58% vs 34%), and to have increased creatine kinase levels (>3× normal) at baseline (11% vs 1%) and during follow-up (10% vs 2%). No difference in survival was noted in subjects with and without single-specificity anti-Ku antibodies.

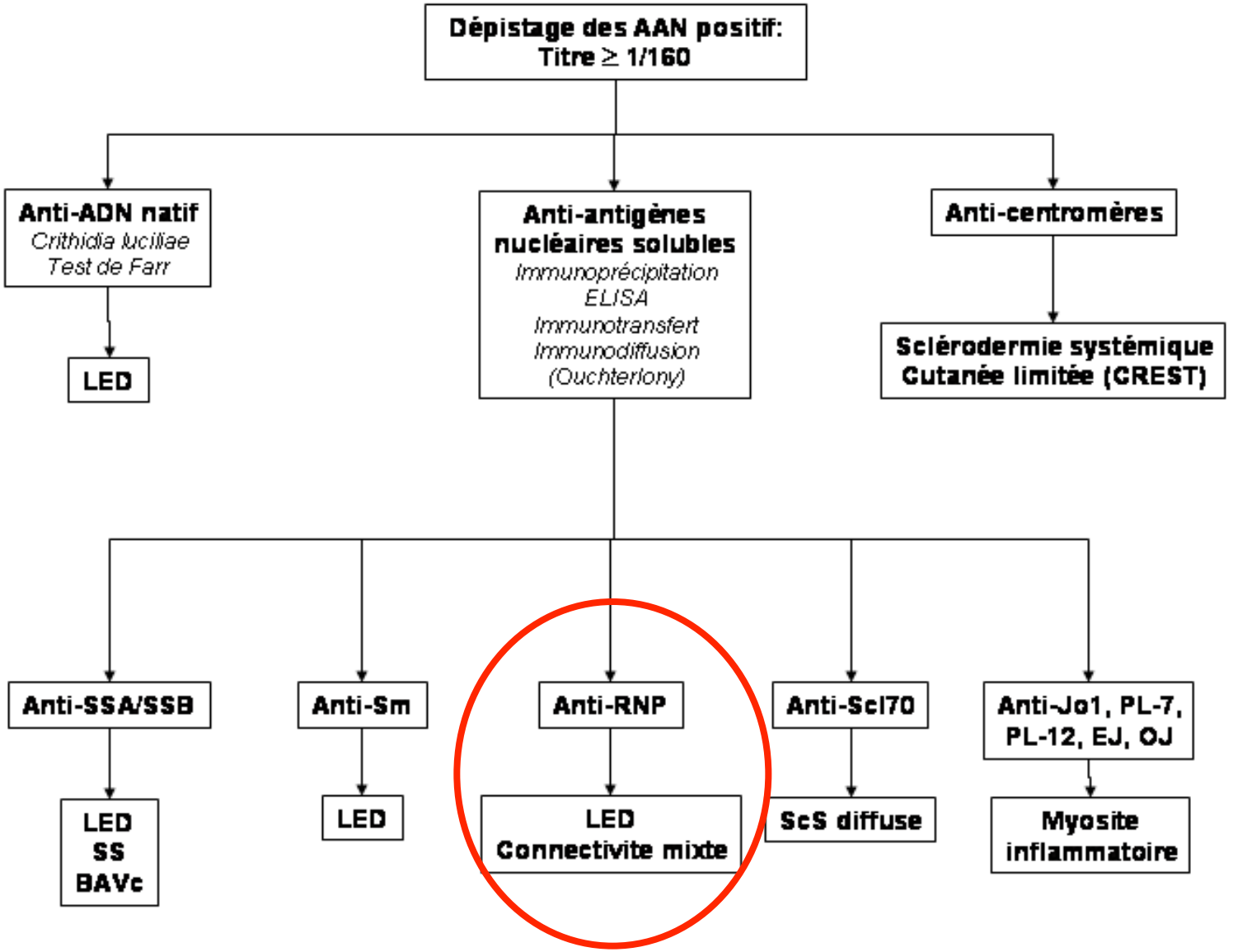
This is the largest cohort to date focusing on the prevalence and disease characteristics of single-specificity anti-Ku antibodies in subjects with SSc. These results need to be interpreted with caution in light of the small sample. International collaboration is key to understanding the clinical correlates of uncommon serological profiles in SSc.

Abbreviations: ACA = anticentromere antibodies, ACR = American College of Rheumatology, ANA = antinuclear antibodies, ARNAP = anti-RNA polymerase III antibodies, ASIG = Australian Scleroderma Interest Group, ATA = antitopoisomerase I

Conduite à tenir devant la mise en évidence d'Ac anti-nucléaires



Conduite à tenir devant la mise en évidence d'Ac anti-nucléaires



RHEUMATOLOGY

Rheumatology 2018;57:255–262
doi:10.1093/rheumatology/kex077
Advance Access publication 29 March 2017

Original article

Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study

Silje Reiseter[1,2], Ragnar Gunnarsson[2], Trond Mogens Aaløkken[3], May Brit Lund[4], Georg Mynarek[3], Jukka Corander[5], Joanna Haydon[6] and Øyvind Molberg[1,2]

Rheumatology key messages

- Interstitial lung disease is typically modest with slow progression and stable disease equally present.
- Progression of lung disease was evident in 1/5 of patients resulting in lung function deterioration.
- Risk factors for lung disease were male gender, high anti-RNP titres, anti-ro52 antibodies and absence of arthritis.

FIG. 2 Kaplan–Meier curves for interstitial lung disease involving ⩾5% and <5% of total lung capacity

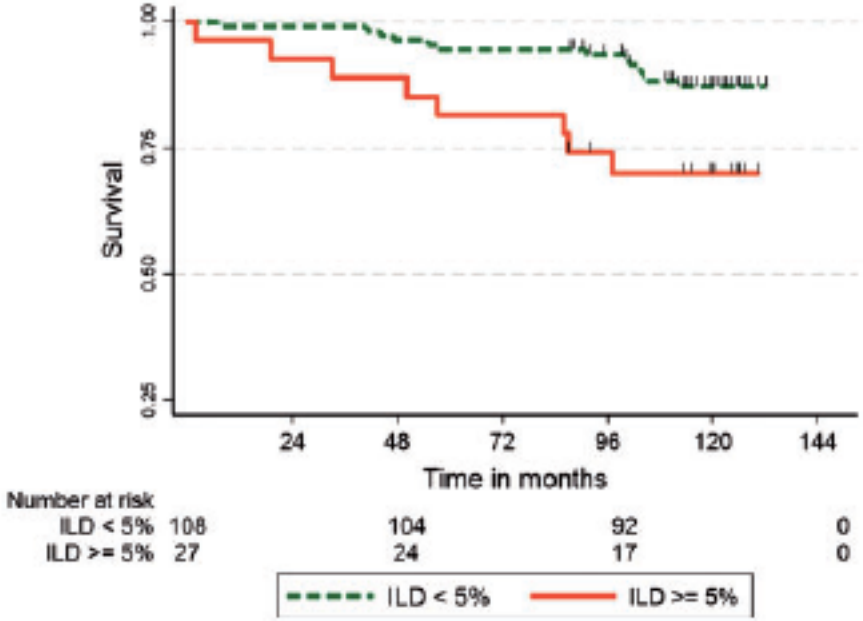


TABLE 4 Effect of interstitial lung disease on all-cause mortality in the MCTD cohort

Interstitial lung disease	Univariable HR (95% CI)	P-value	Multivariable[a] HR (95% CI)	P-value
Model 1: ⩾5% of TLV	2.8 (1.6, 2.8)	0.020	2.9 (1.1, 7.9)	0.038
Model 2: ⩾10% of TLV	3.5 (1.3, 9.5)	0.015	3.4 (1.1, 10.2)	0.028
Model 3: per 1% of TLV increase	1.1 (1.0, 1.1)	<0.001	1.1 (1.0, 1.1)	<0.001

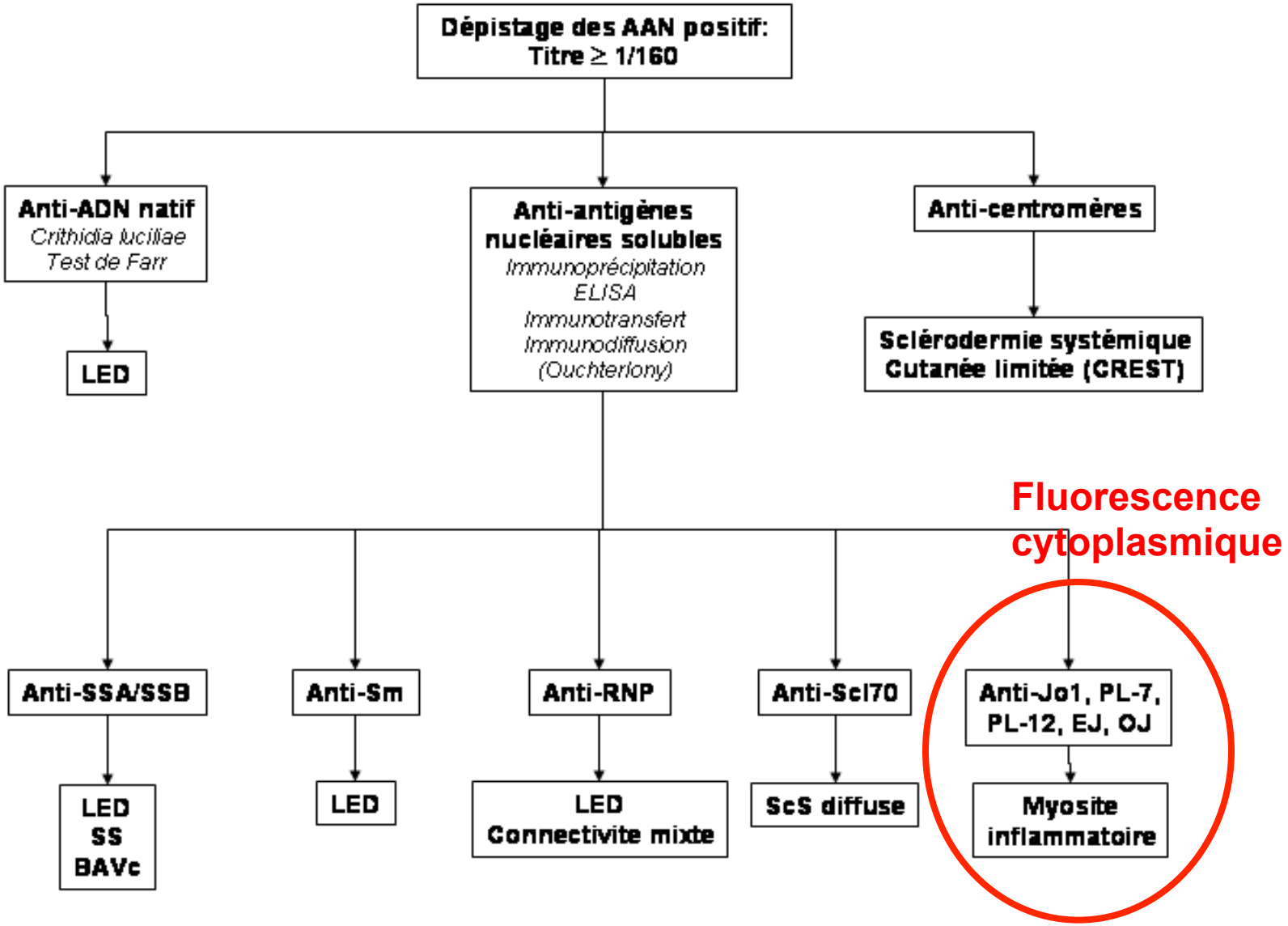
Univariable and multivariable cox regression analyses. [a]Vriables included in the multivariable models: age at baseline, smoking, disease duration at baseline and gender. TLV: total lung volume.

TABLE 3 Predictors of interstitial lung disease progression in MCTD analysed by cox regression

Clinical predictors	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Alarcon criteria	0.26 (0.10, 0.67)	0.005		
FVC % of predicted	0.95 (0.93, 0.98)	<0.001		
DLCO % of predicted	0.94 (0.92, 0.97)	<0.001		
ESR (per 10 mm increase)	1.5 (1.2, 1.9)	<0.001		
% ILD of TLV	1.1 (1.1, 1.1)	<0.001	1.1 (1.0, 1.1)	0.002
Arthritis	0.15 (0.06, 0.36)	<0.001	0.22 (0.08, 0.61)	0.004
Anti-RNP value (per 50 U/l increase)	1.4 (1.1, 1.8)	0.009	1.5 (1.1, 2.0)	0.008
Age at baseline	1.0 (1.0, 1.1)	0.065	1.1 (1.0, 1.1)	0.028
Male gender	2.0 (0.9, 4.6)	0.112	4.0 (1.4, 11.5)	0.011
Anti-ro-52 positivity	3.2 (1.3, 7.7)	0.01	3.5 (1.2, 10.2)	0.023

DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; TLV: total lung volume.

Conduite à tenir devant la mise en évidence d'Ac anti-nucléaires



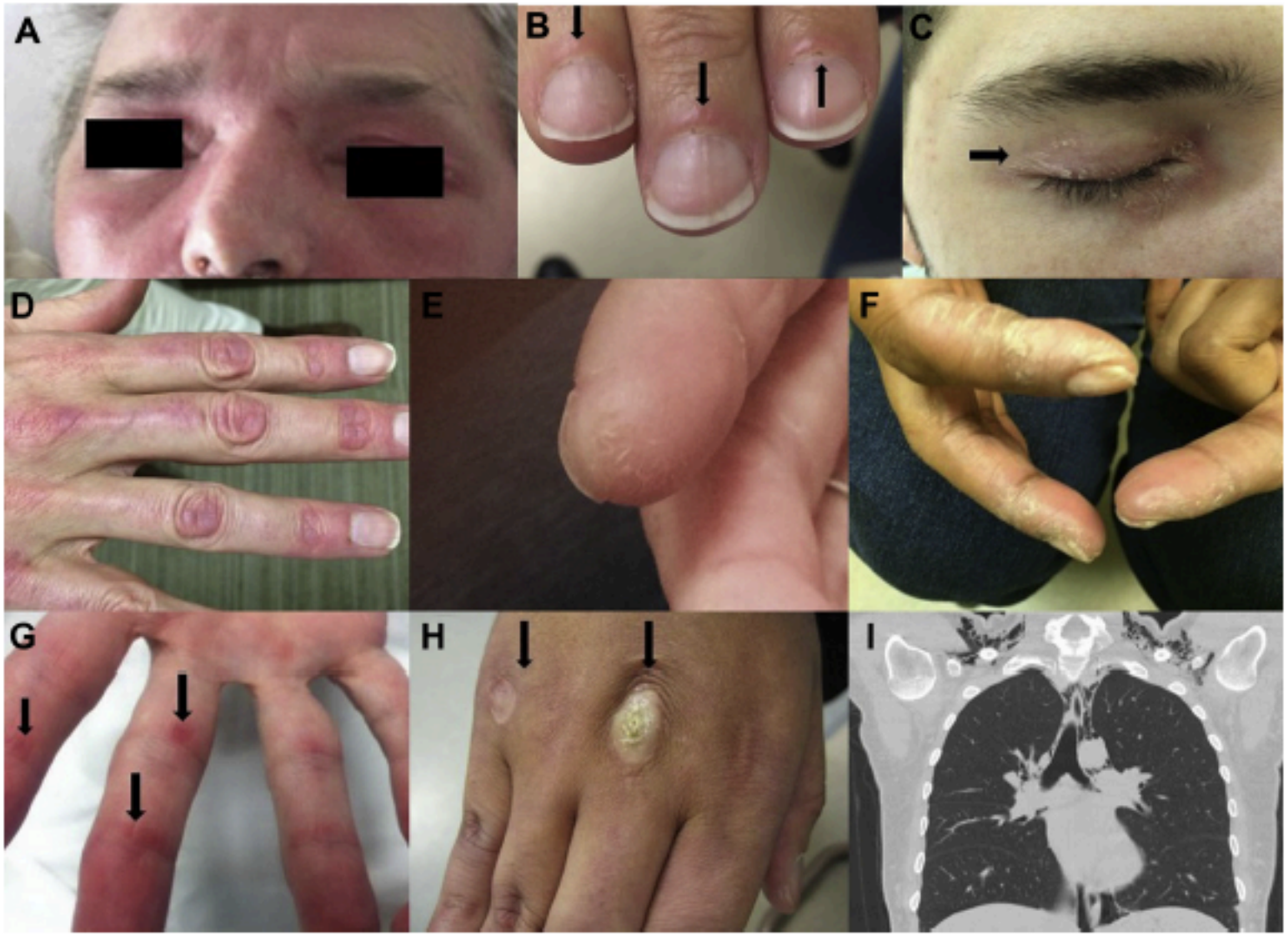
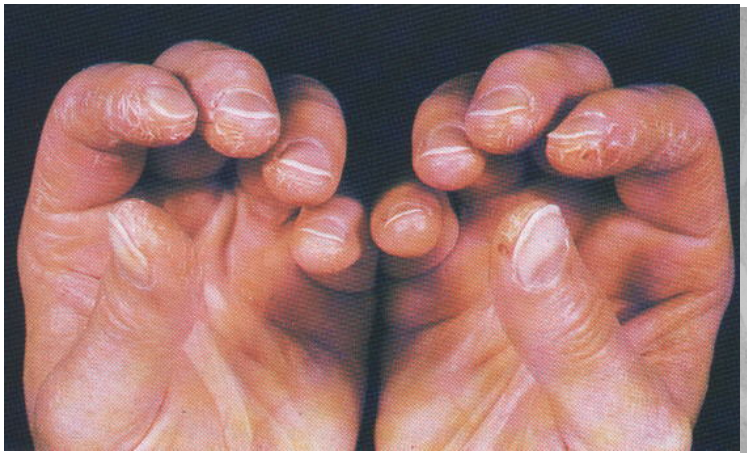


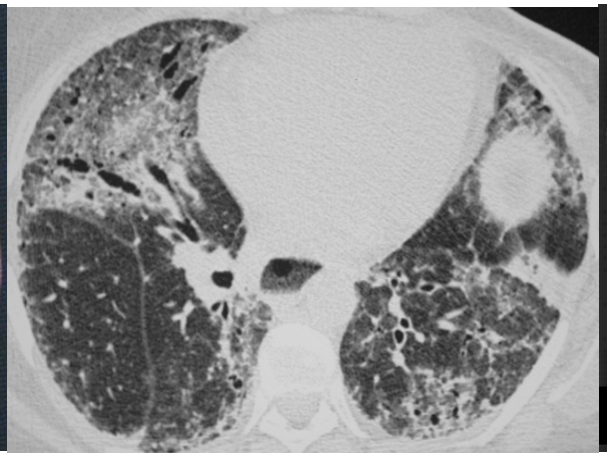
Figure 3 – *Clinical characteristics seen in the autoimmune myositis. A, Diffuse erythema of the face in a patient with dermatomyositis and interstitial lung disease (ILD). B, Periungual erythema (down arrows) of fingers with ischemic vascular changes (up arrow) in the periungual area in a patient with dermatomyositis. C, Eyelid erythema and scaling seen in dermatomyositis. D, Gottren papules over the extensor surfaces of the fingers with periungual erythema in dermatomyositis. E, Cracking in the distal tips of the fingers of a patient with antisynthetase syndrome: "mechanics hands." F, Mechanics hands in the antisynthetase syndrome. G, Nodular erythematous lesions on the palmar surface of the hand seen in melanoma differentiation-associated gene 5 (MDA5) antibody-related ILD. H, Healing ulcerating plaques on the dorsal surface of the hand in a patient with MDA-5 antibody-related ILD. I, Pneumomediastinum in dermatomyositis.*

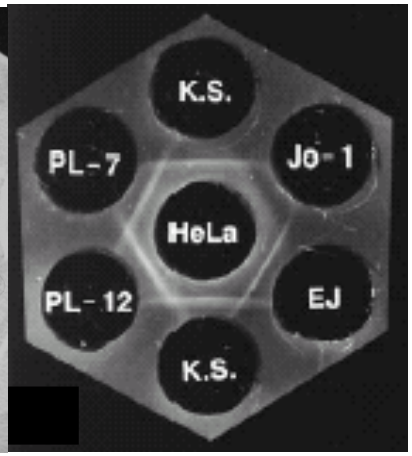
Doyle T et al. CHEST 2017

Ac anti-synthétase

- **Myopathies inflammatoires**
  - ✓**AutoAc: 56% (muscle spécifiques: 38%)**
  - ✓**Ac anti-Jo-1 (histidyl-ARNt-synthétase): 18-20%**
  - ✓**Autres Ac anti-synthétase PL-7, PL-12, EJ, OJ, KS: 3-6%**
- **Techniques**
  - ✓**ELISA, Immunodot, Immunodiffusion**
- **Clinique**
  - ✓**Arthrites, PID, myosite, main de mécanicien**







Brouwer R et al. Ann Rheum Dis 2001;60:116-23
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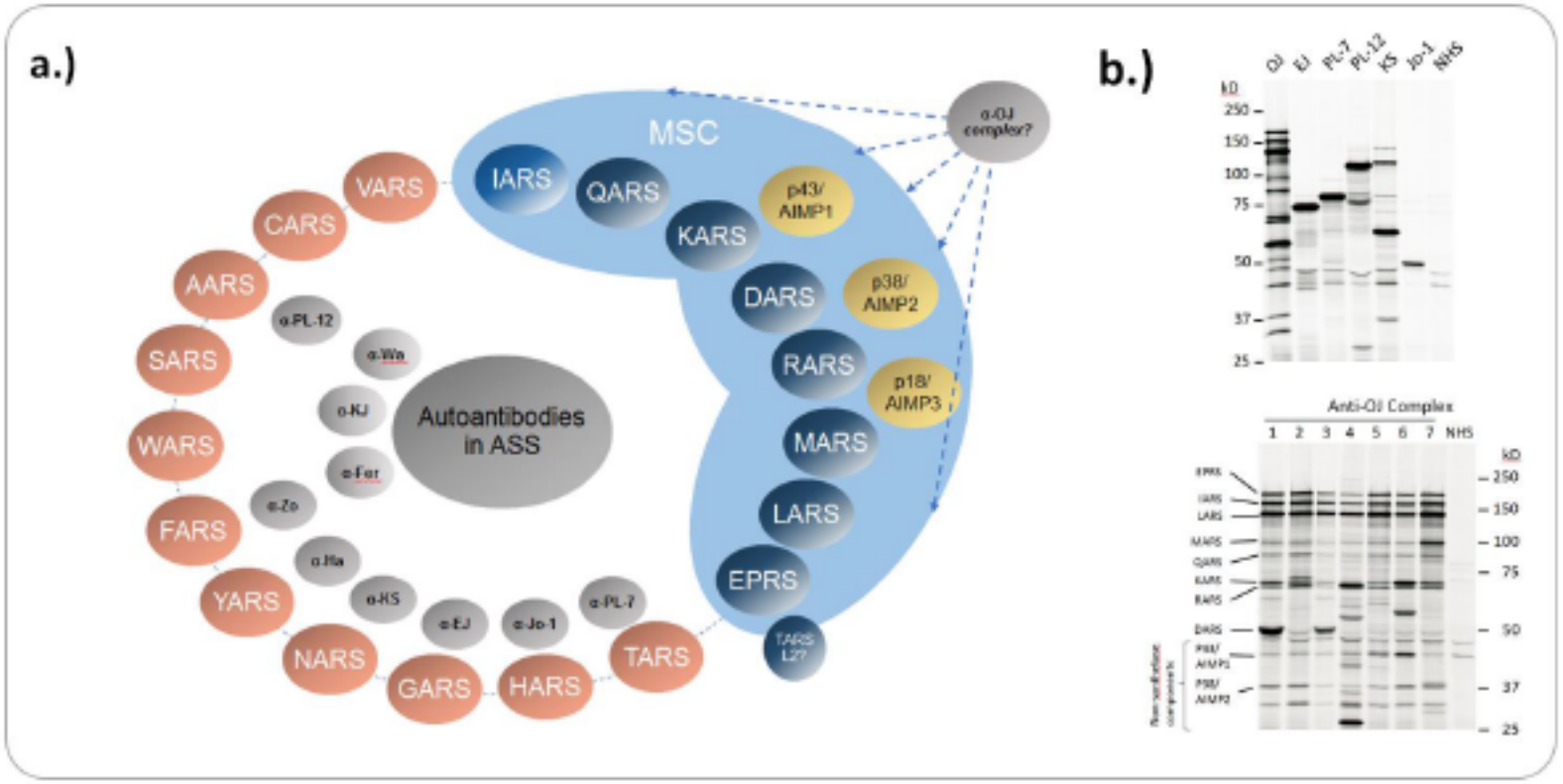

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Table 1 Autoantibodies targeted at aminoacyl-tRNA synthetases or proteins associated with translation

Autoantibody	Autoantigen	ARS class	Molecular weight in kDa (IP)	Clinical phenotype	Prevalence in IIM (%)
Aminoacyl-tRNA synthetases					
Anti-Jo-1[55]	Histidyl-tRNA synthetase (HARS)	II	50	ASS/ILD	25-30%
Anti-PL-12 [56]	Alanyl-tRNA synthetase (AARS)	II	110	ASS/ILD [57]	2-5%
Anti-PL-7 [58]	Threonyl-tRNA synthetase (TARS)	II	80	ASS/ILD [59]	2-5%
Anti-EJ [11]	Glycyl-tRNA synthetase (GARS)	II	75	ASS/ILD	< 2%
Anti-KS [60]	Asparaginyl-tRNA synthetase (NARS)	II	65[60]	ILD, arthritis, sicca syndrome [60,61]	< 2% [60]
Anti-OJ [11]	Components of the MSC	I (IRS)	150+170/130/75	ASS/ILD	< 5% [1,2]
Anti-YRS/Anti-Ha [62]	Tyrosyl-tRNA synthetase (YARS)	I	59	ASS/ILD	Rare
Anti-Zo [63]	Pheynlalanyl-tRNA synthetase (FARS)	II	60/70	ASS/ILD	Rare
Anti-WRS [64]	Tryptophanyl-tRNA synthetase (WARS)	I	120	SLE, RA, malignancy [65,66]	NA
Proteins associated with translation					
Anti-Mas [67]	Selenocysteine-seryl-tRNA-protein complex	NA	48	AIH, IIM	2% [68]
Anti-KJ [69]	Translocation factor	NA	30/43	ASS-like syndrome	Rare
Anti-Wa [70]	NEFA/nucleobindin-2 [71]	NA	48	ASS-like syndrome	Rare
Anti-Fer [72]	Eukaryotic elongation factor Ia [73]	NA	Unknown	ASS-like syndrome	Rare

Vulsteke JB et al. Autoimmunity Rev 2019

Clinical follow-up predictors of disease pattern change in anti-Jo1 positive anti-synthetase syndrome: Results from a multicenter, international and retrospective study

	New accompanying features		
	Yes	No	p value*
Patients number (%)	40 (24)	125 (76)	–
Female sex (%)	29 (72.5)	94 (75)	0.734
Median age in years at disease onset (IQR)	49 (41–60.5)	54 (42–64)	0.307
Median follow-up in months (IQR)	102.5 (69–167)	84 (44–144)	0.347
Baseline triad manifestations			
Isolated arthritis (%)	19 (47.5)	30 (24)	0.005
Isolated myositis (%)	6 (15)	21 (17)	0.789
Isolated ILD (%)	3 (7.5)	21 (17)	0.148
Arthritis and myositis (%)	6 (15)	20 (16)	0.880
Arthritis and ILD (%)	2 (5)	12 (9)	0.365
Myositis and ILD (%)	4 (10)	21 (17)	0.298
Final triad manifestations			
Isolated arthritis (%)	1 (2.5)	4 (3.5)	0.822
Isolated myositis (%)	0 (0)	5 (4)	0.200
Isolated ILD (%)	1 (2.5)	14 (11)	0.097
Arthritis and myositis (%)	3 (7.5)	20 (16)	0.178
Arthritis and ILD (%)	4 (10)	18 (14)	0.477
Myositis and ILD (%)	6 (15)	26 (21)	0.421
Arthritis, myositis and ILD (%)	25 (62.5)	38 (30.5)	0.001
New development of classic triad manifestations (%)	32 (80)	63 (50.5)	0.001
Median (IQR) time in months to ex-novo occurrence of triad findings	14 (8–51)	16 (37–49.5)	0.715

ILD: interstitial lung disease. RP: Raynaud phenomenon. MHs: mechanic hands. Others: Chi-square test. IQR: Interquartile range.

* Independent Sample *t*-test or Welch-test (if unequal variances).

Bartoloni E et al. Autoimmunity Reviews 2017

Table 2 Clinical features of patients with anti-OJ autoantibodies described in literature

Study (authors) (year, reference)	Primary diagnosis	Patients (n)	Myositis (n/n)	DM skin lesions (n/n)	MH (n/n)	ILD (n/n)	Arthritis (n/n)	RP (n/n)	Fever (n/n)
Detected or confirmed by RNA and/or protein IP									
Targoff et al. (US, 1993, [12])	IIM	9	8/9	3/9	NA	8/9	6/9	1/9	NA
Friedman et al. (US, 1996, [31])	CTD/ILD	2	1/2	0/2	NA	2/2	1/2	0/2	0/2
Gelpi et al.* (US, 1996, [15])	ASS	1	1/1	0/1	NA	1/1	1/1	0/1	1/1
Ohosone et al. (Japan, 1998, [43])	PM-RA	1	1/1	0/1	NA	1/1	1/1	1/1	0/1
Sato et al.** (Japan, 2007, [44])	IIM/ILD	7	4/7	0/7	NA	7/7	4/7	0/7	NA
Koreeda et al. (Japan, 2010, [29])	ILD	1	0/1	1/1	NA	1/1	1/1	1/1	0/1
Noda et al. (Japan, 2011, [45])	DM	1	1/1	1/1	1/	1/1	0/1	0/1	0/1
Kunimasa et al. (Japan, 2012, [30])	IIM-ILD	2	2/2	0/2	1/2	2/2	0/2	0/2	1/2
Hamaguchi et al.** (Japan, 2013, [35])	ASS	8	2/8	1/8	3/8	8/8	1/8	1/8	NA
Johnson et al. (US, 2014, [46])	ILD	2	1/2	0/2	0/2	2/2	NA	NA	0/2
Hamada et al. (Japan, 2017, [37])	JPM	1	1/1	0/1	0/	0/1	1/1	1/1	1/1
Noguchi et al.** (Japan, 2017, [1])	IIM***	14	14/14***	8/14	NA	12/14	4/14	0/14	7/14
Pauling et al. (GB, 2017, [47])	SSc	1	1/1	0/1	NA	NA	1/1	1/1	NA
Kapoor et al. (US, 2018, [48])	ASS	1	1/1	1/1	NA	0/1	1/1	0/1	0/1
Total (n/n, %)		**51**	**38/51 (75%)**	**15/51 (29%)**	**5/14 (36%)**	**45/50 (90%)**	**15/49 (31%)**	**6/49 (12%)**	**10/26 (38%)**
Detected by IB									
Hervier et al. (France, 2011, [36])	ASS	1	1/1	0/1	0/	1/1	0/1	1/1	NA

Vulsteke JB et al. Autoimmunity Rev 2019

RHEUMATOLOGY

Rheumatology 2017;56:999–1007
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Advance Access publication 4 March 2017

Original article

A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies

Iago Pinal-Fernandez[1,*], Maria Casal-Dominguez[2,*], Julio A. Huapaya[2,*], Jemima Albayda[2], Julie J. Paik[2], Cheilonda Johnson[2], Leann Silhan[2], Lisa Christopher-Stine[2,†], Andrew L. Mammen[1,†] and Sonye K. Danoff[2,†]

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A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies

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Rheumatology key messages

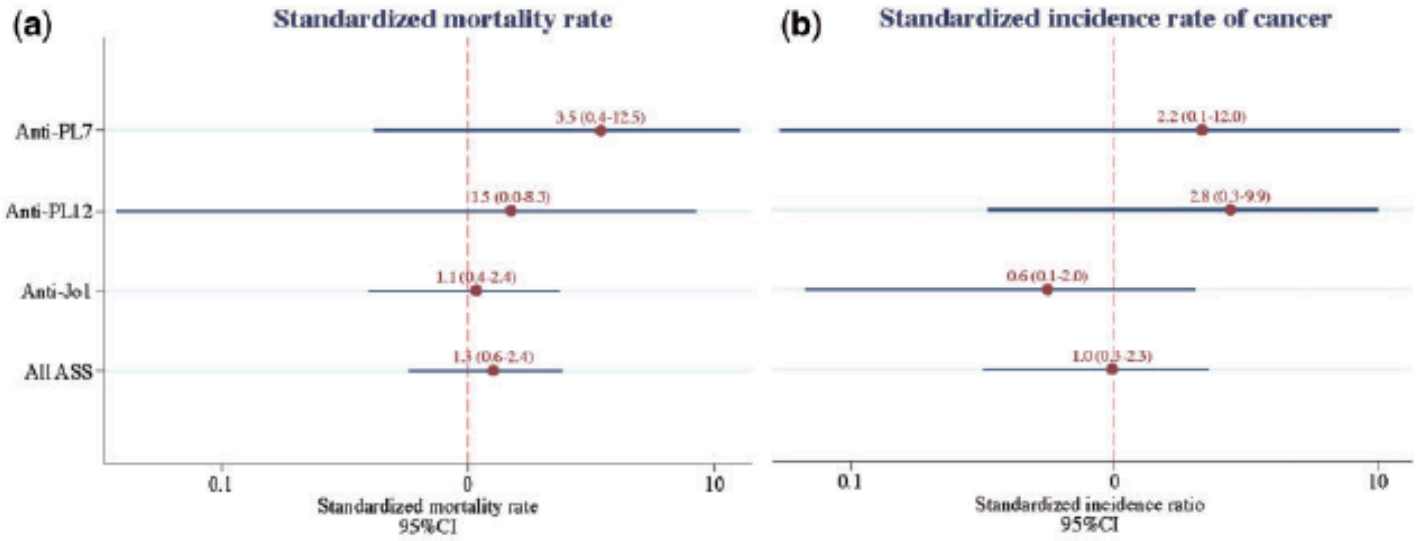
- Different anti-synthetase autoantibodies are associated with phenotypically distinct subgroups within the anti-synthetase spectrum.
- Anti-PL7 and anti-PL12 syndromes are characterized by more severe interstitial lung disease.
- Black race is a major prognostic factor associated with lung disease severity.

TABLE 4 Multivariate longitudinal analysis of muscle and lung involvement in patients with the anti-synthetase syndrome

	Mean strength Coefficient (95% CI)	CK concentration (logarithmic scale) Coefficient (95% CI)	%FVC Coefficient (95% CI)	%DLCO Coefficient (95%CI)
Autoantibody (compared with anti-Jo1)				
Anti-PL12	0.28 (−0.27, 0.82)	**−0.42 (−0.71, −0.14)****	**−9.70 (−17.56, −1.84)***	**−10.47 (−19.71, −1.24)***
Anti-PL7	0.32 (−0.25, 0.89)	0.03 (−0.27, 0.33)	−3.92 (−13.63, 5.80)	**−13.95 (−25.42, −2.48)***
Time from onset to visit (1 year)	0.02 (−0.01, 0.06)	**−0.04 (−0.07, −0.02)*****	**0.89 (0.28,1.51)****	−0.09 (−0.49, 0.31)
Age of onset (each 10 years)	−0.05 (−0.18, 0.09)	**−0.09 (−0.17, −0.02)***	0.59 (−1.61, 2.80)	−2.15 (−4.76, 0.46)
Female *vs* male	−0.12 (−0.51, 0.28)	−0.12 (−0.33, 0.10)	−4.73 (−11.00, 1.54)	2.04 (−5.18, 9.26)
Black *vs* white	0.04 (−0.36, 0.45)	0.08 (−0.13, 0.29)	**−17.53 (−23.87, −11.18)*****	**−11.73 (−19.13, −4.32)****

Multilevel regression with random slopes and random intercepts. Multivariate analysis was adjusted by time from onset, age at onset, sex, race and immunosuppressant drugs (CS dose and treatment with IVIGs, rituximab, MMF, MTX or AZA). Bold values are statistically significant. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

FIG. 2 Standard mortality and cancer incidence rates



ORIGINAL

Clinical characteristics of dermatomyosits/polymyositis associated interstitial lung disease according to the autoantibody

Tomoo Kishaba[1], Rita McGill[2], Yuichiro Nei[1], Sachi Ibuki[3], Masashi Momose[1, 4], Kenta Nishiyama[1, 5], Hiroaki Nagano[1], and Shin Yamashiro[1]

[1]*Department of Respiratory Medicine, Okinawa Chubu Hospital, Uruma, Okinawa, Japan,* [2]*Division of Nephrology, University of Chicago, Illinois, USA,* [3]*Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan,* [4]*Division of Internal Medicine, Miyako Hospital, Miyakojima, Okinawa, Japan,* [5]*Division of Internal Medicine, Hokubu Hospital, Nago, Okinawa, Japan*

The Journal of Medical Investigation Vol. 65 2018

	Antibody unknown (n=30)	Anti-ARS antibody (n=18: Anti-Jo-1 14, Anti PL-7 2, Anti KS 1, Anti OJ 1)	Anti-MDA-5 antibody (n=4)	p-value
Age	55.5 (17, 80)	60.5 (26, 76)	45.5 (23, 55)	0.135
Gender (M/F)	9/21	6/12	1/3	0.940
Smoking (Pack-year)	0 (0, 1400)	13.8 (0, 45)	27 (0, 90)	0.245
Fever (%)	30	38.9	50	0.661
Cough (%)	26.7	55.6	75	0.051
Dyspnea (%)	40	55.6	75	0.316
Myalgia (%)	66.7	44.4	25	0.147
Arthralgia (%)	33.3	27.8	50	0.693
Raynaud (%)	6.7	5.6	0	0.867
Rash (%)	63.3	16.7	100	< 0.001
Subungual erythema (%)	26.7	11.1	100	0.002
Splinter Hemorrahge (%)	13.3	11.1	50	0.139
Mechanic Hand (%)	16.7	11.1	0	0.621
Erythema (%)	46.7	16.7	100	0.006
Gottron's Sign (%)	36.7	5.6	100	0.001
Heliotrope Rash (%)	26.7	0	75	0.003
Sausage Finger (%)	26.7	5.6	75	0.010
Initial PSL dose (mg/day)	40.1±19.6	44.4±15.9	52.5±9.6	0.292
Combination therapy (%)	40	66.7	75	0.711
Survival time (months)	84.3	22.9	1.00	< 0.001

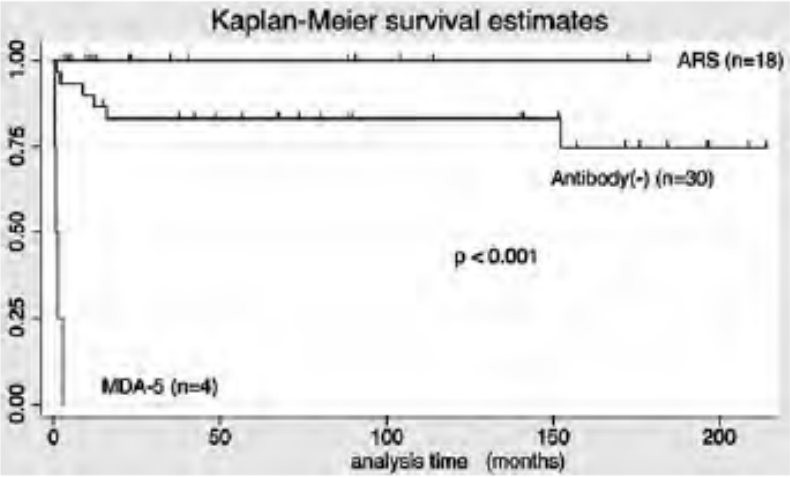


Figure 4. Kaplan-Meier survival curve
Anti MDA-5 antibody positive patients showed statistically significant poor survival compared to other two groups. (Log rank = $p < 0.001$)

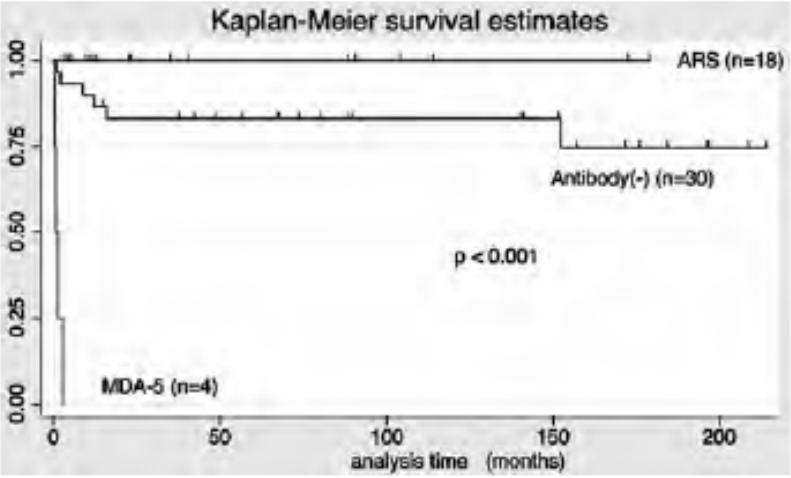


Figure4. Kaplan-Meier survival curve
Anti MDA-5 antibody positive patients showed statistically significant poor survival compared to other two groups. (Log rank = p < 0.001)

	Antibody Type	Cause of Death	Interval from Initial treatment (months)
Case 1 89y F	Unknown	Pneumonia	152.4
Case 2 44y F	Unknown	Pneumonia	12.2
Case 3 80y F	Unknown	Pneumonia	1.9
Case 4 80y M	Unknown	Pneumonia	8.6
Case 5 50y M	MDA-5	Respiratory failure	0.3
Case 6 41y F	MDA-5	Respiratory failure	2.7
Case 7 57y F	Unknown	Cancer	15.8
Case 8 56y F	Unknown	Pneumonia	1.0
Case 9 56y F	MDA-5	Respiratory failure	1.3
Case 10 23y F	MDA-5	Respiratory failure	0.7

ORIGINAL ARTICLE

Distinctive cutaneous and systemic features associated with specific antimyositis antibodies in adults with dermatomyositis: a prospective multicentric study of 117 patients

M. Best,[1] M. Jachiet,[2] N. Molinari,[3,4] F. Manna,[3] C. Girard,[1] V. Pallure,[5] A. Cosnes,[6] D. Lipsker,[7] T. Hubiche,[8] J.-L. Schmutz,[9] Y. Le Corre,[10] N. Cordel,[11] M. Dandurand,[12] O. Dereure,[1,13] B. Guillot,[1,13] A. Du-Thanh,[1,13] C. Bulai Livideanu,[14] F. Chasset,[15] J.-D. Bouaziz,[2] C. Francès,[15] D. Bengoufa,[16] T. Vincent,[17] D. Bessis,[1,13,*] and on behalf of the Study Group of Systemic Diseases in Dermatology (EMSED: Étude des Maladies Systémiques en Dermatologie)

Table 3 Estimated risk of cancer, interstitial lung disease and calcinosis in the presence of pertinent parameters (uni- and multivariate analysis)

	Pertinent parameters	Univariate analysis			Multivariate analysis		
		OR	CI 95%	*P* value	OR	CI 95%	*P* value
Cancer	Lateral hip erythema	2	0.74–5.37	0.169	2.75	0.93–8.13	0.0675
	Cutaneous ulceration and/or necrosis	2	0.74–5.37	0.169	3.1	1.05–9.15	**0.041**
	Oral manifestations	0.36	0.097–1.36	0.1338	0.26	0.07–0.95	**0.041**
Interstitial lung disease	Anti-MDA5-positive	27.49	7.16–105.52	**<0.0001**	25.35	4.41–145.68	**0.0003**
	Lateral hip erythema	4	0.99–16.22	0.0523	8.44	1.39–51.08	**0.0203**
	Mechanic's hands	6.57	1.63–25.99	**0.0073**	6.59	1.17–37.14	**0.0327**
Calcinosis	Anti-NXP-2-positive	6.67	1.01–44.1	**0.0491**	9.77	1.22–78.44	**0.032**

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Scandinavian Journal of Rheumatology

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Describing and expanding the clinical phenotype of anti-MDA5-associated rapidly progressive interstitial lung disease: case series of nine Canadian patients and literature review

S Hoa, Y Troyanov, MJ Fritzler, IN Targoff, S Chartrand, AM Mansour, E Rich, H Boudabbouz, J Bourré-Tessier, M Albert, JR Goulet, M Landry & JL Senécal

www.impactjournals.com/oncotarget/ Oncotarget, 2017, Vol. 8, (No. 44), pp: 76129-76140

Research Paper

Assessment of anti-MDA5 antibody as a diagnostic biomarker in patients with dermatomyositis-associated interstitial lung disease or rapidly progressive interstitial lung disease

Liubing Li[1,*], Qian Wang[1,*], Xiaoting Wen[1,*], Chenxi Liu[1,*], Chanyuan Wu[1], Funing Yang[1,2], Xiaofeng Zeng[1] and Yongzhe Li[1]

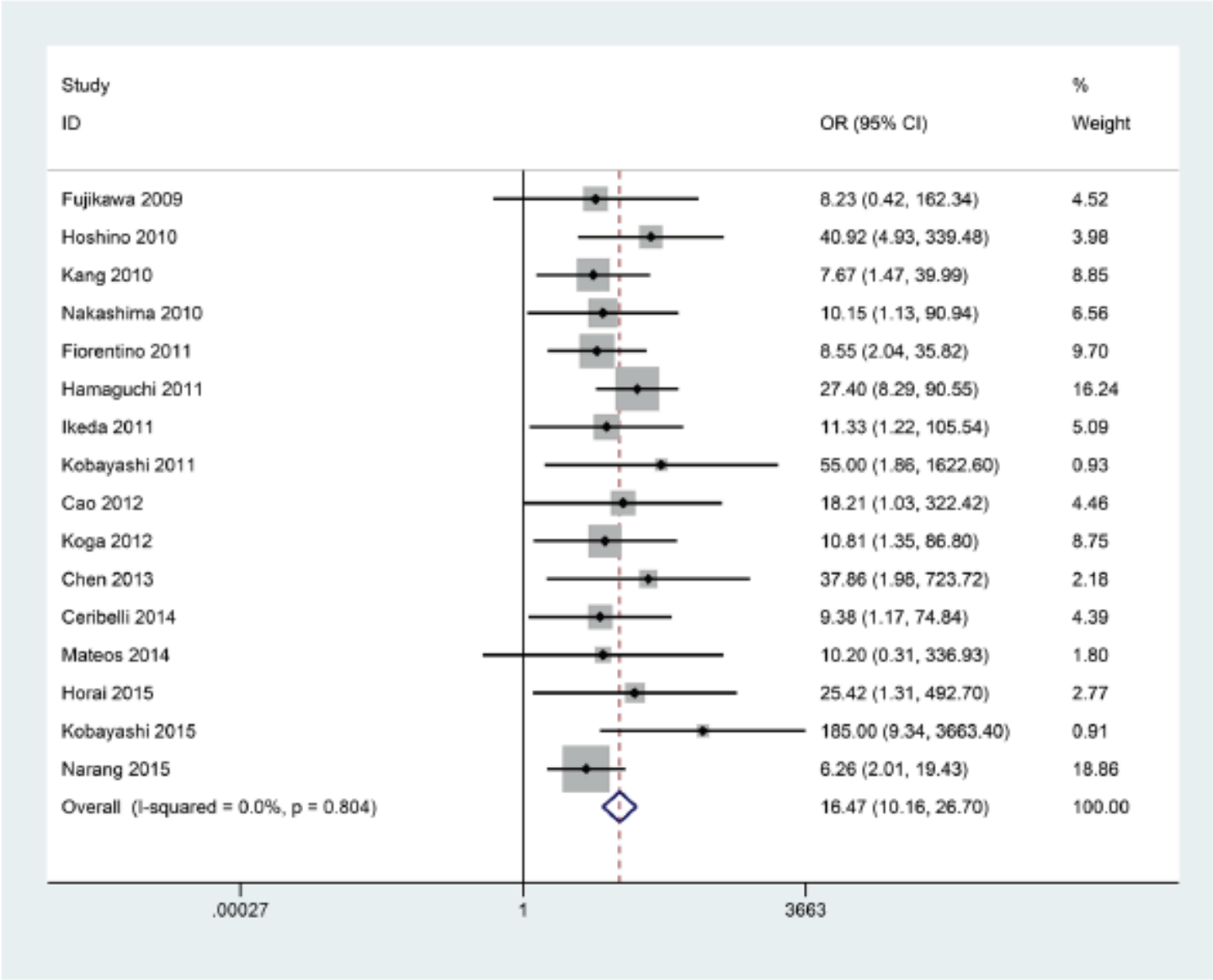


Figure 2: Forest plot of the association between anti-MDA5 antibody and ILD risk of DM patients with 491 DM with ILD versus 605 DM without ILD.

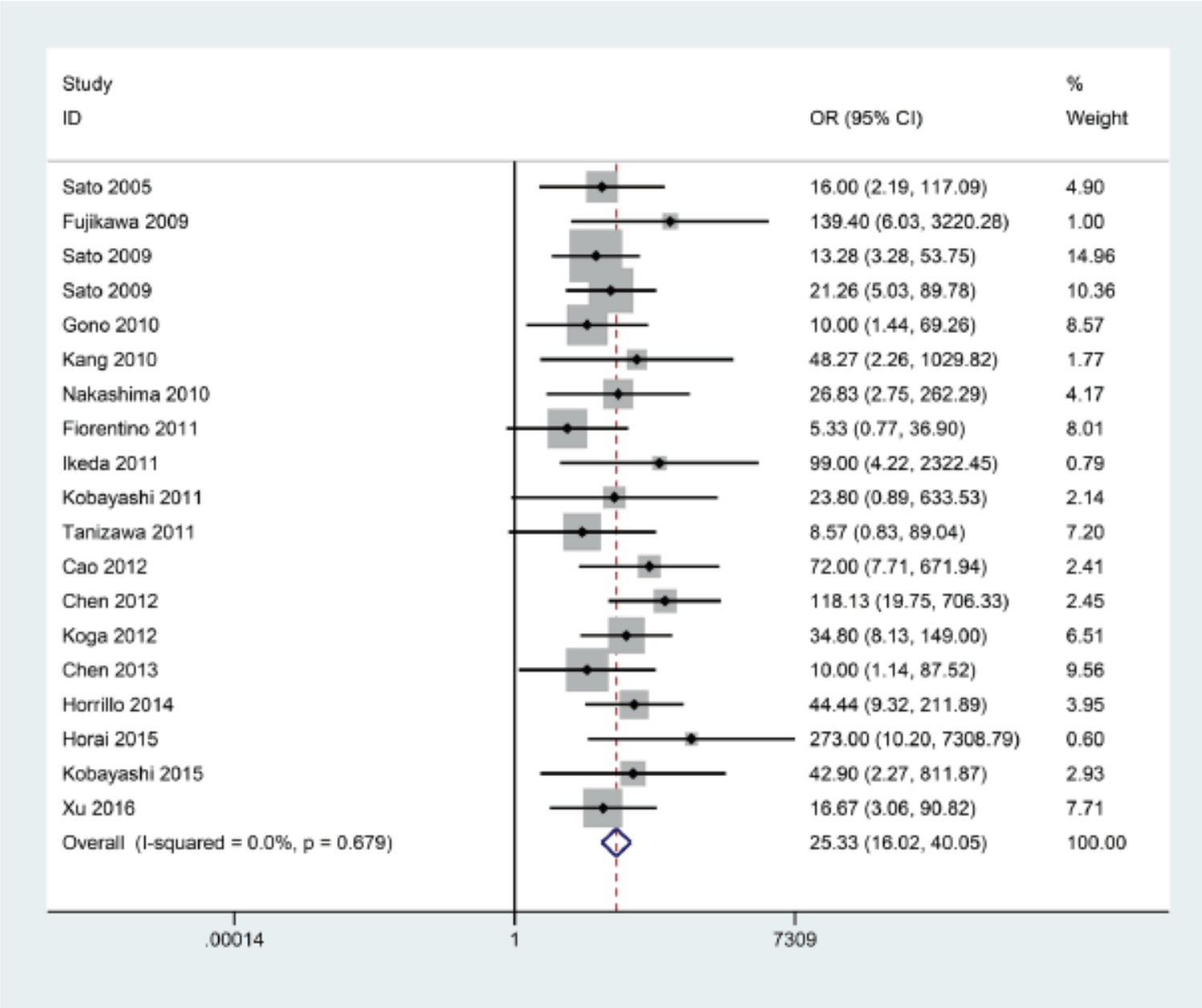
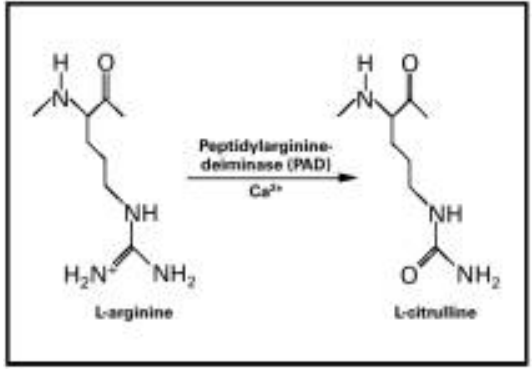


Figure 3: Forest plot of the association between anti-MDA5 antibody and RPILD risk of DM patients with 186 DM with RPILD versus 790 DM without RPILD.

Ac anti-CCP



- **Ac anti-peptide cyclique citrulliné**
- **ELISA (tests de deuxième génération)**
- **Marqueurs spécifiques de <u>polyarthrite rhumatoïde</u>**
  - ✓**Très spécifiques (89-98%), bonne sensibilité (41-88%) pour le diagnostic de PR**
    - ✓**Sensibilité (74.0% vs 69.7%) et spécificité (94.5% vs 81.0%) des Ac anti-CCP meilleure que FR au cours de la PR**
- **Prédictif de la survenue d'érosions**
- **Intérêt au cours des PR « séronégatives »**
  - ✓**Spécificité 92%, sensibilité 60%**
  - ✓**Une PR sans FR et sans anti-CCP n'est pas une PR**

Forslind K, Ann Rheum Dis 2004; 63:1090-5.
Herold M, Clin Dev Immunol; 12:131-5
Sauerland U, Ann NY Acad Sci, 2005;1050:314-8.
Quinn MA, Rheumatology 2005 (e pub ahead of print)

Ac anti-CCP

- **Faux positifs moins fréquents avec anti-CCp qu'avec FR**
  - ✓**LED: 18.3% (FR) vs 12.7% (CCP)**
  - ✓**Syndrome de Sjögren: 73.3% (FR) vs 3.3% (CCP)**
  - ✓**Hépatite chronique: 24.7% (FR) vs. 1.3% (CCP)**

Autres faux positifs

- ✓**Rhumatisme psoriasique (7.8%)**
- ✓**Sclérodermie systémique (< 2%)**

Anti-CCP + raideur matinale: spécificité 99% pour le diagnostic de PR

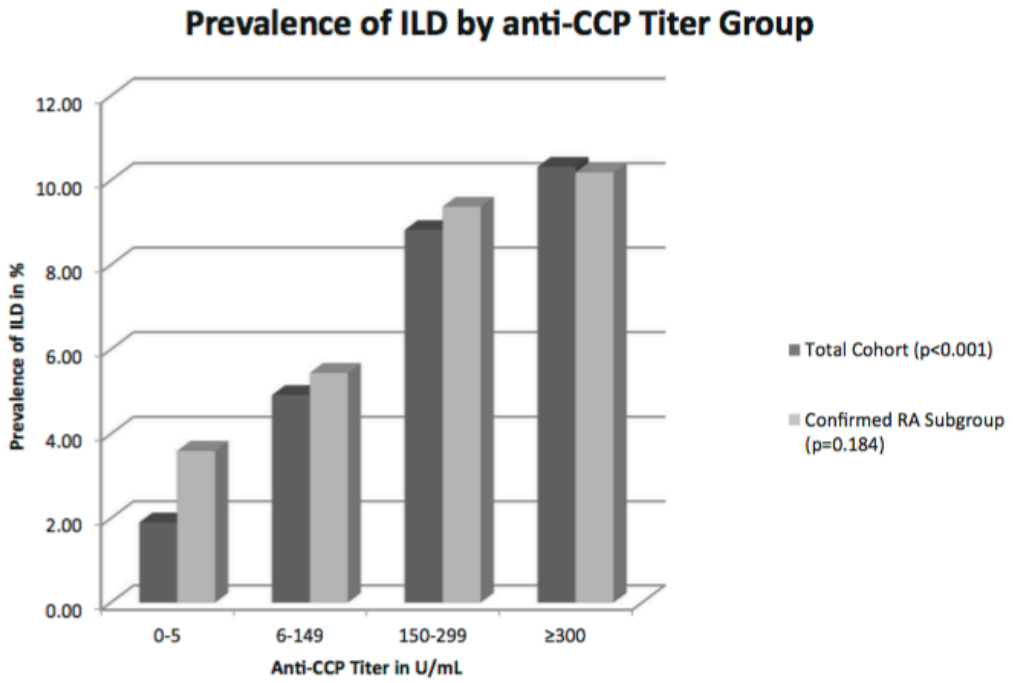
Vander Cruyssen B, Ann Rheum dis, 64:1145-9
Herold M, Clin Dev Immunol; 12:131-5
Sauerland U, Ann NY Acad Sci, 2005;1050:314-8.
Avouac, Ann Rhum Dis 2006

Clinical Rheumatology (2019) 38:1201–1206
https://doi.org/10.1007/s10067-018-04421-0

BRIEF REPORT

Elevated anti-cyclic citrullinated peptide antibody titer is associated with increased risk for interstitial lung disease

Chase S. Correia[1] · Melissa R. Briones[2] · Rong Guo[3] · Rochella A. Ostrowski[2]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

P.-A. Juge, J.S. Lee, E. Ebstein, H. Furukawa, E. Dobrinskikh, S. Gazal, C. Kannengiesser, S. Ottaviani, S. Oka, S. Tohma, N. Tsuchiya, J. Rojas-Serrano, M.I. González-Pérez, M. Mejía, I. Buendía-Roldán, R. Falfán-Valencia, E. Ambrocio-Ortiz, E. Manali, S.A. Papiris, T. Karageorgas, D. Boumpas, K. Antoniou, C.H.M. van Moorsel, J. van der Vis, Y.A. de Man, J.C. Grutters, Y. Wang, R. Borie, L. Wemeau-Stervinou, B. Wallaert, R.-M. Flipo, H. Nunes, D. Valeyre, N. Saidenberg-Kermanac'h, M.-C. Boissier, S. Marchand-Adam, A. Frazier, P. Richette, Y. Allanore, J. Sibilia, C. Dromer, C. Richez, T. Schaeverbeke, H. Lioté, G. Thabut, N. Nathan, S. Amselem, M. Soubrier, V. Cottin, A. Clément, K. Deane, A.D. Walts, T. Fingerlin, A. Fischer, J.H. Ryu, E.L. Matteson, T.B. Niewold, D. Assayag, A. Gross, P. Wolters, M.I. Schwarz, M. Holers, J.J. Solomon, T. Doyle, I.O. Rosas, C. Blauwendraat, M.A. Nalls, M.-P. Debray, C. Boileau, B. Crestani, D.A. Schwartz, and P. Dieudé

Table 2. Genotypic Association of *MUC5B* rs35705950 Single-Nucleotide Polymorphism in Patients with RA, with and without ILD, and Unaffected Controls.*

Variable	France†	Greece	The Netherlands	United States–1	United States–2	Mexico	Japan	China	Multiethnic Replication Sample	Combined Analysis
No. of persons										
Controls	1229	1795	249	500	—	347	315	1013	4219	5448
RA without ILD	105	—	—	68	72	69	300	—	509	614
RA-ILD	118	56	40	99	48	55	182	22	502	620
Minor allele frequency of *MUC5B* rs35705950 — %										
Controls	10.9	3.8	9.0	10.7	—	5.3	0.2	0.8	—	—
RA without ILD	12.9	—	—	11.0	12.5	3.6	0.5	—	—	—
RA-ILD	32.6	26.8	30.0	28.8	13.5	16.4	1.1	2.3	—	—
Genotypic association test										
RA without ILD vs. controls										
Crude odds ratio for RA without ILD (95% CI)	1.2 (0.8–1.8)	—	—	1.0 (0.6–1.8)	—	0.7 (0.2–1.6)	3.2 (0.4–64.3)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Crude P value	0.40	—	—	0.91	—	0.42	0.32	—	0.90	0.60
Adjusted odds ratio for RA without ILD (95% CI)‡	1.3 (0.8–1.9)	—	—	1.0 (0.5–1.7)	—	0.7 (0.2–1.7)	3.7 (0.5–75.1)	—	1.0 (0.6–1.5)	1.1 (0.8–1.5)
Adjusted P value‡	0.28	—	—	0.99	—	0.42	0.26	—	0.83	0.54
RA-ILD vs. controls										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.8–5.2)	13.2 (7.6–22.9)	5.6 (2.9–11.2)	4.1 (2.7–6.3)	—	3.4 (1.8–6.2)	7.1 (1.0–138.6)	3.0 (0.2–15.6)	5.5 (4.2–7.2)	4.7 (3.8–5.8)
Crude P value	3.8×10^{-17}	2.2×10^{-20}	5.0×10^{-7}	5.8×10^{-11}	—	1.1×10^{-4}	0.08	0.30	3.9×10^{-35}	1.3×10^{-49}
Adjusted odds ratio for RA-ILD (95% CI)‡	3.8 (2.8–5.2)	13.2 (7.6–23.0)	4.9 (2.2–11.5)	4.1 (2.7–6.3)	—	3.6 (1.8–7.3)	5.5 (0.6–119.1)	4.9 (0.3–27.5)	5.5 (4.2–7.3)	4.7 (3.9–5.8)
Adjusted P value‡	9.7×10^{-17}	6.2×10^{-20}	1.2×10^{-4}	5.6×10^{-11}	—	2.2×10^{-4}	0.16	0.14	4.7×10^{-35}	1.3×10^{-49}
RA-ILD vs. RA without ILD										
Crude odds ratio for RA-ILD (95% CI)	3.8 (2.2–6.8)	—	—	5.4 (2.6–11.7)	1.1 (0.5–2.5)	5.7 (2.1–18.6)	2.2 (0.5–11.4)	—	3.1 (2.0–5.0)	3.4 (2.4–4.8)
Crude P value	5.9×10^{-6}	—	—	7.9×10^{-6}	0.80	0.002	0.30	—	5.3×10^{-7}	1.6×10^{-11}
Adjusted odds ratio for RA-ILD (95% CI)§	3.1 (1.6–6.3)	—	—	NA	NA	3.8 (1.2–13.3)	3.1 (0.3–28.0)	—	2.9 (1.1–8.4)	3.1 (1.8–5.4)
Adjusted P value§	9.4×10^{-4}	—	—	NA	NA	0.03	0.30	—	0.04	7.4×10^{-5}

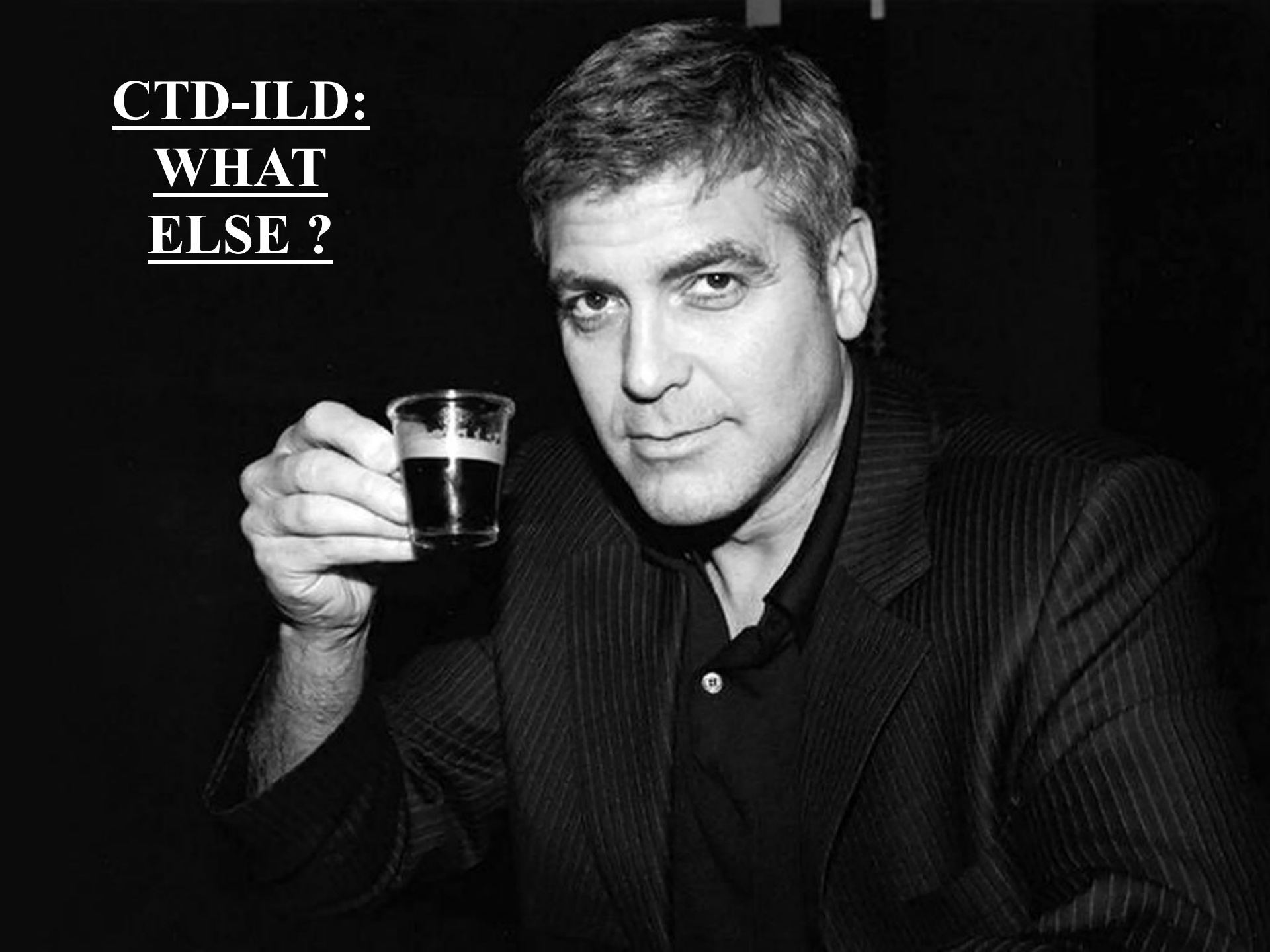
* The two case series from the United States are designated United States–1 and United States–2. CI denotes confidence interval, and RA-ILD rheumatoid arthritis–associated interstitial lung disease.

† The case series from France represents the discovery population.

‡ P values and odds ratios were adjusted for sex and country of origin.

§ P values and odds ratios were adjusted for sex, age at inclusion, smoking status (ever smoked vs. never smoked), and country of origin. Some odds ratios and P values are not available (NA) because not all covariates were available for adjustment.

CTD-ILD: WHAT ELSE ?



Vascularites associées aux ANCA

Interstital lung disease in ANCA vasculitis

Marco A. Alba[a,1], Luis Felipe Flores-Suárez[b], Ashley G. Henderson[c], Hong Xiao[a], Peiqi Hu[a], Patrick H. Nachman[d], Ronald J. Falk[d], and J. Charles Jennette[a,*,2]

Autoimmun Rev. 2017 July ; 16(7): 722–729. doi:10.1016/j.autrev.2017.05.008.

Country, year Reference center	Patients	Age (mean, range)	Male (%)	ANCA pattern	Follow-up (mean, range)	Chronology of PF-ANCA-V	Full vasculitis development	Outcome
[26] Japan, 2004 Respiratory	31 PF ANCA+	69 yr (45–87)	55	MPO 100%	120 Mo	Preceding 100%	MPA 8/31 (25%)	Dead 13/31 (41%) 5-yr survival 50%
[13] France, 2008 Respiratory	29 PF: 17 ANCA+	66 yr (55–77)	88	P-ANCA 82% C-ANCA 18%	57 Mo	Preceding 76% Concomitant 24%	MPA 7/17 (41%)	Dead 10/17 (58%) 5-yr survival 60%
[16] Japan, 2009 Respiratory	53 PF: 19 ANCA+	69 yr (52–80)#	37	MPO 89% PR3 11%	From 1 to 90 Mo	Preceding 100%	MPA 4/19 (21%)	Dead 6/19 (31%) 5-yr survival 60%
[27] Japan, 2012 Respiratory/ Pathology	224 PF: 13 ANCA+	62.1 yr	67	MPO 69% PR3 31%	39.1 Mo (19 to 72)	None	None	Dead 4/13 (30%)
[58] Japan, 2013 Internal Medicine	61 PF: 9 ANCA+	69 yr (57–75)	100	MPO 100%	40 Mo (1–121)#	Preceding 100%	MPA 2/9 (22%)	Dead 6/9 (66%)
[49] China, 2014 Respiratory	8 PF ANCA+	72.6 yr (60–80)	50	MPO 75% PR3 12.5% P- and C-ANCA12.5%	NS	NS	NS	NS
[50] Japan, 2015 Respiratory	504 PF: 36 ANCA+	72 yr	61	MPO 55% PR3 45%	2.42 yr (1.38–4.92)#	Preceding 100%	MPA 3/36 (8%)	5-yr survival 40%
[59] Japan, 2016 Respiratory	120 PF: 12 ANCA+	65.2 yr (48–74)#	66	MPO 100%	72 Mo (14–195)#	Preceding 100%	MPA 3/12 (25%)	Dead 5/12 (41%)
[48] China, 2014 Respiratory	19 MPA + PF	63.6 yr (44–75)	42	MPO 100%	29.9 Mo (8–93)#	Preceding 68% Concomitant 32%	MPA 100%	Dead 6/19 (31%)
[14] United States, 1990 Nephrology/ Internal Medicine	3 MPA + PF	73 yr	33	P-ANCA 67%	120 Mo	Preceding 33% Concomitant 67%	MPA 100%	Dead 3/3100%
[22] Japan, 2000 Internal Medicine	4 MPA + PF	67 yr	50	MPO 100%	NS	Preceding 100%	MPA 100%	Dead 3/4 (75%)
[21] Canada, 2003 Respiratory	6 MPA + PF	70 yr (63–78)	50	P-ANCA 100%	36 Mo	Preceding 100%	MPA 100%	Dead 5/8 (83%)
[15] France, 2009 Internal Medicine	12 ANCA-V + PF	70.7 yr (64–78)	75	MPO 100%	49.2 Mo (7–116)	Preceding 25% Concomitant 66% Posterior 8%	MPA 10/12 83% GPA 2/12 17%	Dead 5/12 (41%)
[17] Greece, 2010 Pathophysiology	33 MPA: 13 MPA + PF	57 yr	69	P-ANCA 85% P- and C-ANCA 8%	38 Mo	Preceding 53%	MPA 100%	Dead 6/13 (46%) 5-yr survival 60%
[18] UK, 2011 Respiratory/ Nephrology	194 MPA: 14 MPA + ILD	67.3 yr (51–85)	72	MPO 100% (tested 13/13)	7.5 yr	Preceding 14% Concomitant 64% Posterior 21%	MPA 100%	Dead 10/14 (71%)
[51] France, 2014 Internal medicine	49 ANCA-V + PF	68 yr (58–74)#	61	MPO 88% PR3 4% Other 8%	48 Mo (14–88)#	Preceding 45% Concomitant 43% Posterior 12%	MPA 40/49 (82%) GPA 9/49 (18%)	Dead 18/49 (36%)
[19] Mexico, 2015 Respiratory	40 MPA: 17 MPA + PF	54.2 yr	53	MPO 90% entire cohort	43 Mo (11–213)#	Preceding 82%	MPA 100%	Dead 9/17 (41%)
[20] Argentina, 2015 Respiratory	28 MPA: 9 MPA + PF	60 yr	56	MPO 100%	61.2 Mo	Preceding 55% Concomitant 45%	MPA 100%	Dead 4/9 (44%)
All series	991 PF: 145 ANCA + 149 ANCA-V + PF	68.1 yr 64.7 yr	65.5 56	MPO 83%, PR3 15% MPO 92%	– –	Preceding or concomitant 100% Preceding or concomitant 89%	MPA 20% MPA 96.5%	Dead 41% Dead 55%

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Autoimmun Rev. 2017 July ; 16(7): 722–729. doi:10.1016/j.autrev.2017.05.008.

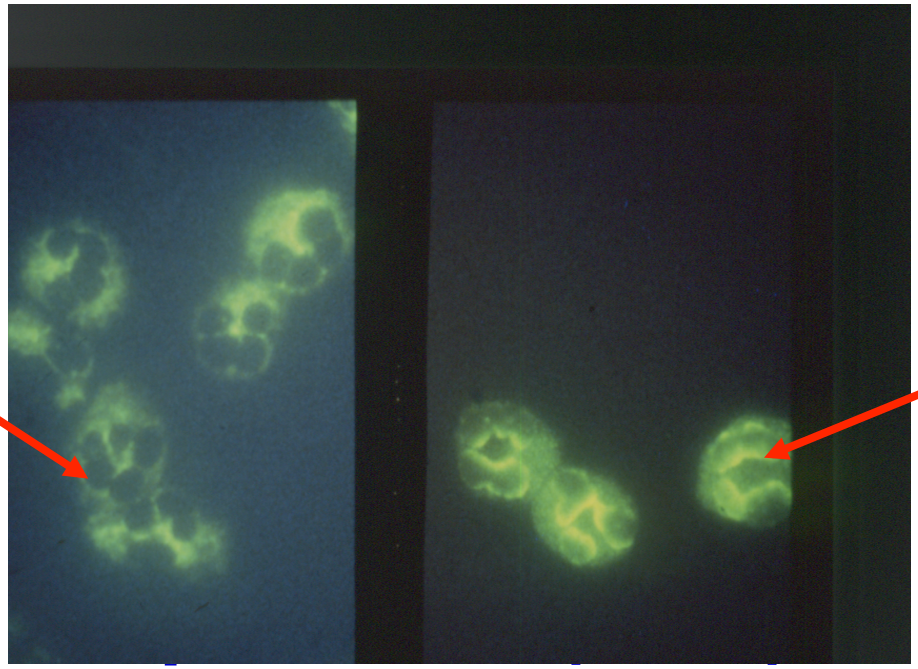
Take-home messages

- Diffuse interstitial lung disease and pulmonary fibrosis may be clinical manifestations of anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis.
- The most common ANCA associated with ILD are those directed against myeloperoxidase (MPO-ANCA).
- Pulmonary fibrosis occurs concurrently or precedes to ANCA vasculitis in the majority of affected individuals.
- Usual interstitial pneumonia (UIP) is the most frequent radiological pattern in ANCA positive disease.
- Interstitial lung disease has an adverse impact on the long-term prognosis of ANCA vasculitis.

Country, J Reference								
[26] Japan, Respiratory								
[13] Franc Respiratory								
[16] Japan, Respiratory								
[27] Japan, Respiratory Pathology								
[58] Japan, Internal Me								
[49] China Respiratory								
[50] Japan, Respiratory								
[59] Japan, Respiratory								
[48] China Respiratory								
[14] Unite States, 199 Nephrolog Internal Me								
[22] Japan, Internal Me								
[21] Canad 2003 Resp								
[15] Franc Internal Me								
[17] Greec Pathophysi								
[18] UK, 2 Respiratory Nephrolog								
[51] France, 2014 Internal medicine	49 ANCA-V + PF	68 yr (58–74) *	61	MPO 88% PR3 4% Other 8%	48 Mo (14–88) *	Preceding 45% Concomitant 43% Posterior 12%	MPA 40/49 (82%) GPA 9/49 (18%)	Dead 18/49 (36%)
[19] Mexico, 2015 Respiratory	40 MPA: 17 MPA + PF	54.2 yr	53	MPO 90% entire cohort	43 Mo (11–213) *	Preceding 82%	MPA 100%	Dead 9/17 (41%)
[20] Argentina, 2015 Respiratory	28 MPA: 9 MPA + PF	60 yr	56	MPO 100%	61.2 Mo	Preceding 55% Concomitant 45%	MPA 100%	Dead 4/9 (44%)
All series	991 PF: 145 ANCA + 149 ANCA-V + PF	68.1 yr 64.7 yr	65.5 56	MPO 83%, PR3 15% MPO 92%	– –	Preceding or concomitant 100% Preceding or concomitant 89%	MPA 20% MPA 96.5%	Dead 41% Dead 55%

Anticorps anti-cytoplasme des polynucléaires neutrophiles

C-ANCA (anti-PR3)



P-ANCA (anti-MPO)

ELISA

IF	PR3	MPO	IF + ELISA
76 %	88 %	91 %	98 %

Hagen EC et al. Kidney Int 1998

Association of *MUC5B* promoter p with interstitial lung disease in myeloperoxidase-antineutrophil c antibody-associated vasculitis

Natsumi Namba,[1,2] Aya Kawasaki,[1] Ken-ei Sada,[3] Fumio Hirano,[4,5] Shigeto Kobayashi,[6] Hidehiro Yamada,[7] Hiroshi Furukawa,[1,8] Kota Shimada,[8,9] Atsushi Hashimoto,[8] Toshihiro Matsui,[8] Kenji Nagasaka,[10] Takahiko Sugihara,[11] Aika Suzuki,[12] Kunihiro Yamagata,[13] Takayuki Sumida,[14] Shigeto Tohma,[8,15] Sakae Homma,[12] Shoichi Ozaki,[7] Hiroshi Hashimoto,[16] Hirofumi Makino,[17] Yoshihiro Arimura,[18] Masayoshi Harigai,[19] Naoyuki Tsuchiya,[1] On behalf of Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis (JPVAS)

Table 1 Case-control association study of *MUC5B* rs35705950 with AAV

		Genotype count and frequency				Dominant model (vs healthy controls)		
	n	G/G	T/G	T/T	MAF	OR (95% CI)	P value	FDR Q
EMEA classification								
MPA	291	284 (0.976)	7 (0.024)	0 (0)	0.012	2.23 (0.79 to 6.06)	0.115	
GPA	95	95 (1)	0 (0)	0 (0)	0	0.46 (0.03 to 7.96)*	0.610*	
EGPA	56	56 (1)	0 (0)	0 (0)	0	0.78 (0.04 to 13.5)*	1.00*	
Unclassifiable	32	31 (0.969)	1 (0.031)	0 (0)	0.016	2.97 (0.16 to 16.6)	0.309	
MPO-AAV	382	374 (0.979)	8 (0.021)	0 (0)	0.010	1.96 (0.73 to 5.17)	0.170	
PR3-AAV	60	60 (1)	0 (0)	0 (0)	0	0.73 (0.04 to 12.6)*	1.00*	
AAV-ILD	163	156 (0.957)	7 (0.043)	0 (0)	0.021	3.93 (1.38 to 10.7)	0.008	0.040
AAV without ILD	264	263 (0.996)	1 (0.004)	0 (0)	0.002	0.35 (0.02 to 1.86)	0.317	
MPO-AAV-ILD	149	142 (0.953)	7 (0.047)	0 (0)	0.023	4.34 (1.52 to 11.9)	0.004	0.040
MPO-AAV without ILD	198	197 (0.995)	1 (0.005)	0 (0)	0.003	0.47 (0.03 to 2.54)	0.479	
Healthy controls	842	833 (0.989)	9 (0.011)	0 (0)	0.005	ref		

ORs, 95% CIs and p values were adjusted for sex using logistic regression analysis under the dominant model for T allele.
*In these comparisons, because T/G and T/T genotypes were absent, Fisher's exact test was performed under the dominant model for T allele. For calculation of OR and 95% CI, 0.5 was added to each cell (Haldane-Anscombe correction).
AAV, ANCA-associated vasculitis; EGPA, eosinophilic granulomatosis with polyangiitis; EMEA, EuropeanMedicines Agency; FDR, false discovery rate; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; MAF, minor allele frequency; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

Déficit immunitaire

J Clin Immunol. 2016 May ; 36(4): 377–387. doi:10.1007/s10875-016-0271-8.

Copa Syndrome: A Novel Autosomal Dominant Immune Dysregulatory Disease

Timothy J. Vece[#1], Levi B. Watkin[#1,3], Sarah Nicholas[1,3], Debra Canter[3], Michael C. Braun[1], R. Paul Guillerman[4], Karen W. Eldin[2], Grant Bertolet[1,3], Scott McKinley[1], Marietta de Guzman[1,3], Lisa Forbes[1,3], Ivan Chinn[1,3], and Jordan S. Orange[1,3]

Abstract

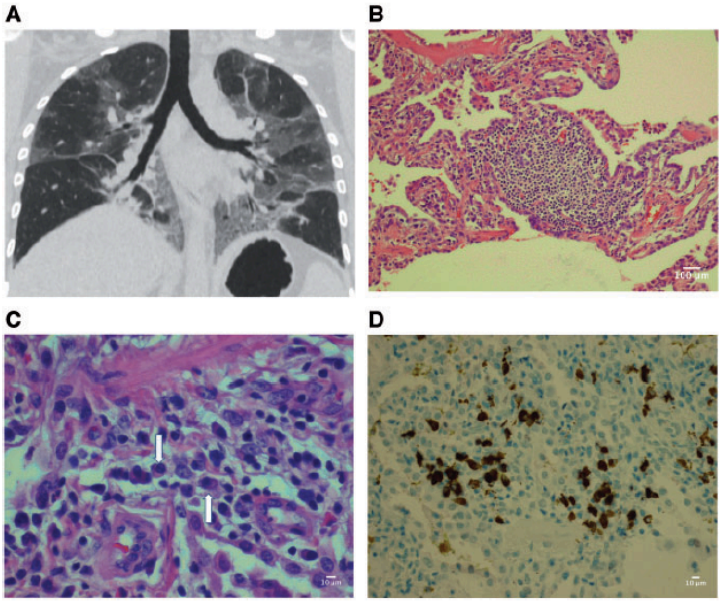
Inherently defective immunity typically results in either ineffective host defense, immune regulation, or both. As a category of primary immunodeficiency diseases, those that impair immune regulation can lead to autoimmunity and/or autoinflammation. In this review we focus on one of the most recently discovered primary immunodeficiencies that leads to immune dysregulation: "Copa syndrome". Copa syndrome is named for the gene mutated in the disease, which encodes the alpha subunit of the coatomer complex-I that, in aggregate, is devoted to transiting molecular cargo from the Golgi complex to the endoplasmic reticulum (ER). Copa syndrome is autosomal dominant with variable expressivity and results from mutations affecting a narrow amino acid stretch in the *COPA* gene-encoding COPα protein. Patients with these mutations typically develop arthritis and interstitial lung disease with pulmonary hemorrhage representing a striking feature. Immunologically Copa syndrome is associated with autoantibody development, increased Th17 cells and pro-inflammatory cytokine expression including IL-1β and IL-6. Insights have also been gained into the underlying mechanism of Copa syndrome, which include excessive ER stress owing to the impaired return of proteins from the Golgi, and presumably resulting aberrant cellular autophagy. As such it represents a novel cellular disorder of intracellular trafficking associated with a specific clinical presentation and phenotype.

Maladie associée aux IgG4

More than meets the eye: IgG4-related disease presenting as isolated interstitial lung disease

Rheumatology 2017;56:1630–1631

Aprajita Jagpal[1], David R. Crowe[2], Joao A. de Andrade[3,4], Maria del Pilar Acosta Lara[3] and Iris Navarro-Millan[1]



Rheumatology key message

- IgG4-related disease can present as isolated interstitial lung disease with a pattern consistent with non-specific interstitial pneumonia.

Biomédicaments

Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry)

Marta Pérez-De-Lis, Soledad Retamozo, Alejandra Flores-Chávez, Belchin Kostov, Roberto Perez-Alvarez, Pilar Brito-Zerón & **Manuel Ramos-Casals** ...show less

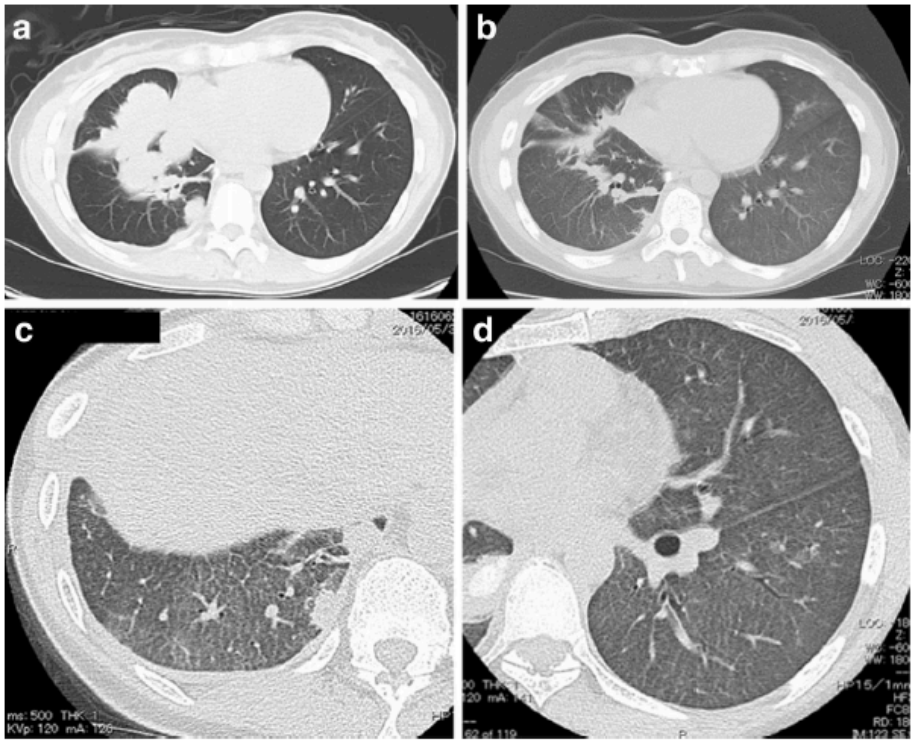
Journal
Expert Opinion on Drug Safety ›
Volume 16, 2017 - Issue 11

Areas covered: The BIOGEAS Registry currently collects information about nearly 13,000 reported cases of autoimmune diseases developed in patients exposed to biologics, including more than 50 different systemic and organ-specific autoimmune disorders, of which psoriasis (n=6375), inflammatory bowel disease (n=845), demyelinating CNS disease (n=803), interstitial lung disease (n=519) and lupus (n=369) were the most frequently reported. The main biologics involved were anti-TNF agents in 9133 cases (adalimumab in 4154, infliximab in 3078 and etanercept in 1681), immune checkpoint inhibitors in 913 (ipilimumab in 524 and nivolumab in 225), B-cell targeted therapies in 741 (rituximab in 678), and growth factor inhibitors in 549 cases (bevacizumab in 544). Even though targeting a particular immune molecule may be associated with an excellent clinical response in most patients, an unexpected autoimmune disease may arise in around 8 out of 10,000 exposed patients.

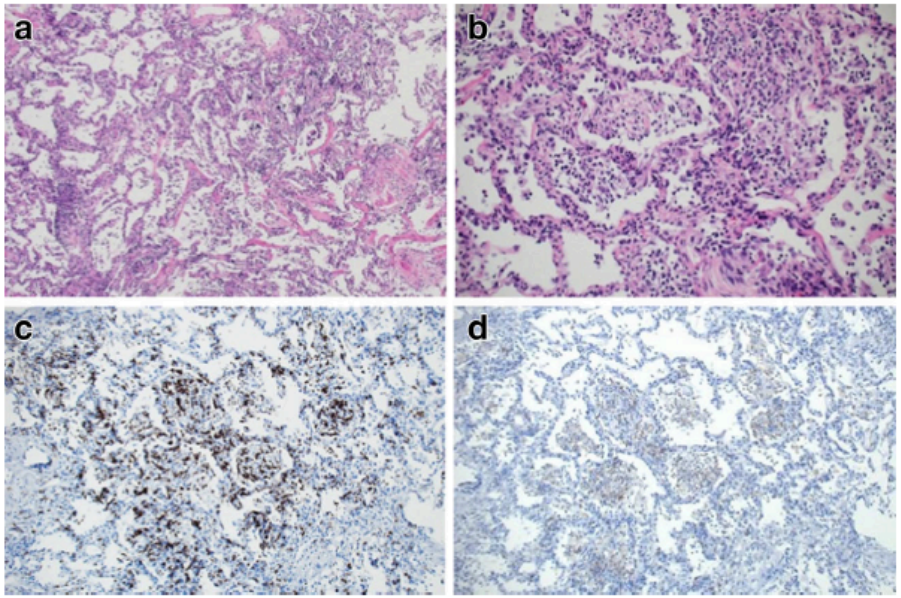
Osimertinib-induced interstitial lung disease after treatment with anti-PD1 antibody

Nobuaki Mamesaya[1] · Hirotsugu Kenmotsu[1] · Mineo Katsumata[2] · Takashi Nakajima[3] · Masahiro Endo[4] · Toshiaki Takahashi[1]

Invest New Drugs (2017) 35:105–107
DOI 10.1007/s10637-016-0389-9



38ans carcinome épidermoïde pulmonaire traité par inhibiteur de tyrosine kinase anti-EGFR et nivolumab



Sciences fondamentales

Autoantibody to scaffold attachment factor B (SAFB): A novel connective tissue disease-related autoantibody associated with interstitial lung disease

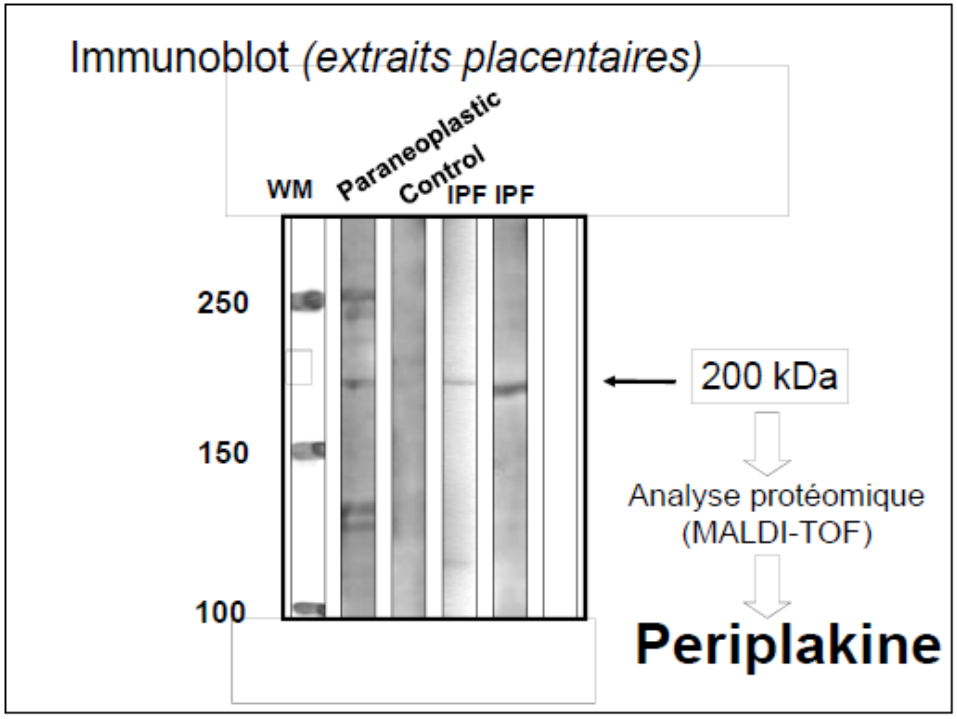
Akiko Takeuchi [a], Takashi Matsushita [a], Kenzo Kaji [a], Yoshinobu Okamoto [a], Masahide Yasui [b], Masayoshi Hirata [c], Naoto Oishi [d], Akira Higashi [e], Mariko Seishima [f], Tomoya Asano [g, 1], Manabu Fujimoto [a, h], Masataka Kuwana [i], Kazuhiko Takehara [a], Yasuhito Hamaguchi [a, *]

Clinical characteristics of 10 patients with anti-SAFB antibody.

	1	2	3	4	5	6	7	8	9	10
Age at onset	56	55	49	69	67	59	54	61	59	61
Gender	Female	Male	Female	Male	Female	Female	Female	Male	Female	Male
Diagnosis	lcSSc	IPF	CADM	EP	NSIP	NSIP	dcSSc	Primary Raynaud	lcSSc + PM	NSIP
ANA	×640 (H, Sp)	×2560 (H, Sp)	×1280 (Sp)	×5120 (Sp)	×640 (Sp)	×1280 (Sp)	×5120 (Sp)	×1280 (Sp)	×1280 (Sp)	×1280 (H, Sp)
Other autoantibodies	Th/To, MPO-ANCA	–	–	–	KS	EJ	Topo I	–	SRP	–
Disease duration (years)	3.0	2.0	0.3	0.1	0.5	0.2	10	2.5	2	0.3
Clinical features										
Fever	–	–	+	+	–	–	–	–	–	–
Raynaud's phenomenon	+	–	–	+	–	–	+	+	+	–
Nail fold bleeding	+	–	–	–	–	–	+	+	–	–
Skin thickness	+	–	–	–	–	–	+	–	+	–
Muscle weakness	–	–	–	–	–	–	–	–	+	–
Polyarthritis	–	–	+	–	–	–	–	–	–	–
ILD	+	+	–	+	+	+	+	–	+	+
HRCT finding	NSIP	UIP	–	NSIP	NSIP	NSIP	NSIP	–	NSIP	NSIP
PAH	–	–	–	–	–	–	–	–	–	–
Heart	–	–	–	–	–	–	–	–	–	–
Renal	–	–	–	–	–	–	–	–	–	–
Malignancy	–	–	–	–	–	–	–	–	–	+
Laboratory findings										
KL-6, U/mL	360	648	ND	416	1193	764	955	ND	2540	1137

lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous SSc; PM, polymyositis; CADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IIP, idiopathic interstitial pneumonia; EP, eosinophilic pneumonia; ANA, antinuclear antibody; H, homogenous; Sp, speckled; Topo I, topoisomerase I; HRCT, high-resolution computed tomography; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; PAH, pulmonary arterial hypertension; KL-6, Krebs von den Lungen-6. ND, not done.

Ac anti-periplakine dans les PID idiopathiques



Les Ac anti-périplakine sont associés à une maladie plus sévère

	Ab (+) *(n=16)*	Ab (-) *(n=24)*	p
CPT *[% pred]*	56 ± 3	68 ± 3	***0.008***
CVF *[% pred]*	66 ± 3	79 ± 5	***0.02***
DLCO *[% pred]*	32 ± 3	47 ± 5	***0.03***
PaO_2 *[mmHg]*	62 ± 4	73 ± 2	***0.05***

⇨ Étude prospective N=150 (CIRC APHP, Cohorte COFI)

Taillé et al. AJRCCM 2011

Conclusions

- CTD-ILD et IPAF
- Valeur pronostique et diagnostiques
- Faible spécificité des Ac anti-nucléaires
- DNA natif, ECT, DOT Myosite, anti-CCP, ANCA-MPO
- Anti-synthétase: pas seulement les anti-JO1
- Anti-MDA5 DM et ILD rapidement progressive

- **On ne trouve que ce qu'on cherche: devant une PID d'allure idiopathique, rechercher les arguments en faveur d'une connectivite associée**

Merci pour votre attention !

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