Mixed connective tissue diseases: Classification and clinical manifestations

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- Depuis janvier 2014: Président du groupe d'experts de l'AP-HP, juste prescription

MCTD: Introduction (I)

In 1972, Dr Sharp and colleagues described a new connective tissue disease, characterized by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM) and by the presence of antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1 snRNP). This condition was termed mixed connective tissue disease (MCTD) and proposed as a distinct disease.

Sharp GC et al. Am J Med 1972;52:148-59.
Sharp GC. Kasukawa R, Sharp GC, editors. Amsterdam: Elsevier; 1987. p. 23-32.

MCTD: Introduction (II)

In the original publication, describing MCTD, Sharp made the 4 following claims:

- the syndrome was clinically identifiable by a particular group of features
- the presence of high titers of antibodies to U1 snRNP was a unique (and hence diagnostic) serological feature;
- cerebral, pulmonary, renal involvement, and vasculitis did not occur;
- the condition had a benign prognosis and responded to small doses of corticosteroids.

Sharp GC et al. Am J Med 1972;52:148-59.
Sharp GC. Kasukawa R, Sharp GC, editors. Amsterdam: Elsevier; 1987. p. 23-32.

MCTD: Introduction (III)

Later, after observing the clinical evolution of MCTD patients, Sharp himself agreed that the original concept of MCTD had to be modified and that
(1) Internal organs were at risk for serious complications;
(2) patients were not always steroid responsive;
(3) prognosis was not always benign.

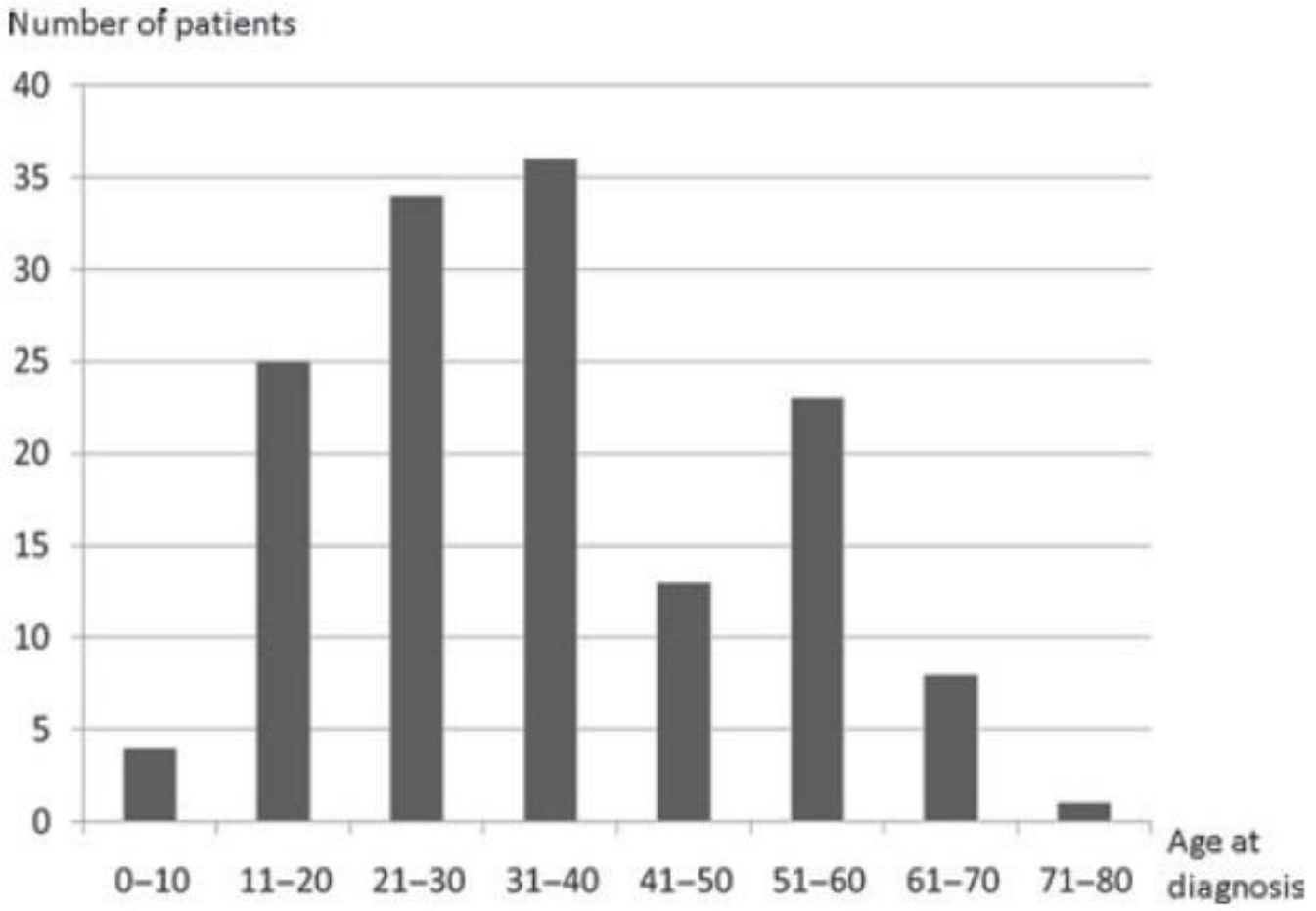
Sharp GC, Anderson PC. J Am Acad Deramtol 1980;2:269-74.
Maddison PJ. Baillières Best Pract Res Clin Rheumatol 2000;14: 111-24.
Bellando Randone S, et al. Curr Rheumatol Rev 2009;5:133-40.

MCTD: epidemiology

- Female to male ratio = 3.3
- Mean age at diagnosis of adult-onset MCTD : 37.9 years (95% CI 35.3 to 40.4 years).
- Point prevalence of living adult MCTD patients in Norway was 3.8 (95% CI 3.2 to 4.4) per 100 000 adults.
- Incidence of adult-onset MCTD in Norway during the period from 1996 to 2005 was 2.1 (95% CI 1.7 to 2.5) per million per year.

Gunnarson R et al. Ann Rheum Dis 2011

The age distribution of the MCTD patients at time of diagnosis.



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Classification criteria for MCTD: 1987

Sharp (1987) (2)	Kasukawa et al (1987) (16)	Alarcón-Segovia et al (1987) (17)
A. Major criteria 1) Myositis, severe 2) Pulmonary involvement a. Diffusion capacity <70% of normal values b. Pulmonary hypertension c. Proliferative vascular lesions on lung biopsy 3) Raynaud's phenomenon or esophageal hypomotility 4) Swollen hands or sclerodactyly 5) Anti ENA ≥1:10,000 and anti-U1 snRNP positive and anti-Sm negative B. Minor criteria 1) Alopecia 2) Leukopenia 3) Anemia 4) Pleuritis 5) Pericarditis 6) Arthritis 7) Trigeminal neuropathy 8) Malar rash 9) Thrombocytopenia 10) Mild myositis 11) History of swollen hands At least 4 major criteria plus anti-U1 snRNP titer of at least 1:4000 (exclusion criterion: positivity for anti-Sm); or 2 major criteria from among 1, 2, and 3 plus 2 minor criteria plus anti-U1 snRNP titer of at least 1:1000	A. Common symptoms 1) Raynaud's phenomenon 2) Swollen fingers or hands B. Anti-U1 snRNP antibody positive C. Mixed symptoms 1. SLE-like findings 1) Polyarthritis 2) Lymphadenopathy 3) Facial erythema 4) Pericarditis or pleuritis 5) Leukopenia (<4000/mm^3) or thrombocytopenia (<100,000/mm^3) 2. SSc-like findings 1) Sclerodactyly 2) Pulmonary fibrosis, restrictive changes of lung (VC < 80%) or reduced diffusion capacity (DLCO < 70%) 3) Hypomotility or dilatation of esophagus 3. PM-like findings 1) Muscle weakness 2) Elevated serum levels of muscle enzymes (CPK) 3) Myogenic pattern on EMG At least 1 of the 2 common symptoms plus positive for anti-U1 snRNP plus 1 or more of the mixed symptoms in at least 2 of the 3 disease categories	A. Serologic 1) Anti-U1 snRNP at a hemagglutination titer of ≥1:1600 B. Clinical 1) Edema in the hands 2) Synovitis 3) Myositis 4) Raynaud's phenomenon 5) Acrosclerosis Serologic criterion plus at least 3 clinical criteria, including either synovitis or myositis

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Sem Arthritis Rheum 2012

Proposed diagnostic criteria for MCTD (I)

	Major criteria	Minor criteria
Sharp (1987)	1. Myositis 2. Pulmonary involvement: a. Diffuse capacity < 70% of normal values b. Pulmonary hypertension c. Proliferative vascular lesions on lung biopsy 3. Raynaud's phenomenon or esophageal hypomotility 4. Swollen hands 5. Anti-ENA Ab > 1:10,000 and anti-U1 RNP Ab positive and anti-Sm negative	1. Alopecia 2. Leukopenia 3. Anemia 4. Pleuritis 5. Pericarditis 6. Arthritis 7. Trigeminal neuropathy 8. Malar rash 9. Thrombocytopenia 10. Mild myositis 11. History of swollen hands

Diagnosis
At least 4 major criteria plus anti-U1-RNP Ab titer of at least 1:4000 or two major criteria from among criteria 1, 2 and 3 plus 2 minor criteria plus anti-U1-RNP Ab titer of at least 1:1000 Exclusion criteria: positivity for anti-Sm Ab

Proposed diagnostic criteria for MCTD (II)

	Common symptoms	Mixed symptoms
Kasukawa (1987)	1. Raynaud's phenomenon 2. Swollen fingers or hands Anti-RNP Ab positive	1. SLE-like symptoms: a. Polyarthritis b. Lymphadenopathy c. Facial erythema d. Pericarditis or pleuritis e. Leukopenia or thrombocytopenia. 2. SSc-like findings: a. Sclerodactyly b. Pulmonary fibrosis, restrictive changes of lung, or reduced diffusion capacity c. Hypomotility or dilatation of esophagus. 3. PM-like findings: a. Muscle weakness b. Elevated serum levels of muscle enzymes (CPK) c. Myogenic pattern on EMG

Diagnosis
At least one of common symptoms plus positivity for anti-RNP Ab plus one signs/symptoms of the mixed symptoms in at least two of the three disease

Proposed diagnostic criteria for MCTD (III)

	Serological criteria	Clinical criteria
Alarcon-Segovia (1987)	Anti-RNP Ab titer > 1:1000	1. Edema in hands 2. Synovitis 3. Myositis, 4. Raynaud's phenomenon 5. Acrosclerosis

Diagnosis
Serological criteria plus at least 3 clinical criteria included either synovitis or myositis

No mention of pulmonary involvement

Proposed diagnostic criteria for MCTD (IV)

	Serological criteria	Clinical criteria
Kahn (1991)	Presence of high titer anti-RNP Ab corresponding to speckled ANA at titer ≥ 1:2000	1. Raynaud's phenomenon 2. Synovitis 3. Myositis 4. Swollen fingers

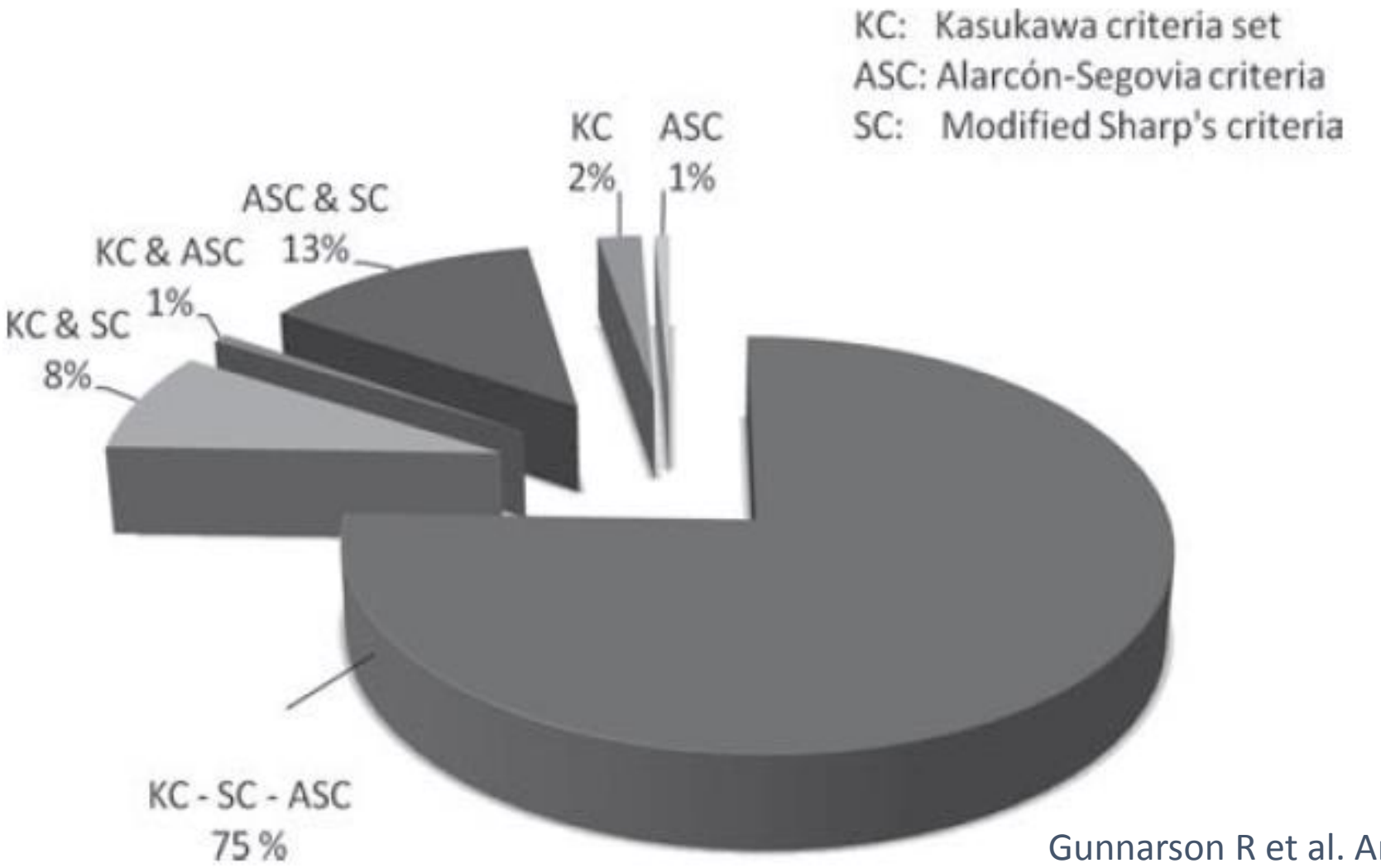
No mention of pulmonary involvement

Diagnosis
Serological criteria plus Raynaud's phenomenon and at least two of the three following signs (synovitis, myositis and swollen fingers)

Proposed diagnostic criteria for MCTD (IV)

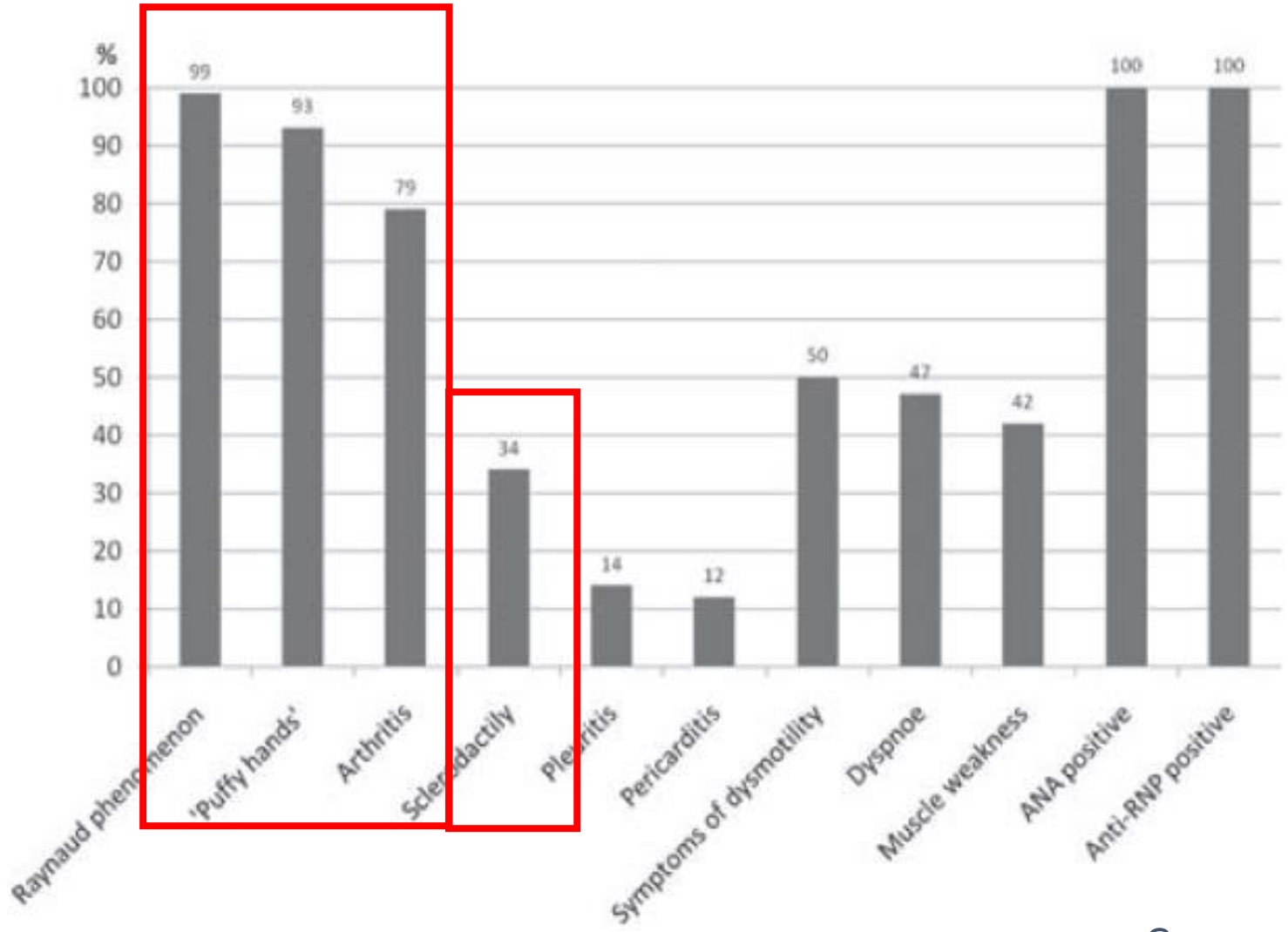
- None of them take into account detection of giant capillaries

The mixed connective tissue disease population fulfilling various combinations of criteria sets.



Gunnarson R et al. Ann Rheum Dis 2011

Most common clinical features and serum autoantibodies in patients with MCTD



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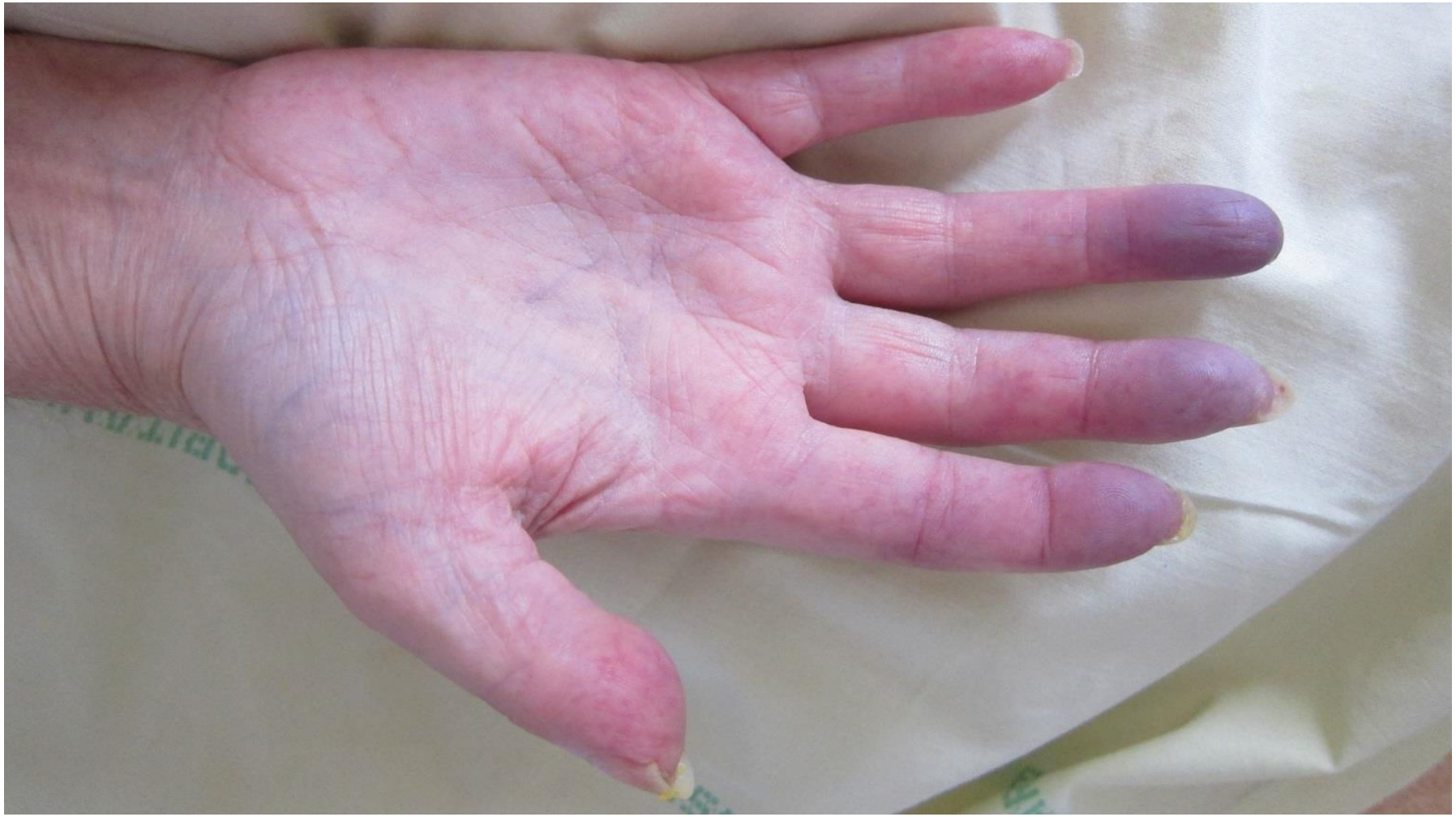
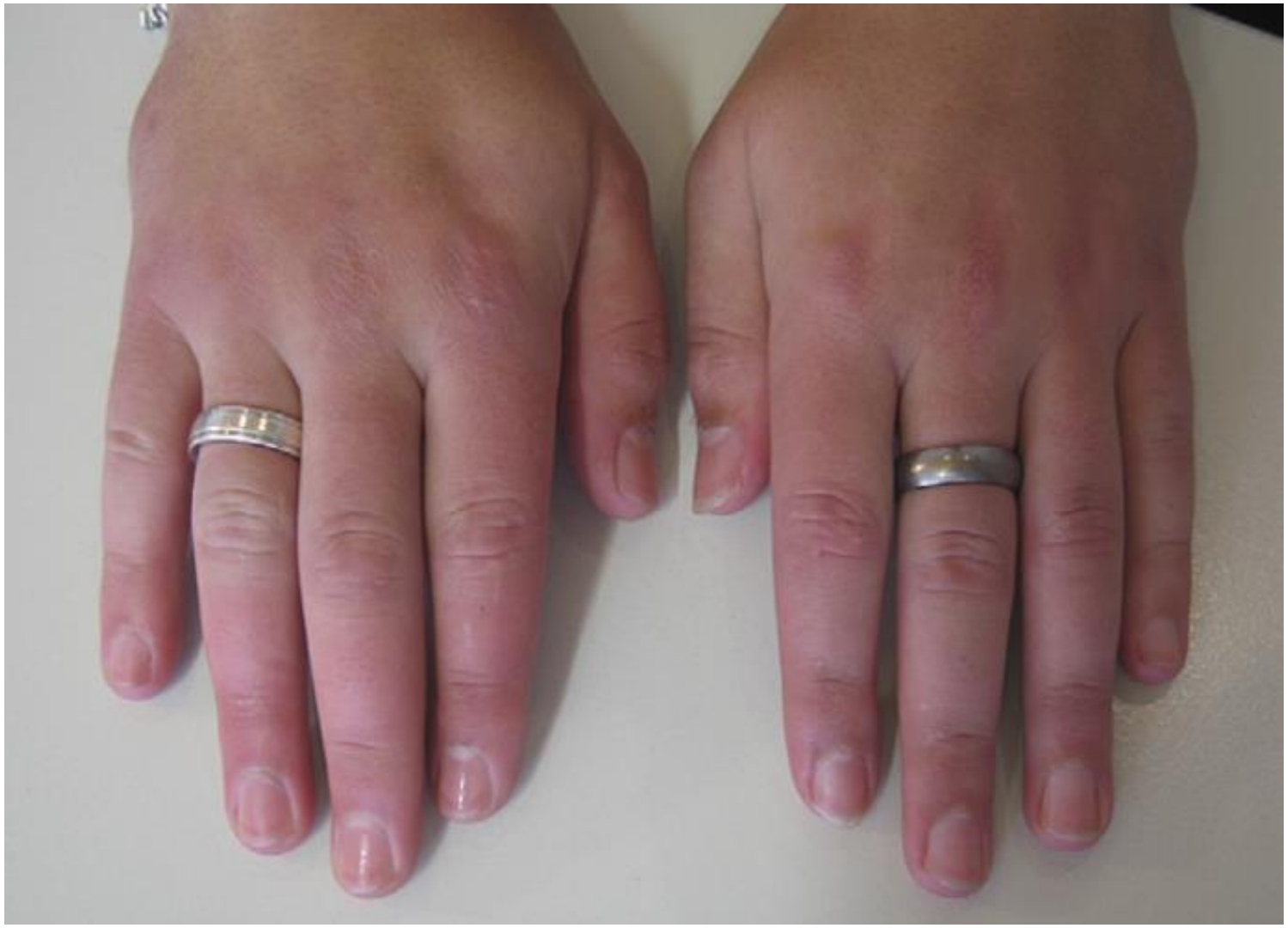
Raynaud’s phenomenon



Swollen / puffy hands



Aringer M. Best Practice & Research Clinical Rheumatology 2007

Table 2 Clinical and Serological Features at the First Visit and in 2008

Clinical and Serologic Features	First Visit, No. of Patients/%	2008,[a] No. of Patients/%
Raynaud's phenomenon	150 (93.2%)	137 (85.1%)
Arthritis/arthralgia	119 (73.9%)	80 (49.7%)
Edema of the hands	117 (72.7%)	74 (46%)
Sclerodactyly	47 (29.2%)	69 (43%)
Hypomotility or dilatation of esophagus[b]	56 (34.8%)	73 (45.3%)
Pulmonary involvement[c]	46 (28.6%)	71 (44.1%)
Pleuritis/pericarditis	35 (21.7%)	30 (18.6%)
Facial erythema	32 (19.9%)	27 (16.8%)
Lymphadenopathy	29 (18%)	22 (13.7%)
Neurological involvement	9 (5.6%)	18 (11.2%)
Renal involvement (nephritis)	11 (6.8%)	16 (9.9%)
Leukopenia/thrombocytopenia	39 (24.2%)	43 (26.7%)
Elevated CPK	45 (27.9%)	31 (19.2%)
ANA	156 (96.9%)	151 (93.8%)
Anti-DNA[d]	27/135 (20%)	25/135 (18.5%)
Anti-RNP[d]	139/139 (100%)	126/139 (90.6%)
Anti-Sm[d]	22/134 (16.4%)	23/134 (17.2%)
Anti-Scl70[d]	15/116 (12.9%)	19/116 (16.4%)
ACA[d]	4/113 (3.5%)	5/113 (4.4%)
Anti-SSA/Ro[d]	31/116 (26.7%)	31/116 (26.7%)
Anti-CCP[d]	Not done	19/114 (16.7%)

[a]For patients who died before 2008, clinical and serological features were collected at the last visit.
[b]Patients with hypomotility or dilatation of esophagus showed by manometry and/or esophageal barium radiograph.
[c]Patients with evidence of interstitial lung disease (ILD) on chest radiograph (CXR) or tomography (CT) scan and/or restrictive pattern on spirometry and/or reduced diffusion capacity.
[d]These data were not provided for all the 161 patients included in the study.

SSc features

SLE features

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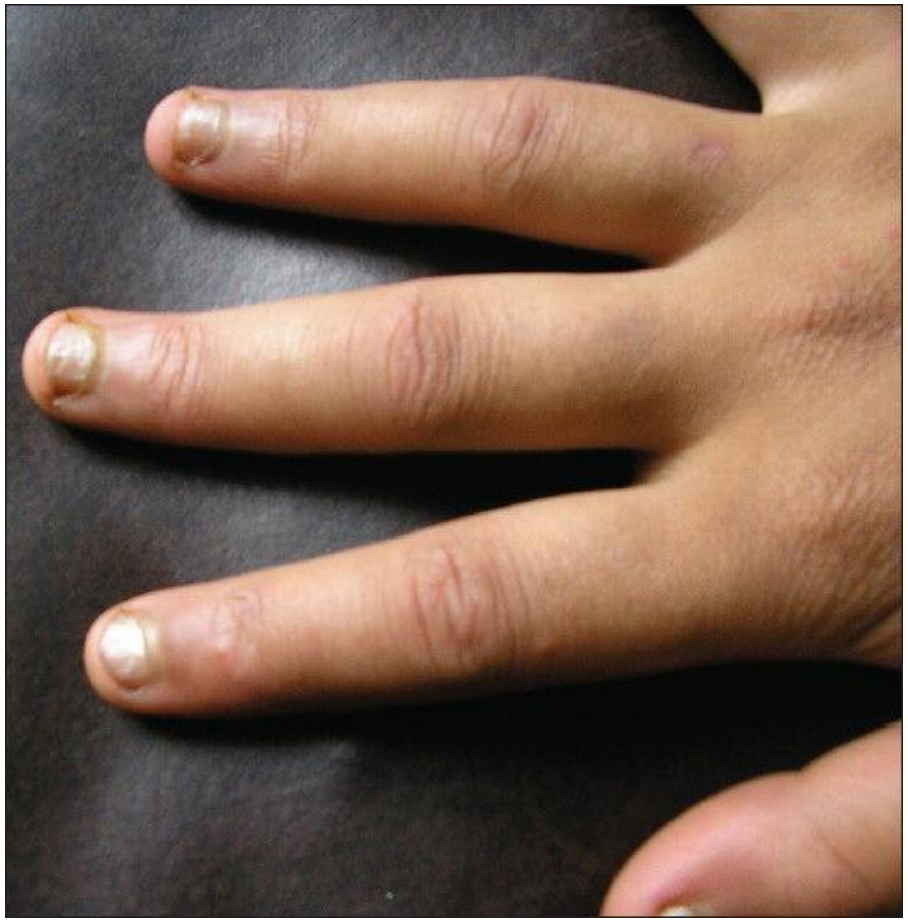
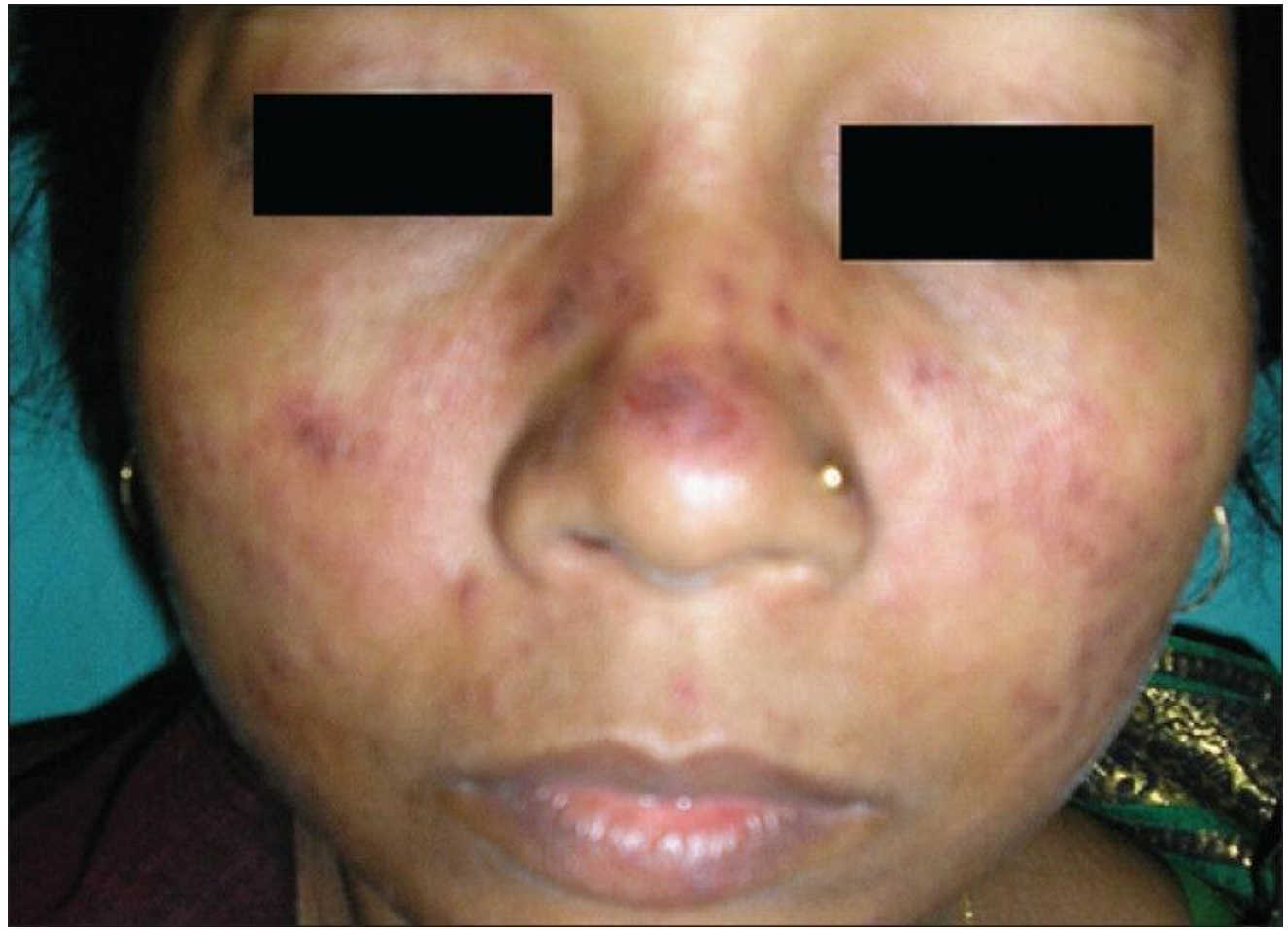
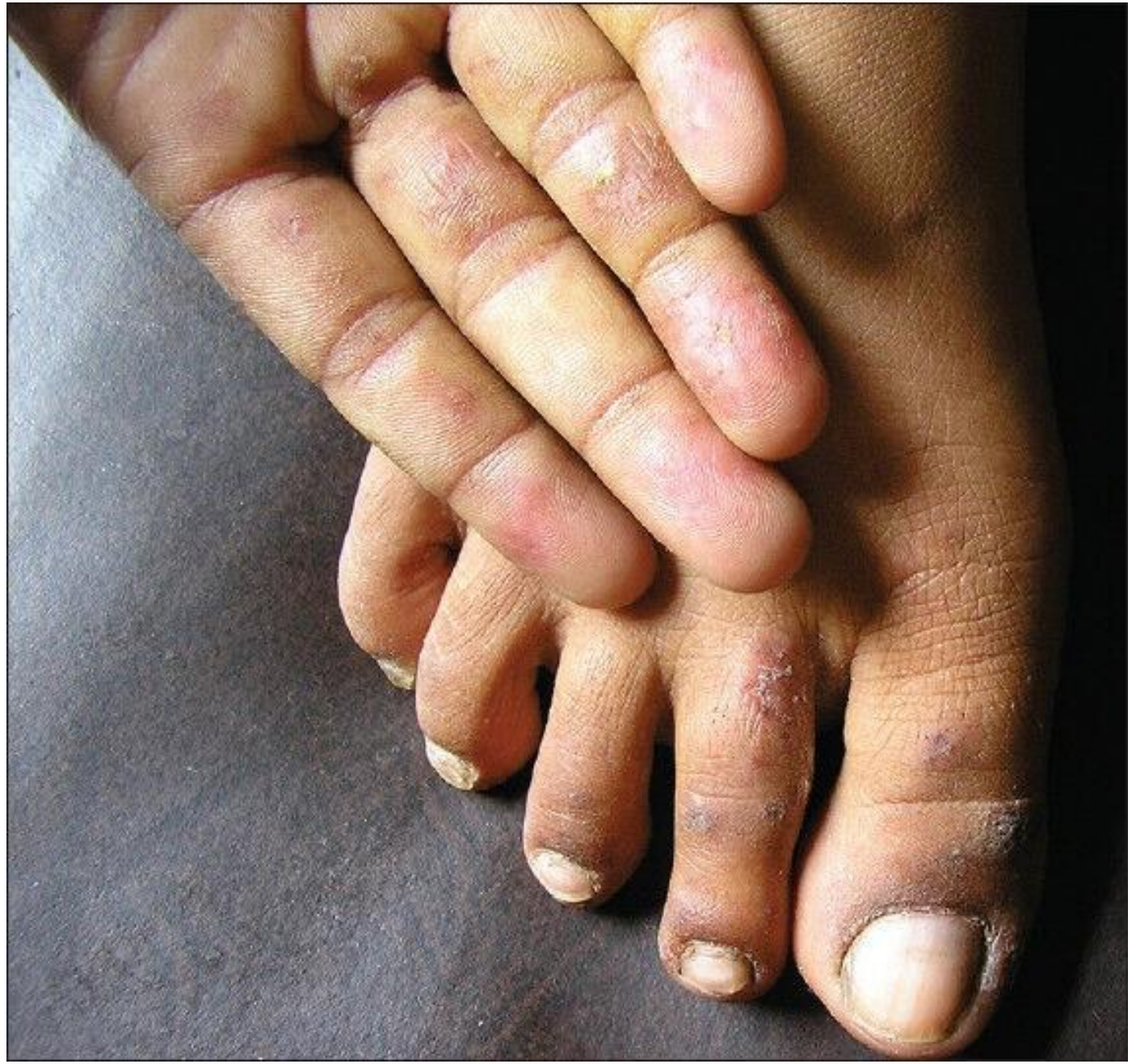
Cumulative clinical features of MCTD

Clinical feature	Prevalence (%)
Musculoskeletal	
Arthritis	85
Myalgias	70
Nodules	40
Jaccoud's arthropathy	30
Myositis	25
Erosions	20
Skin and mucous membranes	
Swollen hands	75
Rash	50
Mucosal ulceration	45
Sclerodactyly	40
Gottron's papules	10
Heliotrope erythema	Rare

Maddison PJ. Bailliere's Clinical Rheumatology, 2000





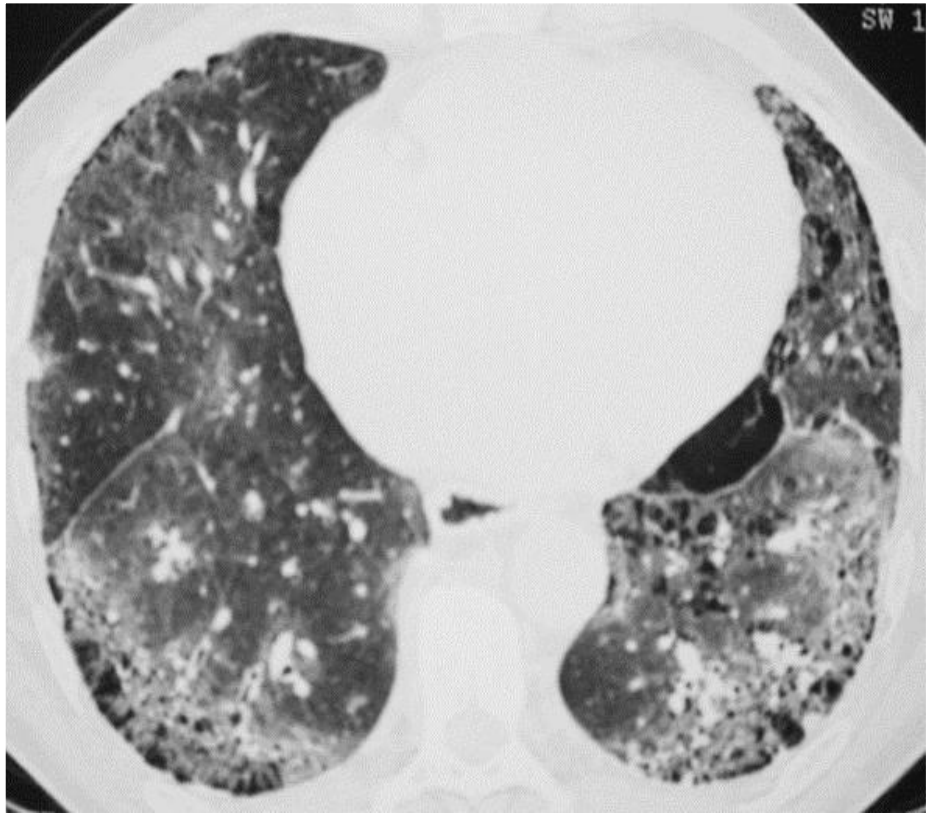


Cumulative clinical features of MCTD

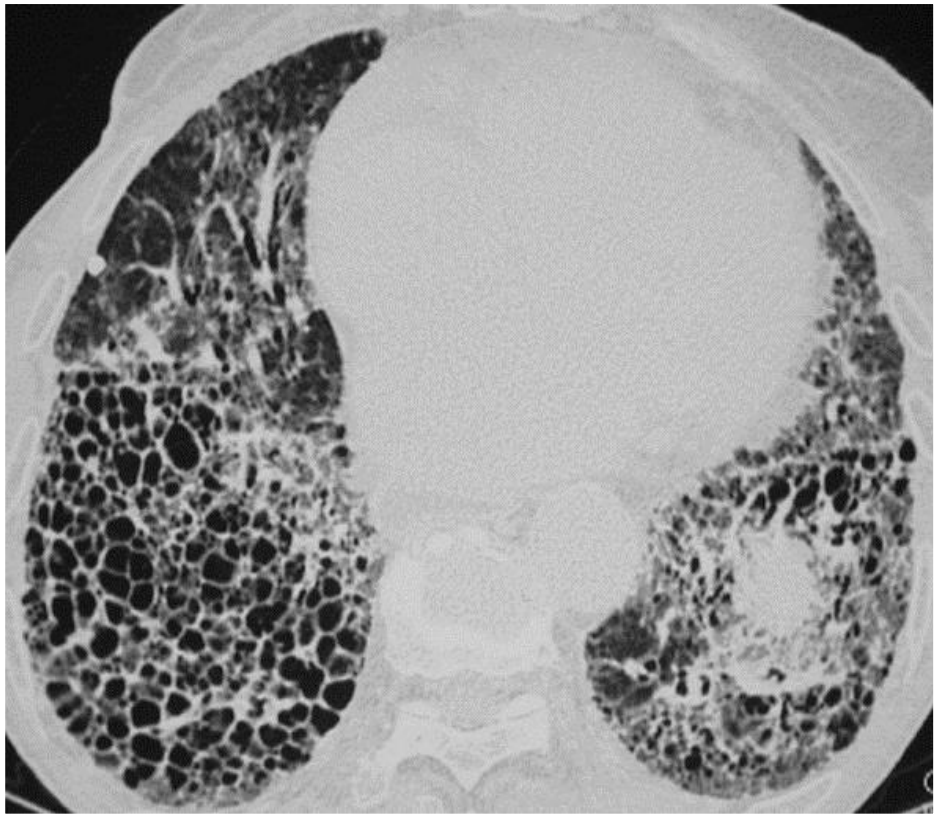
Clinical feature	Prevalence (%)
Cardiovascular	
Raynaud's phenomenon	90
Pulmonary hypertension	30
Pericarditis	20
Myocarditis	Rare
Respiratory	
Reduced CO transfer	75
Pleurisy	30
Gastrointestinal	
Reduced oesophageal motility	80
Malabsorption	Rare

Maddison PJ. Bailliere's Clinical Rheumatology, 2000

Interstitial lung disease

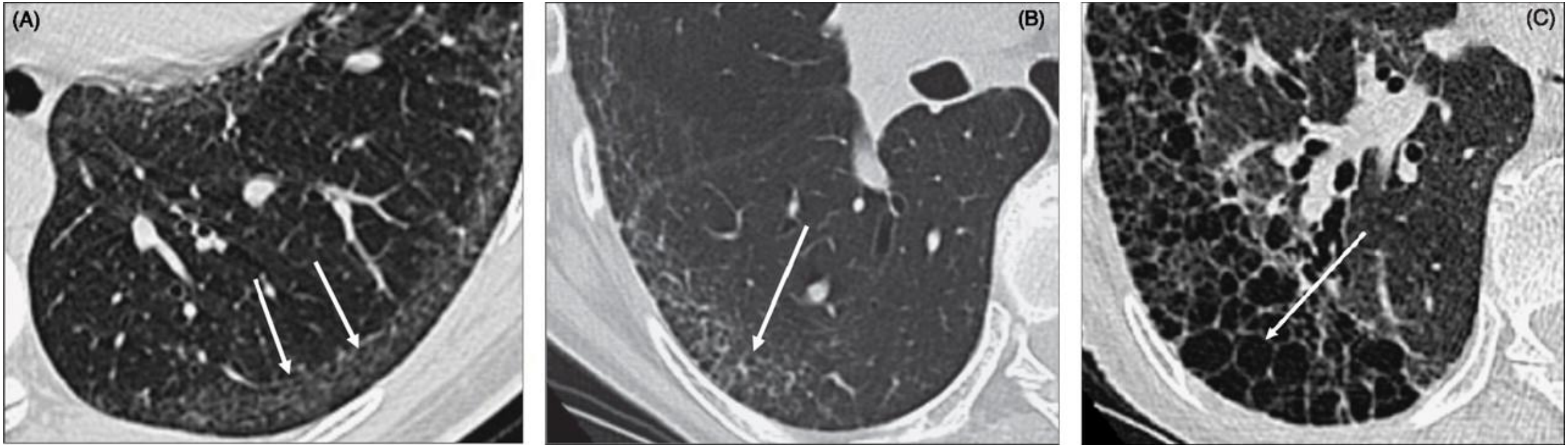


Non specific interstitial pneumonia >>>



Usual interstitial pneumonia

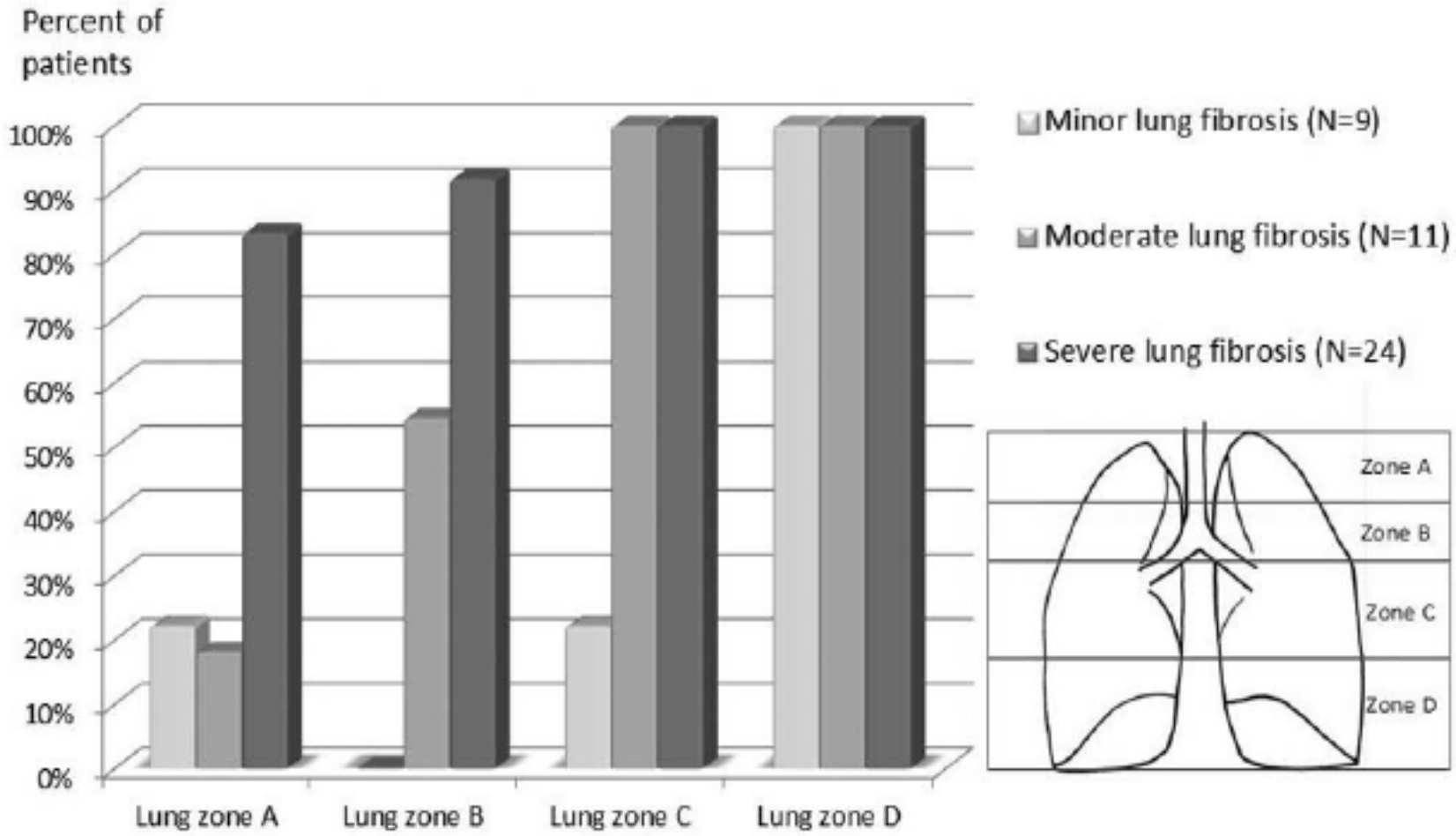
(A–C) Overview of reticular pattern on high-resolution CT of the lungs.



Ragnar Gunnarsson et al. Ann Rheum Dis
doi:10.1136/annrheumdis-2011-201253

ARD

Lung fibrosis distribution in the four lung zones.



Lung zone A: above the aortic arch. Lung zone B: between the aortic arch and the level of the carina.
Lung zone C: between the level of the carina and the level of the inferior pulmonary veins.
Lung zone D: below the inferior pulmonary veins

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

Overview of HRCT lung findings in the patients with MCTD

HRCT findings (n=126)	Patients (n)	%
Normal HRCT	61	48
Abnormal HRCT findings	65	52
Specified HRCT abnormalities		
Reticular pattern type 1*	27	21
Reticular pattern type 2*	20	16
Reticular pattern type 3*	7	6
Ground-glass attenuation	2	2
Interlobular septal thickening	10	8
Nodules	7	6
Bronchiectasis/broncholectasis	11	9
Air trapping	1	1
Emphysema	8	6
Pleural effusion	0	0
Pleural thickenings	3	2

*Reticular pattern type 1, fine intralobular fibrosis without evident cysts; reticular pattern type 2, predominantly microcystic reticular pattern involving air spaces ≤4 mm in diameter; and reticular pattern type 3, a predominantly macrocystic reticular pattern with air spaces >4 mm in diameter. When ground-glass opacification was superimposed a reticular pattern, the abnormality was recorded as being reticular. When fine intralobular fibrosis was superimposed microcystic reticular pattern, the abnormality was recorded as being microcystic reticular pattern.
HRCT, high-resolution CT.

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

Clinical and epidemiological data of 126 patients with MCTD assessed by HRCT of the lungs

Table 2 Clinical and epidemiological data of 126 patients with MCTD assessed by HRCT of the lungs

	Normal HRCT findings	Non-fibrotic HRCT changes	Minor and moderate lung fibrosis	Severe lung fibrosis
Patient characteristics				
Number of patients (%)	61 (48)	21 (17)	20 (16)	24 (19)
Age at inclusion (years)*	40.6 (37.0 to 44.3)	49.8 (42.9 to 56.7)	46.2 (39.1 to 53.3)	50.3 (43.8 to 56.8)
Disease duration at inclusion (years)*	9.8 (7.9 to 11.8)	8.2 (4.7 to 11.7)	13.2 (8.5 to 18.0)	6.4 (3.0 to 9.8)
Female (%)	48 (79)	15 (71)	14 (70)	18 (75)
Juvenile MCTD (<18 years at diagnosis) (%)	10 (16)	1 (5)	3 (15)	0 (0)
Smoking status				
Unknown (%)	14 (23)	6 (29)	5 (25)	3 (13)
Never smoker (%)	27 (44)	5 (24)	6 (30)	12 (50)
Ex-smoker (%)	10 (16)	3 (14)	5 (25)	6 (25)
Current smoker (%)	10 (16)	7 (33)	4 (20)	3 (13)
Symptoms and clinical findings				
Pericarditis in the course of the disease (%)	7 (11)	2 (10)	2 (10)	5 (21)
Pleuritis in the course of the disease (%)	9 (15)	2 (10)	2 (10)	5 (21)
Arthritis in the course of the disease (%)	54 (89)	1 (5)†	13 (65)†	13 (54)†
Arthritis at inclusion (%)	16 (26)	17 (81)†	5 (25)	7 (29)
Myositis in the course of the disease (%)	34 (56)	6 (29)	14 (70)	15 (63)
Raynaud's in the course of the disease (%)	61 (100)	10 (48)	20 (100)	24 (100)
Pulmonary hypertension‡ (%)	2 (3)	0	1 (5)	2 (8)
MCTD criteria				
Alarcon-Segovia criteria (%)	59 (97)	18 (86)	19 (95)	18 (75)†
Sharp's criteria (%)	61 (100)	20 (95)	17 (85)†	24 (100)
Kasukawa criteria (%)	44 (72)	20 (95)†	18 (90)	24 (100)†
Total mortality				
Deaths during the observation period (%)	2 (3)	2 (10)	1 (5)	5 (21)†

*Mean (95% CI of mean).
†Two-tailed p value <0.05 by Fisher exact χ^2 test, compared with the group without HRCT changes.
‡Pulmonary hypertension, defined in 'Methods'.
HRCT, high-resolution CT; MCTD, mixed connective tissue disease.

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

Pulmonary function tests, classification of dyspnoea and functional testing, in 105 patients with MCTD disease with normal HRCT and fibrotic HRCT changes

	Normal HRCT findings (n=61)	Minor and moderate lung fibrosis (n=20)	Severe lung fibrosis (n=24)
Pulmonary function tests			
FVC (litre)	**3.6** (3.4 to 3.8)	**3.4** (3.0 to 3.9)	**2.8** (2.5 to 3.1)
FVC (% of predicted)	**94** (90 to 98)	**89** (83 to 95)	**83** (74 to 92)
FEV1 (litre)	**2.9** (2.7 to 3.1)	**2.7** (2.2 to 3.1)	**2.3** (2.0 to 2.5)
FEV1 (% of predicted)	**90** (86 to 94)	**82** (76 to 89)	**82** (75 to 88)
TLCO (mmol/kPa min)	**7.7** (7.1 to 8.2)	**6.4** (5.4 to 7.3)	**5.2** (4.4 to 6.0)
TLCO (% of predicted)	**80** (77 to 85)	**69** (61 to 77)	**59** (51 to 66)
TLCO/AV (mmol/kPa min/l)	**1.7** (1.5 to 1.9)	**2.2** (1.4 to 3.0)	**1.3** (1.1 to 1.5)
TLCO/AV% (% of predicted)	**91** (87 to 95)	**89** (79 to 100)	**78** (70 to 86)
Dyspnoea classification			
NYHA functional classification*	**1.2** (1.1 to 1.4)	**1.5** (1.2 to 1.7)	**2.0** (1.7 to 2.4)
Functional testing			
6 Min walk test (meters)	**561** (532 to 589)	**534** (462 to 605)	**434** (381 to 491)

Results are shown as mean (95% CI).

*New York Heart Association functional classification was calculated by mean of total NYHA scores (from 1 to 4).[34]
AV, alveolar volume; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York heart Association; TLCO, carbon monoxide transfer factor.

Gunnarsson R et al. Ann Rheum Dis 2012;71:1966–1972.

Examens complémentaires

- Le mauvais pronostic de la PID au cours des MCTD impose son **dépistage systématique**.
- Le bilan doit comporter:
  - tomodensitométrie thoracique haute résolution (TDMHR)
  - épreuves fonctionnelles respiratoires (EFR) avec mesure du coefficient de transfert du monoxyde de carbone (DLCO)
  - test de marche de 6 min avec mesure de la saturation en oxygène et l'estimation de la dyspnée à l'aide de l'indice de Borg.
- EFR avec DLCO/an, plus fréquemment si aggravation
- TDMHR:
  - si normal au départ ne pas le répéter avant 5 ans
  - Si anormal au départ, répéter si aggravation ou tous les 2 à 3 ans.
  - Si possible « low dose »

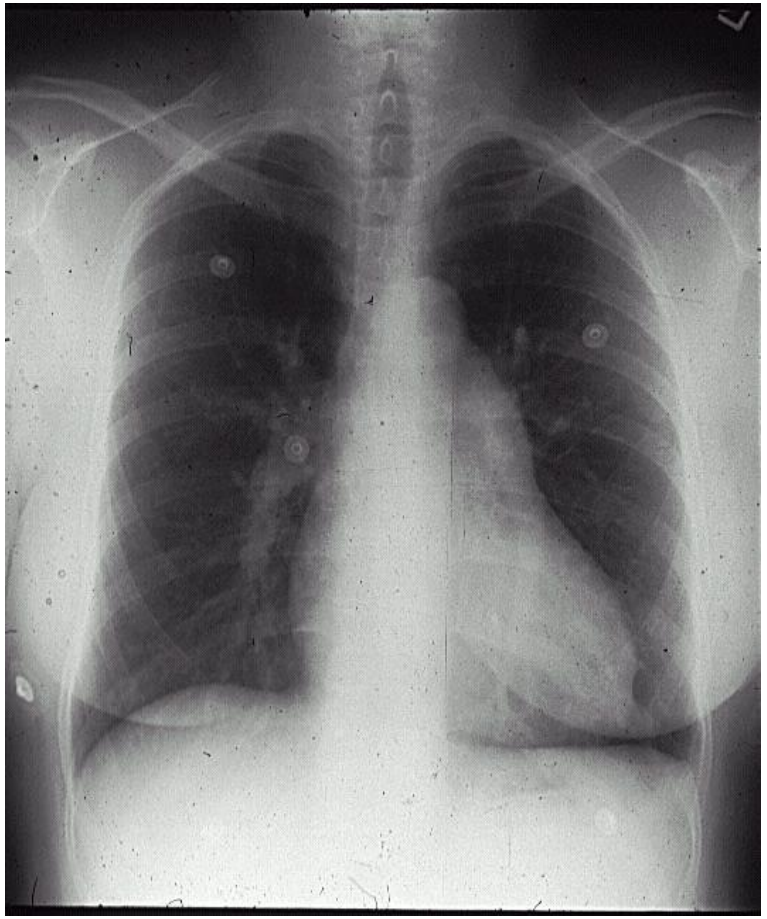
ILD in MCTD: take home message

Severe lung fibrosis is common in MCTD, has an impact on pulmonary function and overall physical capacity and is associated with increased mortality.

Pulmonary hypertension

Definition

Mean pulmonary artery pressure of ≥ 25 mmHg associated with a normal pulmonary artery wedge pressure ≤ of 15 mmHg



Simonneau, G., N. Galiè, et al. (2004). "Clinical classification of pulmonary hypertension." J Am Coll Cardiol 43(12 Suppl S): 5S-12S

Rubin, L. J. (1997). "Primary pulmonary hypertension." N Engl J Med 336(2): 111-117.

Updated classification of pulmonary hypertension

Connective tissue diseases

1. Pulmonary arterial hypertension
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.2.1 BMPR2
   - 1.2.2 ALK-1, ENG, **SMAD9**, **CAV1**, **KCNK3**
   - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
   - 1.4.1 Connective tissue disease
   - 1.4.2 HIV infection
   - 1.4.3 Portal hypertension
   - 1.4.4 Congenital heart diseases
   - 1.4.5 Schistosomiasis

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Persistent pulmonary hypertension of the newborn (PPHN)

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - **2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies**

3. Pulmonary hypertension due to lung diseases and/or hypoxia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: **chronic hemolytic anemia**, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

*5th WSPH Nice 2013. Main modifications to the previous Dana Point classification are in **bold**.
BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simmoneau G et al. J Am Coll Cardiol 2013

Pulmonary arterial hypertension in France : results from a national registry

Humbert M et al. AJRCCM 2006, Feb 2; [Epub ahead of print]

Table 1. Clinical and hemodynamic data at the time of diagnosis of pulmonary arterial hypertension

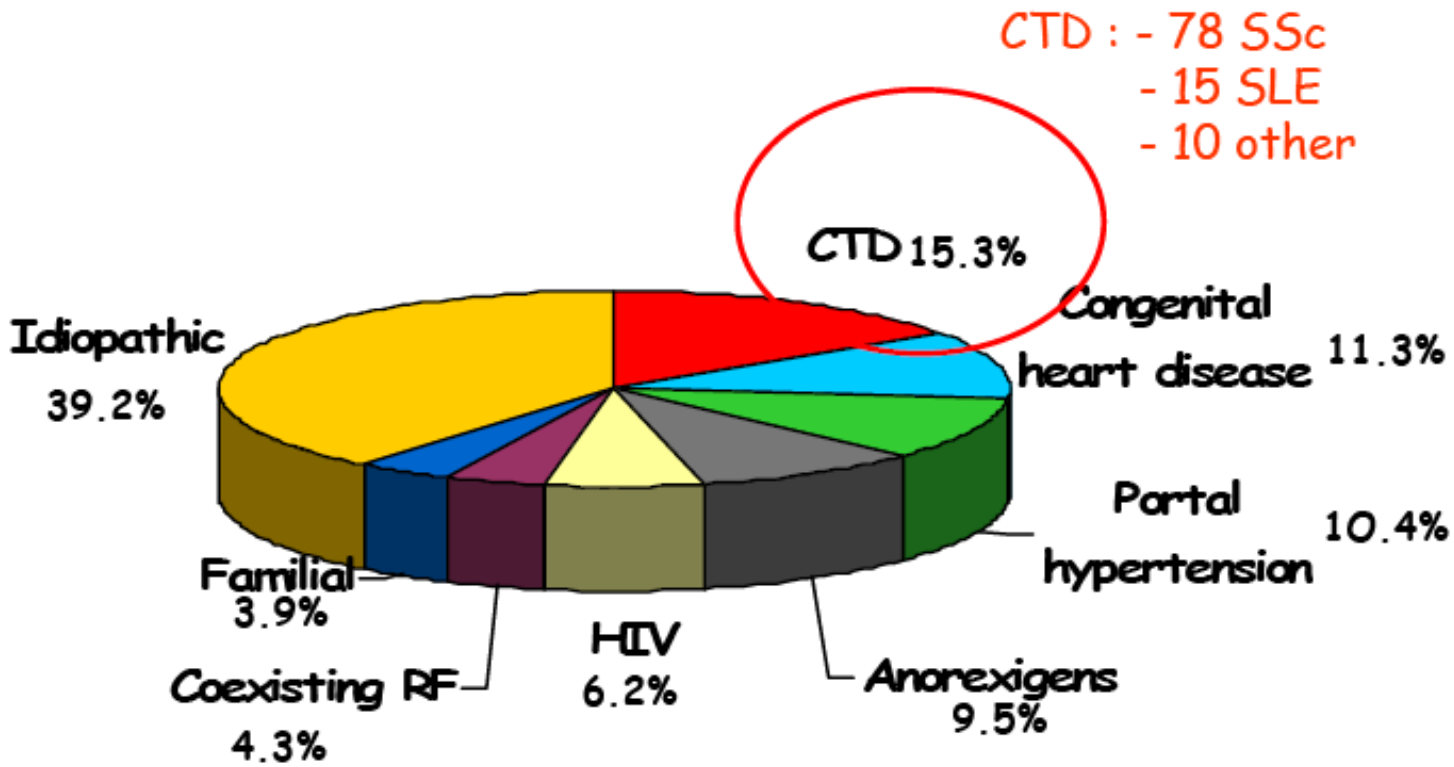
	All cases	Incident cases	Prevalent cases
Disease subtype (%)			
Idiopathic (n=264)	39.2	40.5	38.9
Familial (n=26)	3.9	2.5	4.2
Connective tissue diseases (n=103)	15.3	18.2	14.6
Congenital heart diseases (n=76)	11.3	4.1	12.8
Portal hypertension (n=70)	10.4	14.9	9.4
Anorexigens (n=64)	9.5	3.3	10.8
HIV infection (n=42)	6.2	9.9	5.4
2 co-existing risk factors (n=29)	4.3	6.6	3.8

Data expressed as mean ± SD, and range for age

HIV: human immunodeficiency virus; mPAP: mean pulmonary arterial pressure; n=number of cases; NY York Heart Association; PAWP: pulmonary arterial wedge pressure; PVRI: pulmonary vascular resistance in right atrial pressure; SvO2: venous oxygen saturation

*comparisons are for incident versus prevalent cases of pulmonary arterial hypertension

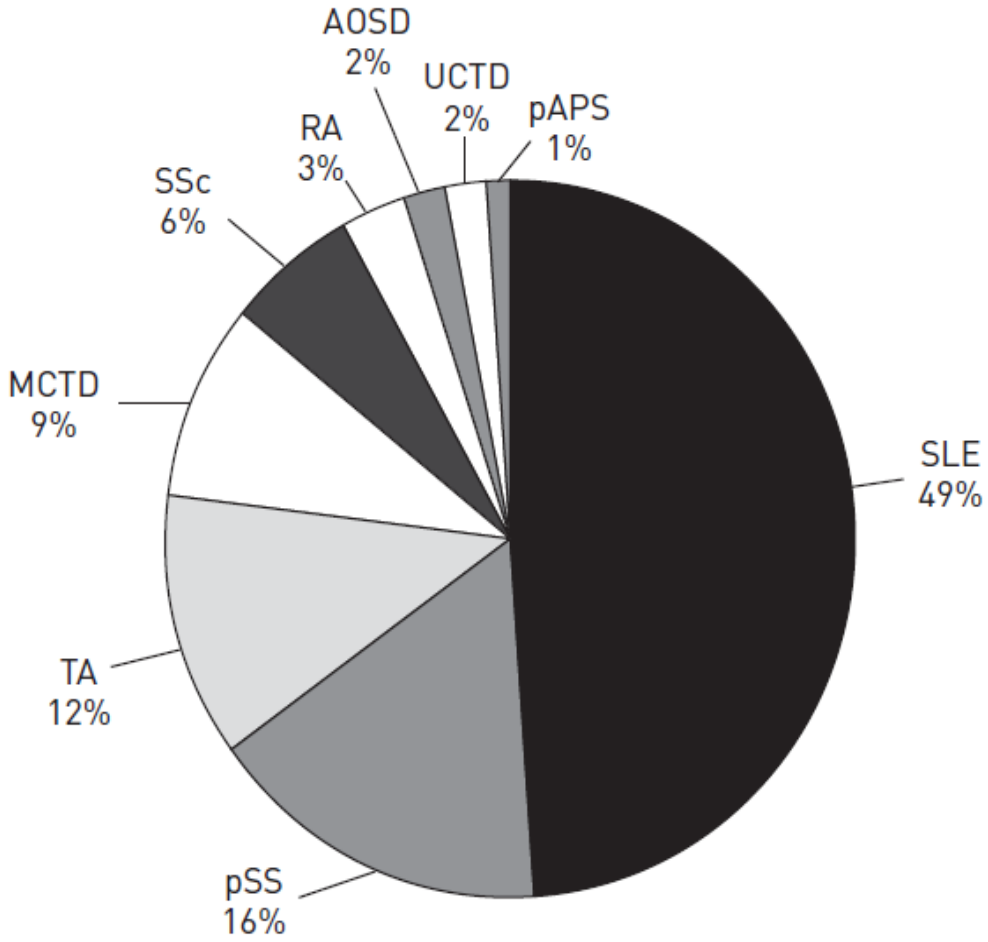
L'HTAP en France: données du registre national



N = 674

Humbert M et al. Am J Respir Crit Care Med 2006;173:1023

Proportions of different underlying connective tissue diseases (CTDs) in 129 patients with CTD-associated pulmonary arterial hypertension (APAH).



Systemic lupus erythematosus (SLE) was the most common underlying type of CTD (n562, 49%), while only 6% of patients had systemic sclerosis (SSc)-APAH. pSS: primary Sjogren syndrome; TA:
Takayasu arteritis; MCTD: mixed connective tissue disease; RA: rheumatoid arthritis; AOSD: adult-onset Still's disease;
UCTD: undifferentiated connective tissue disease; pAPS: primary antiphospholipid syndrome.

HAO YJ et al. Eur Resp J 2014

Prevalence of PH in MCTD

	Alpert *et al.* [14]	Sullivan *et al.* [2]	Burdt *et al.* [3]	Wigley *et al.* [15]
Year published	1983	1984	1999	2005
Country	USA	USA	USA	USA and Canada
MCTD population	Hospital cohort	Hospital cohort	Hospital cohort	Screening, rheumatology practices
Location	University of Missouri	University of Missouri	University of Missouri	50 rheumatology practices
Study design	Cohort follow-up	Cohort follow-up	Cohort follow-up	Cross-sectional
Mean disease duration at inclusion (years)	–	4.5	–	–
Mean follow-up time (years)	–	6.3	15	–
MCTD disease criteria	–	–	Kasukawa	Alarcón-Segovia
Number of patients	38	34	47	94 [11 + 83]
Sex	92% females	91% females	91% females	–
Ethnicity	N/A	82% Caucasians	81% Caucasians	–
Method of screening for PH	32 Echo and 17 RHC	15 RHC	–	Echo
PH verified by RHC, *n* (%)	9 (24)	8 (24)	8 (17)	–[a]
Prevalence of PH, %	24	24	17	19[a]
Prognosis of PH	4 deaths	3 deaths	6 deaths	–

Echo: Doppler echocardiography. [a]The diagnosis of PH was based on Doppler echocardiography with estimated right ventricular systolic pressure (ERVSP) $\geqslant$40 mmHg defined as PH in 18 patients with MCTD.

Gunnarsson R et al. Rheumatology 2013

Prevalence of PH in MCTD

- At inclusion, 2.0% (3/147) had established PH. Two additional PH patients were identified during follow-up, giving a total PH frequency in the cohort of 3.4% (5/147).
- Two had isolated pulmonary arterial hypertension (PAH) and three PH associated with interstitial lung disease (PH-ILD).
- Three PH patients died during follow-up.
- Conclusion: the data from the current unselected MCTD cohort suggest that the prevalence of PH is much lower than expected from previous studies but confirm the seriousness of the disease complication.

Gunnarsson R et al. Rheumatology 2013

PAH - MCTD

- Detection: echocardiography
- Confirmation: right heart catheterism
- Perform regularly:
  - NT pro-BNP
  - PFTS (DLCO)
  - Echocardiography

From: Characterization of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension From REVEAL: Identifying Systemic Sclerosis as a Unique Phenotype

Chest. 2010;138(6):1383-1394. doi:10.1378/chest.10-0260

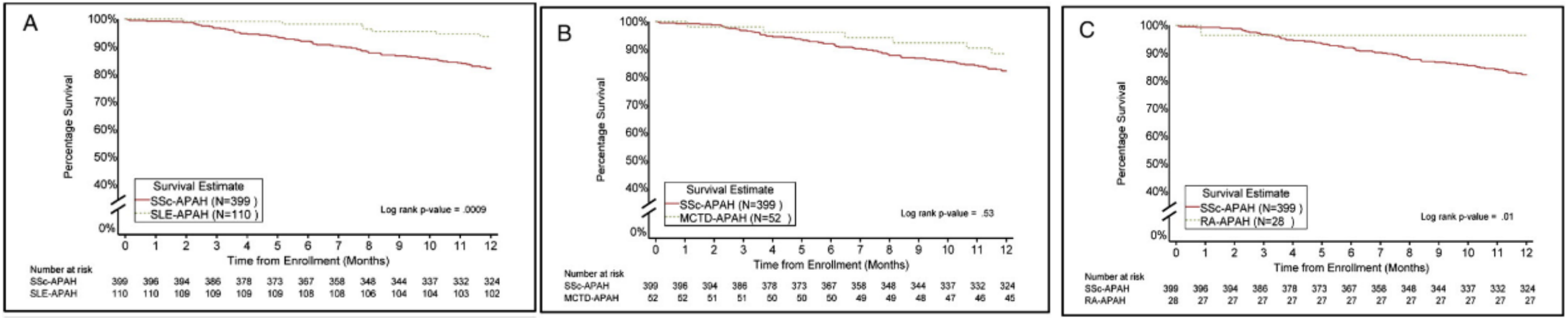


Figure Legend:

Kaplan-Meier curves of 12-month survival in SSc-APAH, SLE-APAH, MCTD-APAH, and RA-APAH. Patients with SSc-APAH had a worse 12-month survival compared with A and C. A, Patients with SLE-APAH (82% vs 94%, P = .0009). C, Patients with RA-APAH (82% vs 96%, P = .01). B, However, patients with SSc-APAH and MCTD-APAH displayed similar 12-month survival outcomes (82% vs 88%, P = .53). MCTD-APAH = mixed connective tissue disease-associated PAH; RA-APAH = rheumatoid arthritis-associated PAH; SLE-APAH = systemic lupus erythematosus-associated PAH; SSc-APAH = systemic sclerosis-associated PAH. See Figure 1 legend for expansion of other abbreviations.

Cumulative clinical features of MCTD

Clinical feature	Prevalence (%)
Neuropsychiatric	
Trigeminal neuropathy	15
Aseptic meningitis	Uncommon
Reticuloendothelial system	
Lymphadenopathy	50
Hepatosplenomegaly	25
Renal	
Glomerulonephritis	10
Hypertensive crisis	Rare

Maddison PJ. Bailliere's Clinical Rheumatology, 2000

Main clinical features in “stable UCTD” as reported in the recent literature.

Author, year,	*N*	Disease duration (mean, years)	Arthralgias/ arthritis	Hematological	Skin	RP	Serositis
Vila LM, 2000	79	4.4	−/15.2%	10% leukopenia, 30.4% anemia, 5.1% TCP	40.5% PS, 25.3% malar rash	6.3%	1.3%
Vaz CC, 2009	184	3.04	66%/32%	19% leukopenia, 15% anemia	17% PS	30%	2%
Bodolay E, 2003	435	5	49%/29.9%	30.3% anemia, 11.3% TCP	23.4%	58.8%	9.8%
Mosca M, 2002	83	10	69%/33%	25% leukopenia, 12% anemia, 6% TCP	17% PS, 3% malar rash	48%	6%
Danieli MG, 1999	165	5	37%/22%	19%	52%	50%	6%

RP = Raynaud’s phenomenon; PS = photosensitivity; TCP = thrombocytopenia.

Mosca M et al. J Autoimmunity 2014

Initial clinical features in 12 children with MCTD

Clinical features at onset	
Raynaud's phenomenon	58% (7/12)
Swollen fingers or hands	50% (6/12)
Polyarthritis	58% (7/12)
Rash	50% (6/12)
Pericarditis	8% (1/12)
Central nerve system symptoms	25% (3/12)
Leukopenia	25% (3/12)
Thrombocytopenia	8% (1/12)
Hemolytic anemia	25% (3/12)
Myositis	8% (1/12)
Sicca syndrome	17% (2/12)

Tsai YY et al. Clin Rheum 2010

Frequencies of categories of disease manifestations in 12 children with MCTD

Disease manifestation	Onset	Follow-up
SLE-like	42%	50%
Scleroderma-like	33%	58%
Myositis (JDM)-like	8%	0%
JRA-like	8%	0%

Tsai YY et al. Clin Rheum 2010

Overlap Syndromes: classification.

Associated with specific autoantibody profile
Mixed connective tissue disease (anti-U1 snRNP)
Anti-synthetase syndrome (anti-tRNA synthetase)
Polymyositis and scleroderma (anti-PM/Scl)
Systemic lupus erythematosus and Sjögren syndrome (anti-La/SSB)
Not associated with specific autoantibody profile
Rhupus syndrome
Systemic sclerosis and Sjögren syndrome
Systemic sclerosis and rheumatoid arthritis
Systemic lupus erythematosus and systemic sclerosis
Rheumatoid arthritis and Sjögren syndrome
Polymyositis and Sjögren syndrome

Anti-U1 snRNP: anti-(U1) small nuclear RNA antibodies.

Iaccarino L et al. Autoimmunity Rev 2013

Number of patients (%) with scleroderma Overlap Syndromes: results from the analysis of six studies.

	Caramaschi [32]	Hudson [34]	Hunzelmann [33]	Balbir-Gurman [35]	Pakozdi [31]	Koschik [36]	Total
Patients with SSc	118	719	1483	165	1700	2425	6610
SSc/CTD Overlap	38 (32.2%)	273 (38%)	162 (10.9%)	40 (24.2%)	332 (20%)	223 (9.2%)	1068 (16.2%)
SSc–PM/DM	2 (5.3%)	N R	N R	19 (47.5%)	127 (42.8%)	134 (60.1%)	282 (44.6%)
SSc–RA	3 (8%)	57 (21.1%)	N R	6 (15.4%)	95 (32%)	14 (6.2%)	175 (19.3%)
SSc–SS	10 (26.3%)	50 (18%)	N R	17 (42.5%)	50 (16.8%)	N R	127 (18.5%)
SSc–SLE	0%	N R	N R	2 (5%)	25 (8.4%)	59 (26.6%)	86 (13.6%)

N R: not reported; SSc: systemic sclerosis; CTD: connective tissue disease; PM/DM: polymyositis/dermatomyositis; RA: rheumatoid arthritis; SS: Sjögren syndrome; SLE: systemic lupus erythematosus.

Iaccarino L et al. Autoimmunity Rev 2013

Clinical classification of SSc

Diffuse cutaneous SSc

- Skin sclerosis proximal to elbows and knees
- Inflammatory features prominent in 1st 3 years
- Anti-Scl-70 or anti-RNA polymerase
- Increased frequency of interstitial lung disease, renal crisis, bowel & cardiac involvement

Limited cutaneous SSc

- No skin sclerosis proximal to elbows and knees
- Anti-centromere antibody (ACA)
- CREST subgroup
- Lung fibrosis, renal crisis & cardiac involvement less common than in dcSSc

Scleroderma sine Scleroderma

- No skin sclerosis

Overlap syndrome

- Features include those of lcSSc or dcSSc with those of other autoimmune disease(s)

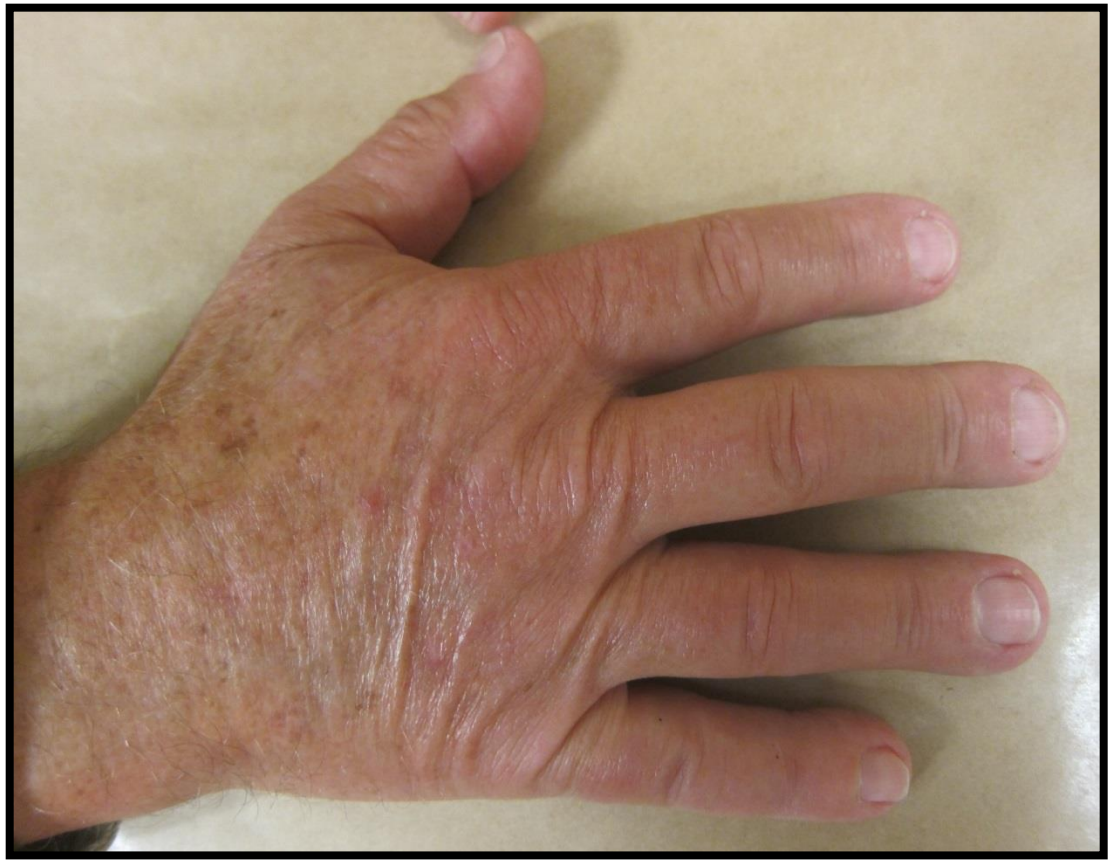
Poormoghim H, *et al. Arthritis Rheum* 2000; 43:444-51,
Denton CP and Black CM, *Trends Immunol* 2005; 26:596-602.

2013 classification criteria for SSc: an ACR/EULAR collaborative initiative (I)

- 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.

van den Hoogen F et al. Ann Rheum Dis 2013

Skin thickening of the fingers (I)

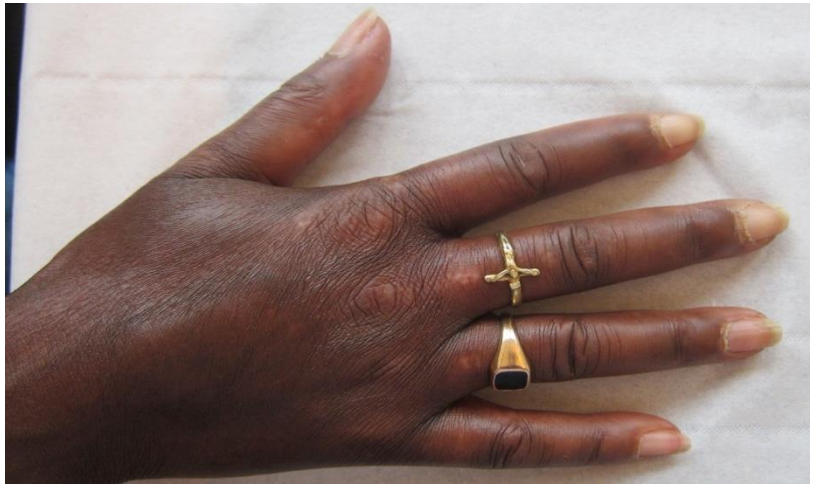


Score = 2

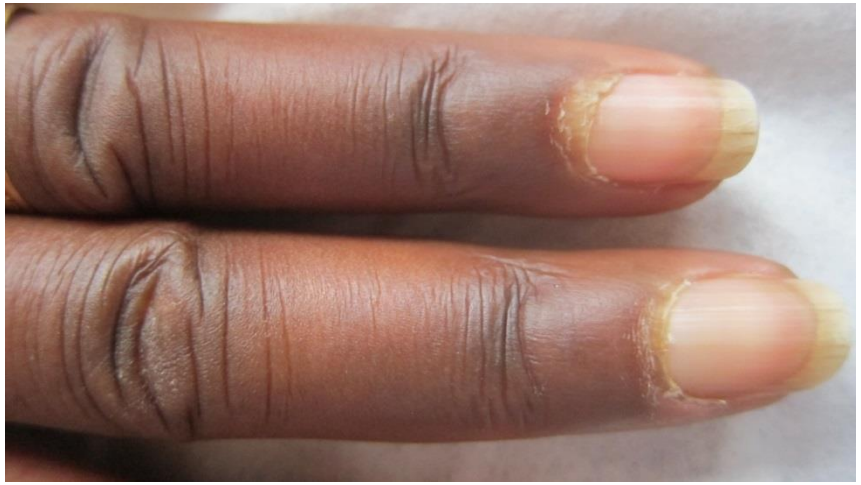
Only count higher score

Puffy fingers

Skin thickening of the fingers (II)

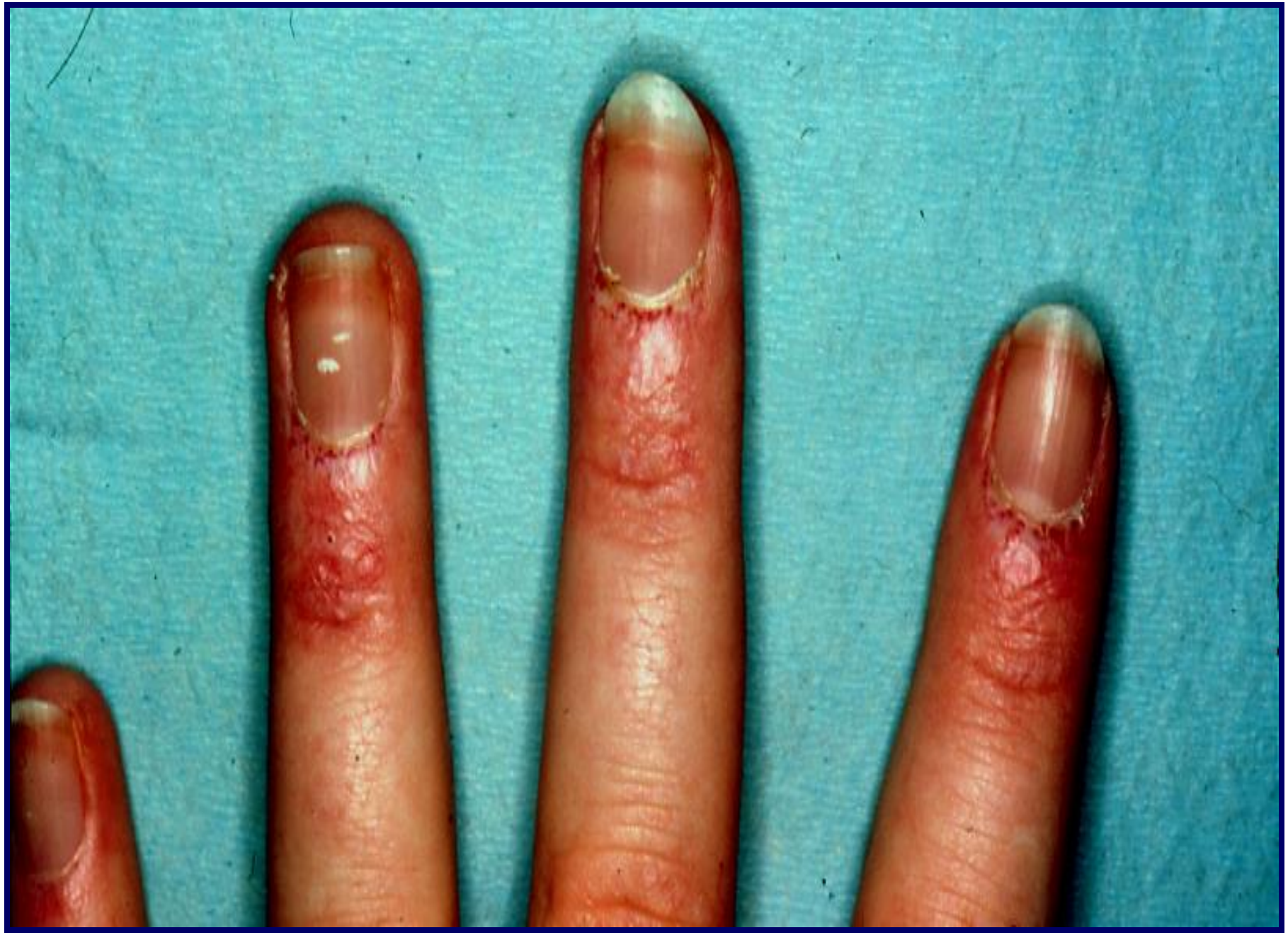


Sclerodactily



Score = 4

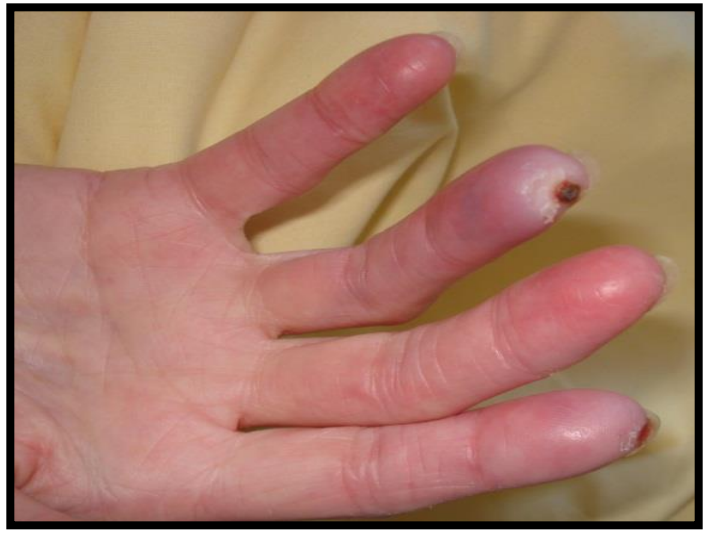
Only count higher score



fingertip lesions

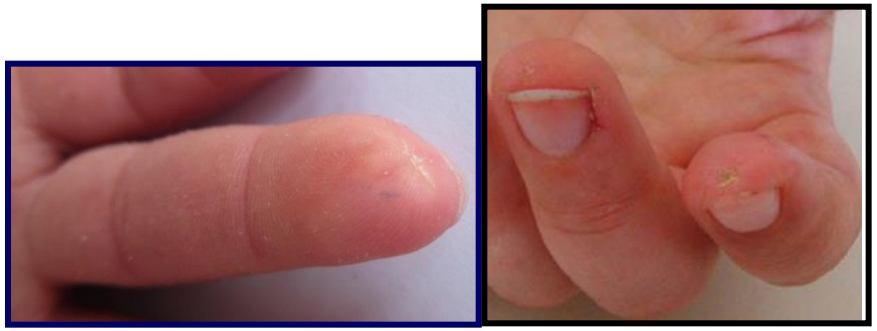
Digital ulcers

Score = 2



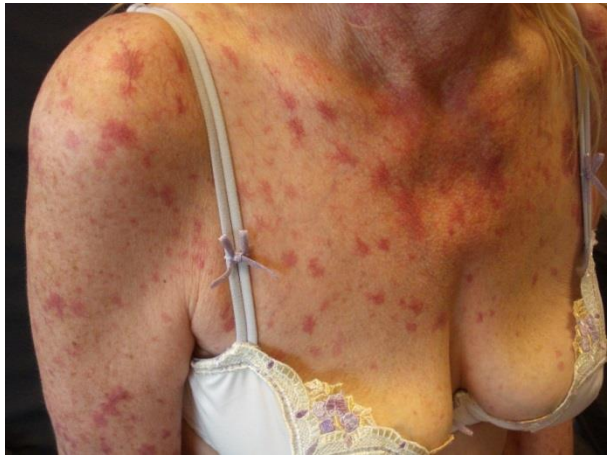
Fingertip pitting scars

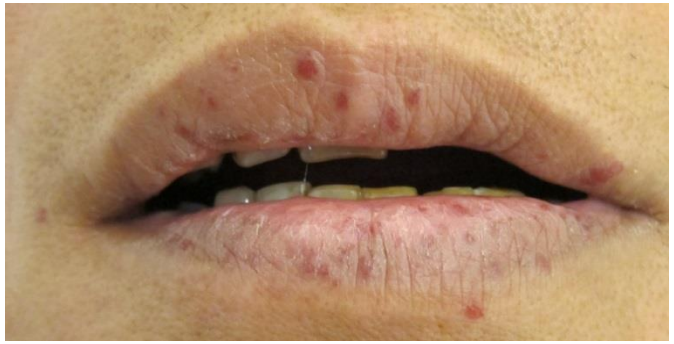
Score = 3

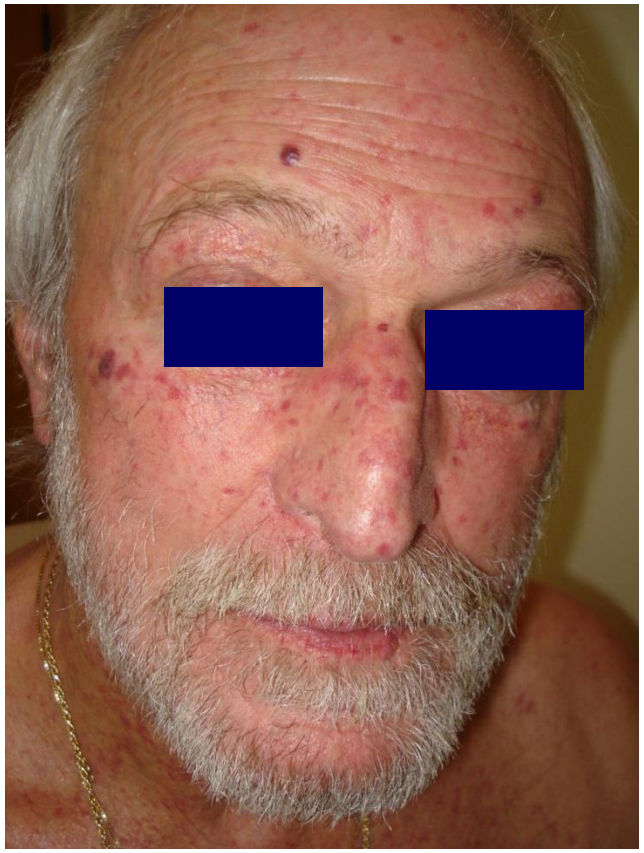


Only count higher score

telangiectasia

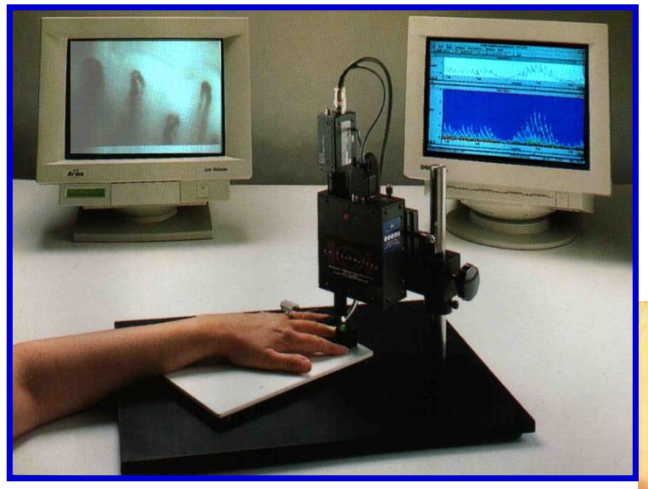


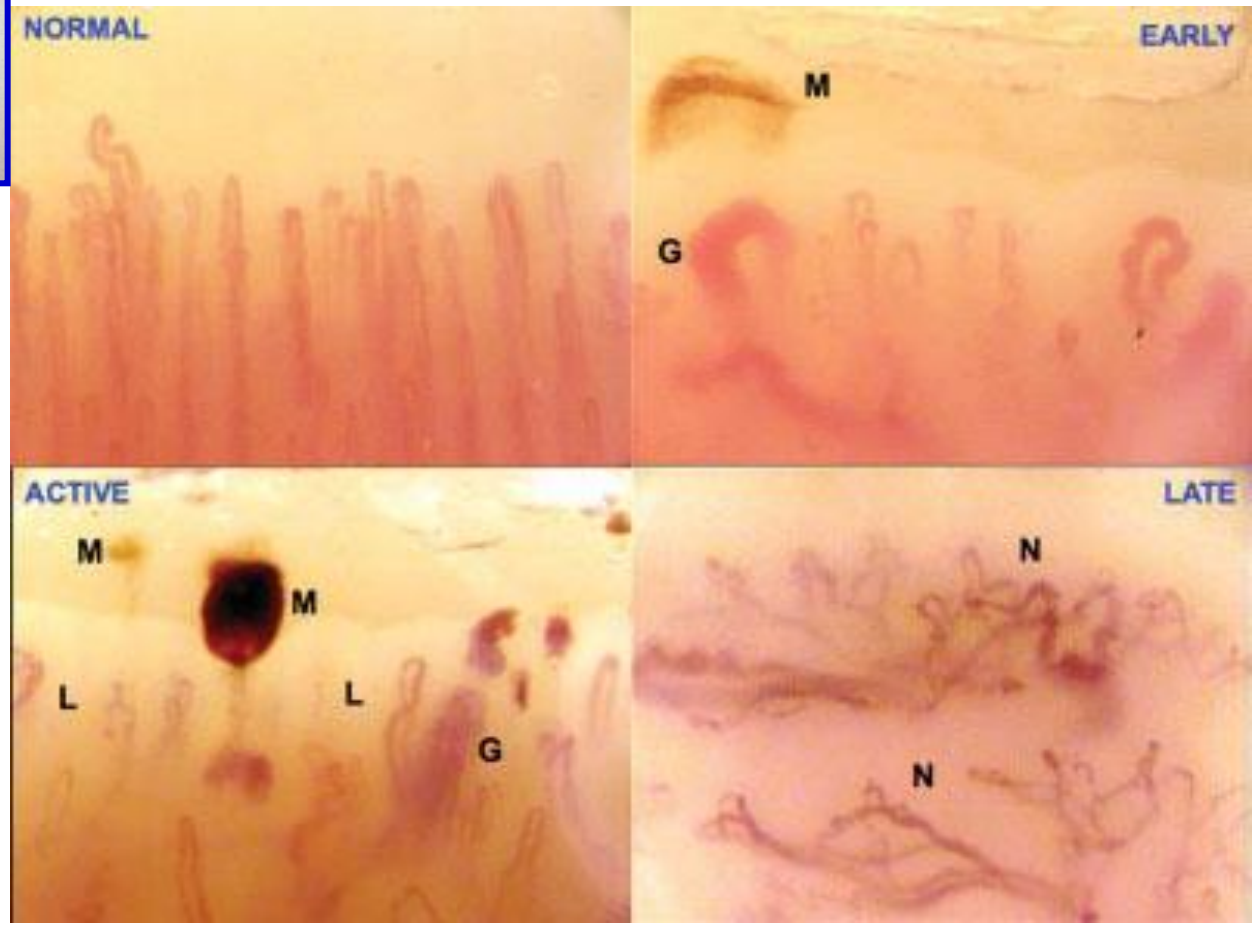




Score = 2

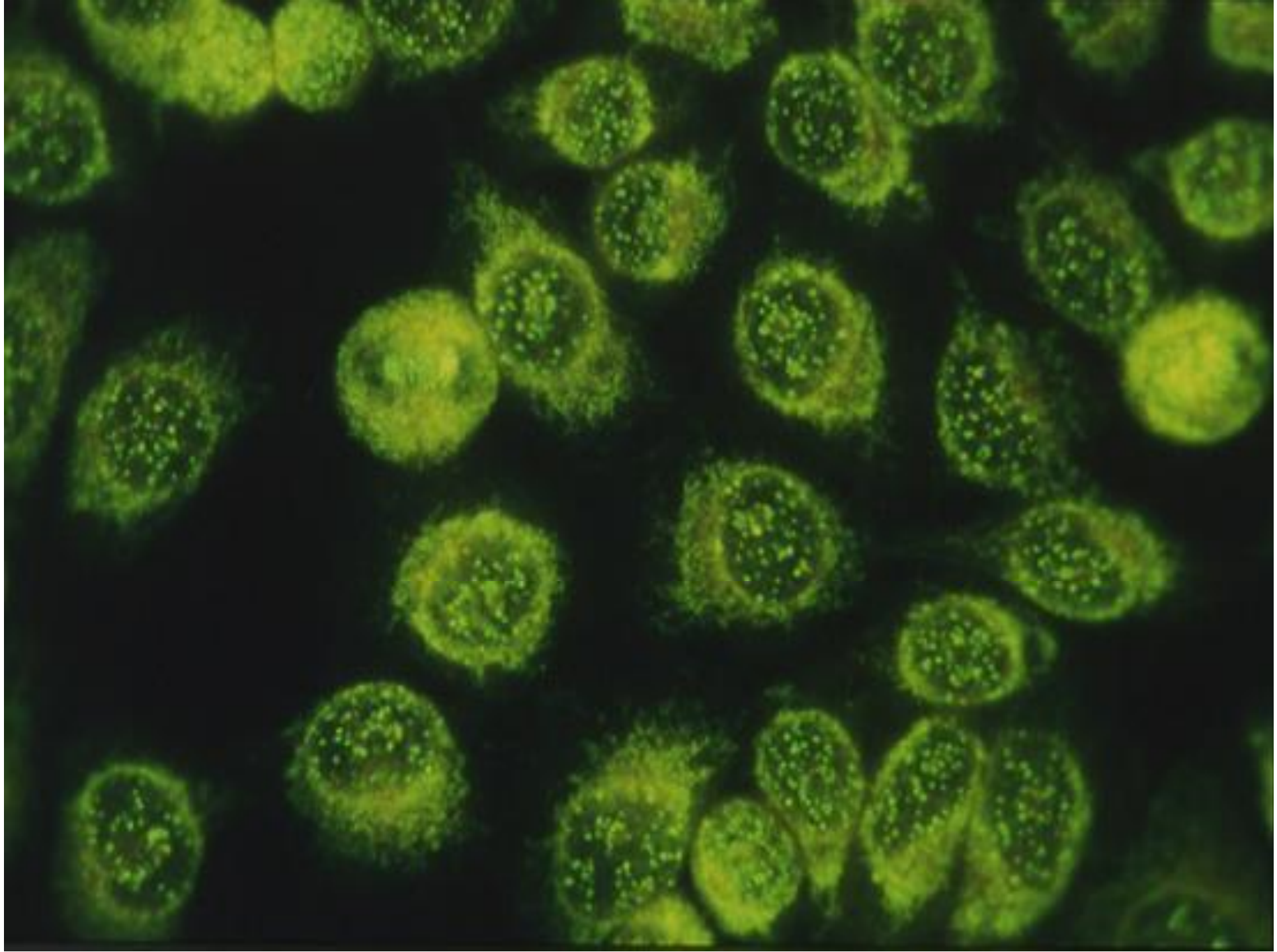
Capillaroscopie



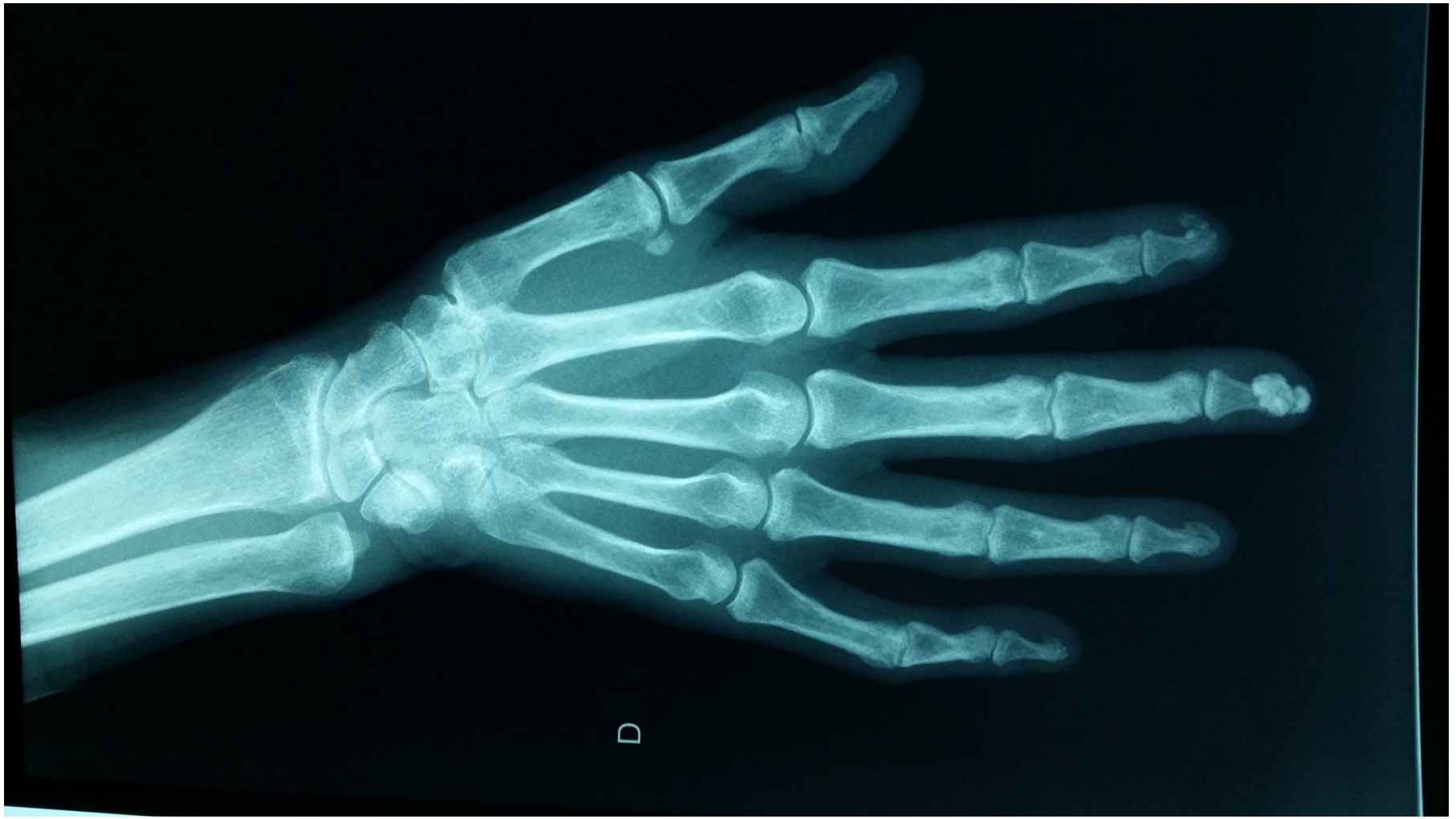


Giant capillaries

- Systemic sclerosis
- MCTD
- Dermatomyositis



Calcinoses



Clinical manifestations in patients with anti-PM/Scl antibody.

	Reichlin [42]	Genth [43]	Oddis [46]	Marguerie [40]	Vandergheyn [41]	Koschik [36]
No. of patients	20	12	23	32	14	76
Raynaud's phenomenon	55%	92%	65%	100%	71%	91%
Arthralgia/ arthritis	50%	58%	83%	97%	85%	84%
Interstitial lung disease	35%	42%	30%	78%	85%	59%
Dysphagia/ deglutition abnormalities	–	36%	–	78%	21%	52%
Renal involvement	–	0%	0%	3%	21%	8%
Sicca syndrome	–	25%	–	34%	43%	–
Scleromyositis	41%	42%	43%	85%	38%	43%

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Autoanticorps

Sclérodermie	myopathie- n=80	myopathie+ n=40	p value
FAN	58/69 (84%)	32/40 (80%)	ns
anti-Scl70	19/68 (28%)	7/39 (18%)	ns
anti-centromère	21/66 (32%)	2/39 (5%)	$<10^{-3}$
anti-SSA / SSB	9/66 (14%)	7/40 (18%)	ns
anti-RNP	2/64 (3%)	6/40 (15%)	<0.05
anti-DNA	4/62 (7%)	2/39 (6%)	ns
anti-PM/Scl	1/62 (2%)	4/36 (14%)	<0.05
anti-Ku	0/na	1/na	-

Ranque et al, ARD 2008

Sclérodermie et myopathie avec anticorps anti-PM/Scl

- Prévalence
  - 10-50% des SSc avec myosite ont des AC anti-PM/Scl
  - 43-58% des SSc avec AC anti-PM/Scl ont une myosite
- Atteinte clinique
  - classiquement modérée
  - mais atteinte pharyngée/oesophagienne possible
- Histologie ~ PM ou DM > non inflammatoire
- Réponse aux corticoides
  - classiquement excellente à faible dose
  - mais corticorésistance >50% dans les études récentes*

Oddis, Arthritis 1992; Jablonska, Clin Rheumatol 1998
**Ranque, ARD 2008; *Diot, Rev Med Int 2009*

Sclérodermie et myopathie avec anticorps antiU1-RNP

- Connectivite mixte (syndrome de Sharp):
  - définition = AC anti U1-RNP + signes cliniques évocateurs
  - myosite présente dans 20-75% des cas
  - 20-30% évoluent vers sclérodermie

- Dans la sclérodermie :
  - myopathie fréquente si RNP+
    27% de myosite si RNP+ versus 5% si RNP- et PmSCL-[1]
  - bon pronostic
    >90% de rémissions avec ou sans corticoides[2]

Steen et al, Arthritis 2005, Burdt et al, Arthritis 1999

Prevalence of autoantibodies in Sjögren syndrome overlapping with systemic lupus erythematosus.

Prevalence of autoantibodies in Sjögren syndrome overlapping with systemic lupus erythematosus.

	Gilboe et al. [65]			Manoussakis et al. [66]			Baer et al. [67]		
	SLE/SS	SLE	p	SLE/SS	SLE	p	SLE/SS	SLE	p
Anti-Ro/SSA	89%	36%	<0.05	38.5%	23.9%	0.008	45.3%	26.8%	<0.001
Anti-La/SSB	56%	11%	<0.05	38.5%	7.0%	<0.001	22.1%	10%	<0.001
Rheumatoid factor	–	–	–	64%	28.6%	<0.001	–	–	–
Anti-dsDNA	44%	60%	ns	69.2%	77.3%	ns	45.4%	59.1%	<0.001
Anti-Sm	–	–	–	7.7%	11.3%	ns	9.7%	17.3%	0.004
Anti-U1RNP	–	–	–	11.5%	12.7%	ns	13.3%	28.8%	<0.001
Anti-cardiolipin	–	–	–	45.8%	52.9%	ns	41.7%	49.1%	0.03

SLE: systemic lupus erythematosus; SS: Sjögren syndrome.

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Table 6. Characteristics of SLE patients with anti-U1RNP followed at the Royal National Hospital for Rheumatic Diseases, Bath, UK.

Clinical feature	SLE patients with anti-U1RNP ($n = 56$)	SLE patients without anti-U1RNP ($n = 152$)
Raynaud's phenomenon	95%	43%
Myositis	23%	3%
Fulfill MCTD criteria (Alarcón-Segovia and Villareal[50])	56%	3%

Data in table are unpublished observations from Bath, UK.

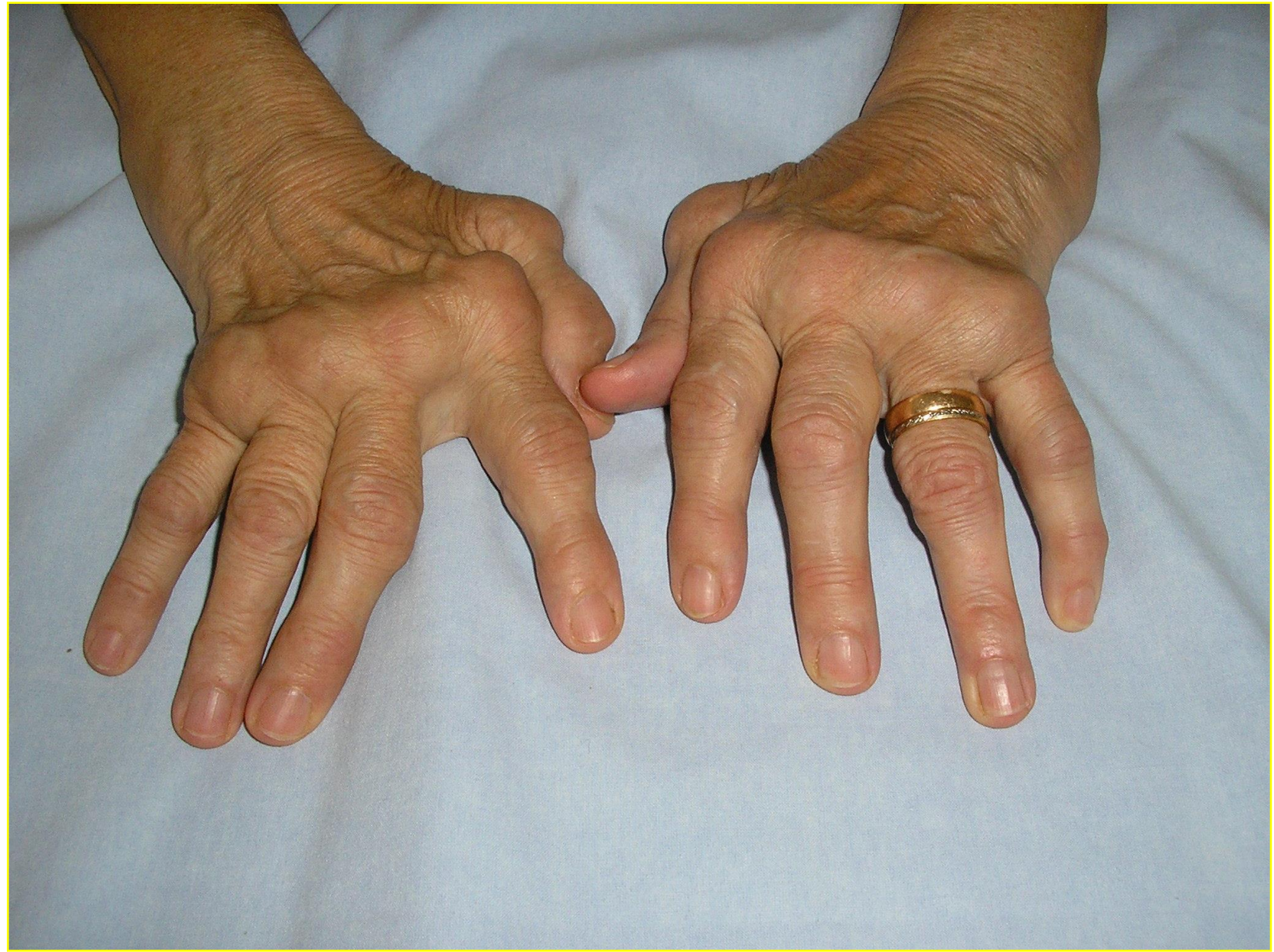
Alarcon-Segovia D & Villareal M. Excerpta Medica, 1987.

Table 4 Evolution of Patients with the Initial Diagnosis of MCTD (Patients who satisfied either Kasukawa, Alarcón, or Sharp's Criteria at diagnosis were analyzed separately)

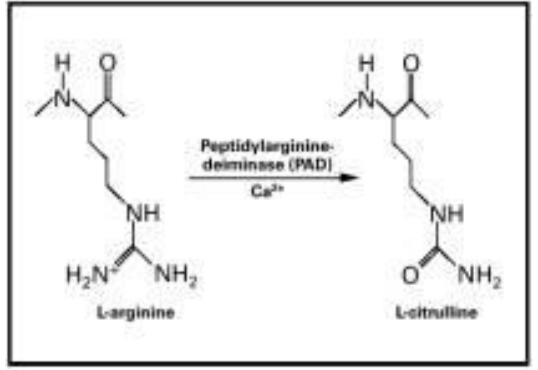
Criteria Fulfilled at the Diagnosis	Patients (%) Still Affected by MCTD and Evolved into Another CTD in 2008					
	MCTD	SSc[a]	SLE[a]	RA[a]	Overlap Syndrome[c]	Undifferentiated Disease[d]
Kasukawa	57.9% (17.4%MCTD only[a] + 40.5%MCTD + other CTDs[b])	17.3%	9.1%	2.5%	1.6%	11.6%
Alarcón-Segovia	49.9% (7.5%MCTD only[a] + 42.4%MCTD + other CTDs[b])	16.9%	9%	1.6%	4.1%	18.5%
Sharp	52.2% (13.4%MCTD only[a] + 38.8%MCTD + other CTDs[b])	13.4%	6%	0%	10.5%	17.9%

[a]Patients who satisfied classification criteria for only 1 CTD (MCTD, SSc, SLE, or RA).
[b]Patients who satisfied both classification criteria for MCTD and for 1 or more other CTDs (SSc, SLE, PM/DM) or for RA.
[c]Patients who satisfied classification criteria for 2 or more CTDs without satisfying those for MCTD.
[d]Patients with clinical features typical for a CTD who did not satisfy any criteria for a definite CTD.

Cappelli S et al.
Sem Arthritis Rheum 2012



Ac anti-CCP (I)



- **Ac anti-peptide cyclique citrulliné**
- **ELISA (tests de deuxième génération)**
- **Marqueurs spécifiques de polyarthrite rhumatoïde**
  - ✓**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 (II)

- **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

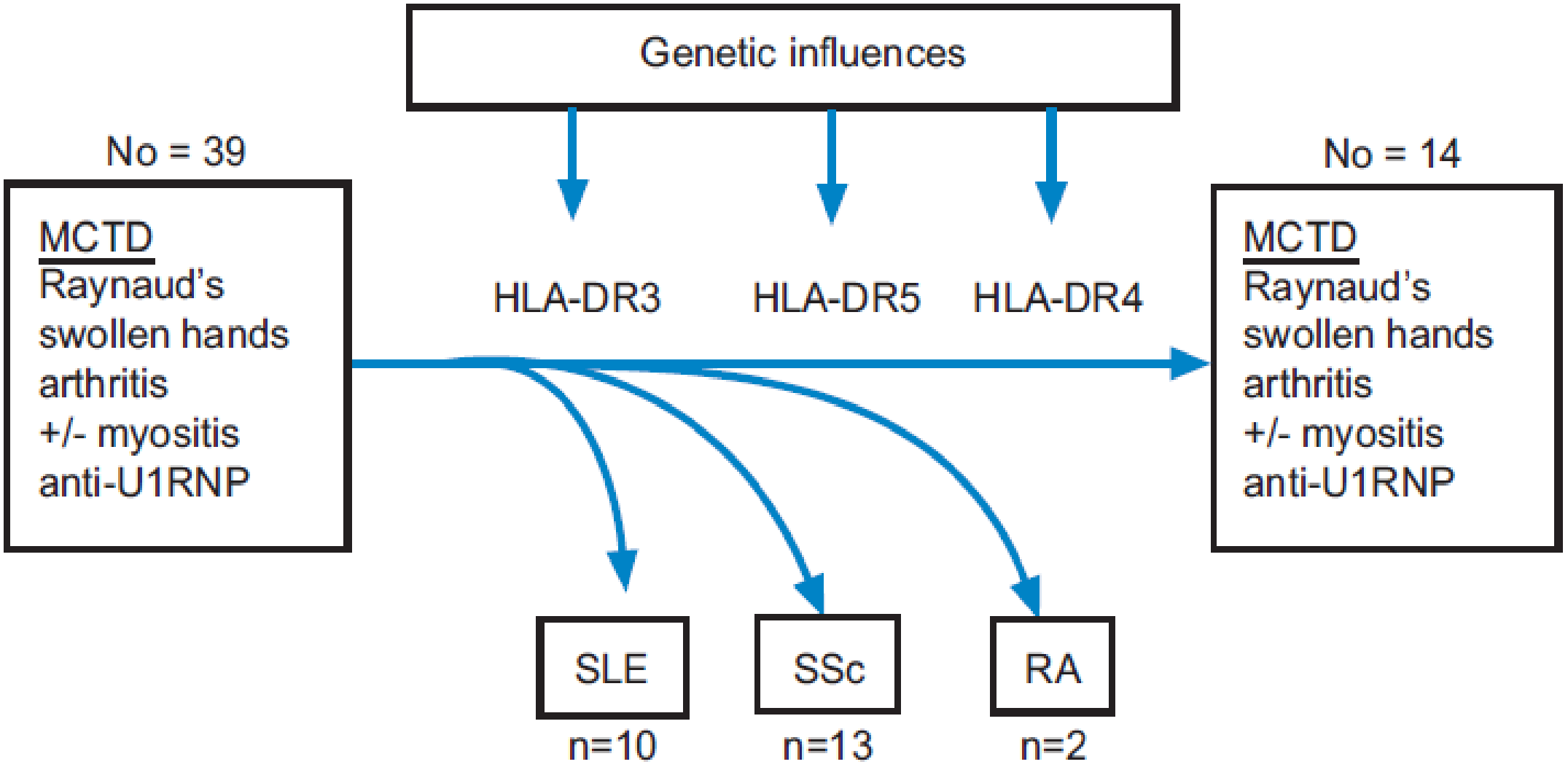
Vander Cruyssen B, Ann Rheum dis, 64:1145-9
Herold M, Clin Dev Immunol; 12:131-5
Sauerland U, Ann NY Acad Sci, 2005;1050:314-8.
Avouac, Ann Rhum Dis 2006

Table 5 Evolution into Another CTD in Patients with Different Disease Duration (mean 7.9 yr) (Patients who satisfied either Kasukawa, Alarcón, or Sharp's Criteria at Diagnosis were analyzed separately)

Criteria Fulfilled at the Diagnosis	Patients (%) Evolved into Another CTD		
	Disease, yr		
	0 to 5	5 to 10	>10
Kasukawa	15.2%	39.2%	41.7%
Alarcón	20.4%	34.9%	50%
Sharp	20.6%	43.5%	30%

Cappelli S et al.
Sem Arthritis Rheum 2012

Evolution of MCTD phenotype: influence of genetic factors (after Gendi et al55).



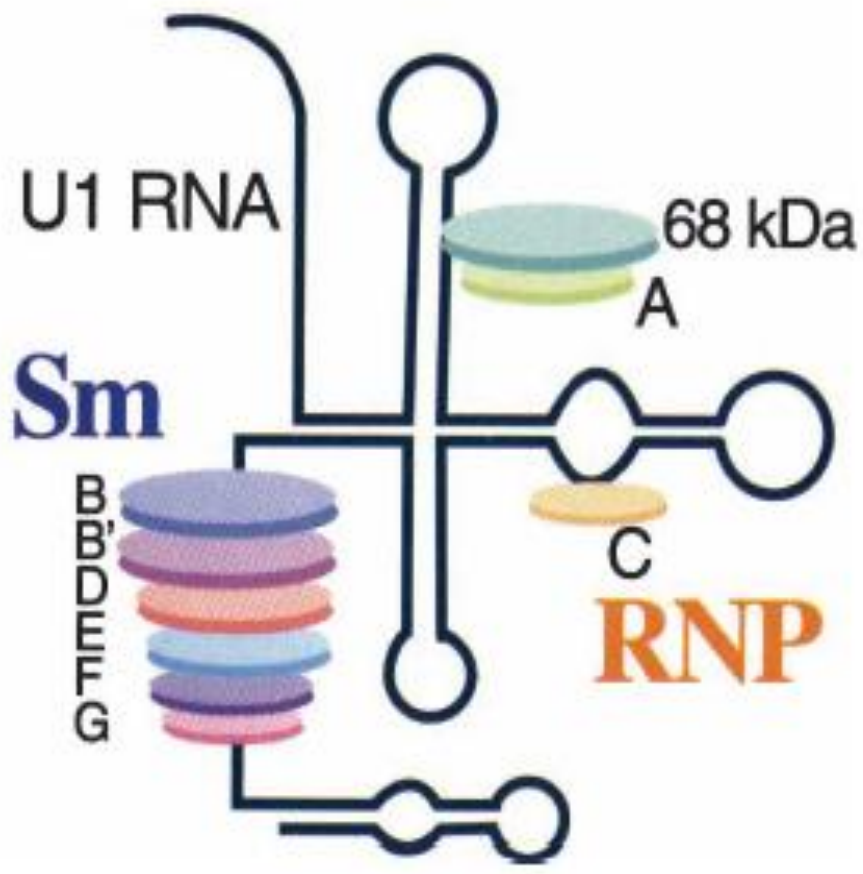
Gendi NS, et al. Arthritis and Rheumatism

Table 7 Evolution of MCTD in Previous Works

Author (yr)	Evolution	Disease Duration	Number of Patients	Conclusions
Nimelstein et al (1980) (24)	59% SSc, 5.9% SLE, 5.9% RA	8 yr (follow-up)	25	"MCTD spontaneously evolves into SSc"
Van den Hoogen et al (1994) (21)	46% MCTD, 21% SSc, 15% SLE, 9% RA, 9% Overlap syndrome	5 yr (follow-up)	46	"The majority of patients have or will develop a classified CTD within 5 years"
Gendi et al (1995) (19)	36% MCTD, 34% SSc, 25% SLE, 5% RA	20 yr (mean disease duration)	46	"MCTD is, for most patients, an intermediate stage in a progression to an other CTD"
Burdt et al (1999) (20)	21% SSc, 13% SLE	15 yr (mean duration of follow-up)	47	"It does not appear that MCTD frequently evolves into SSc or SLE"
Cappelli et al (present 2011)	57.9% MCTD, 17.3% SSc, 9.1% SLE, 2.5% RA, 1.6% Overlap Syndrome, 11.6% UCTD (Kasukawa) 49.9% MCTD, 16.9% SSc, 9%SLE, 1.6% RA, 4.1% Overlap syndrome, 18.5% UCTD (Alarcón) MCTD 52.2%, 13.4% SSc, 6% SLE, 0% RA, 10.5% Overlap syndrome, 17.9% UCTD (Sharp)	7.8 yr (mean disease duration)	161	"More than half of patients, maintained their initial clinical and serological features and remained classified as MCTD; this supports the existence of MCTD as a distinct entity"

Cappelli S et al.
Sem Arthritis Rheum 2012

Structure of U1 sn RNP.
Protein components of the U1 sn RNP particle, complexed with RNA



Migliorini P et al. Autoimmunity 205

Anti-RNP immunity: Implications for tissue injury and the pathogenesis of connective tissue disease

- U1-RNP antibodies increase the production of inflammatory cytokines by mononuclear cells.
- Antibodies to U1-RNP upregulate adhesion molecules and serve as anti-endothelial cell antibodies and are likely to contribute to the development of tissue injury in certain patients with connective tissue diseases.
- Modified U1-RNP proteins are antigenically distinct and generate specific antibody responses that are associated with features of connective tissue disease.
- The Toll like receptor response mediates disease phenotype in an animal model of mixed connective tissue disease based on U1-70kDa immunity in the presence of U1-RNA.
- The relative contributions of these aspects of U1-RNP immunity in the pathogenesis of human connective tissue disease has yet to be delineated.

Keith MP et al. Autoimmunity Rev 2007

Autoantibodies as predictors of organ involvement

Table 6 Autoantibodies (First Visit) as Predictors of a Specific Organ Involvement, Sclerodactyly, or Serositis (2008)

	Renal Involvement		Neurological Involvement		Pulmonary Involvement	
	OR (95%CI)	*P*	OR (95%CI)		OR (95%CI)	*P*
Anti-DNA	1.1 (0.9 to 1.3)	NS	1.0 (0.9 to 1.2)	NS	0.9 (0.7 to 1.2)	NS
Anti-Sm	1.3 (1.1 to 1.5)	0.004	1.0 (0.8 to 1.2)	NS	1.1 (0.8 to 1.4)	NS
Anti-SSA/ro	1.0 (0.9 to 1.1)	NS	1.2 (1.0 to 1.4)	0.014	1.4 (1.1 to 1.7)	0.010
Anti-Scl70	1.0 (0.8 to 1.2)	NS	0.9 (0.7 to 1.1)	NS	1.3 (0.9 to 1.7)	NS
ACA	0.9 (0.6 to 1.2)	NS	1.2 (0.8 to 1.7)	NS	0.9 (0.5 to 1.5)	NS

OR, odds ratio; CI, confidence interval; NS: not significant; *P*, multivariate analysis.

Table 6 Continued

	Hypomotility or Dilatation of Esophagus		Sclerodactyly		Pleuritis/Pericarditis	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Anti-DNA	0.9 (0.7 to 1.2)	NS	0.9 (0.7 to 1.1)	NS	1.3 (1.1 to 1.5)	0.009
Anti-Sm	1.0 (0.7 to 1.3)	NS	0.9 (0.7 to 1.2)	NS	1.2 (0.9 to 1.4)	NS
Anti-SSA/ro	1.2 (0.9 to 1.5)	NS	1.0 (0.8 to 1.3)	NS	1.3 (1.1 to 1.6)	0.001
Anti-Scl70	1.4 (1.0 to 1.8)	0.048	1.0 (0.7 to 1.3)	NS	1.1 (0.9 to 1.3)	NS
ACA	1.3 (0.7 to 2)	NS	1.9 (1.1 to 3.1)	0.019	1.2 (0.9 to 1.7)	NS

Cappelli S et al.
Sem Arthritis Rheum 2012

Table 1. Autoantibodies and associated symptoms in connective tissue diseases.

Autoantibodies to	At least 90% of patients with the disease have
Syndromes/diseases with one lead autoantibody	
tRNA synthetases	Inflammatory myositis
SRP	Inflammatory myositis
Mi-2	Dermatomyositis
Topoisomerase	Raynaud's, diffuse cutaneous scleroderma
Centromere	Raynaud's, sclerodactyly
RNA polymerase	Raynaud's, diffuse cutaneous scleroderma
U3/Fibrillarin	Raynaud's, diffuse cutaneous scleroderma
Th/To	Raynaud's, sclerodactyly
Pm/Scl	Raynaud's, sclerodactyly
U1-RNP	Raynaud's, arthralgias/arthritis
Syndromes/diseases with variable combinations of lead autoantibodies	
dsDNA, Sm	No specific features (features of immune complex deposition)

Aringer M. Best Practice & Research Clinical Rheumatology 2007

MCTD: prognosis

- 280 patients with MCTD diagnosed between 1979 and 2011
- 22 of 280 patients died: causes of death were pulmonary arterial hypertension (PAH) in 9 patients, thrombotic thrombocytopenic purpura in 3, infections in 3, and cardiovascular events in 7.
- The 5, 10, and 15-year survival rates were 98%, 96%, and 88%, respectively.
- The deceased patients were younger at the diagnosis of MCTD compared to patients who survived (35.5 ± 10.4 vs 41.8 ± 10.7 yrs; $p < 0.03$), while there was no difference in the duration of the disease ($p = 0.835$).
- The presence of cardiovascular events ($p < 0.0001$), esophageal hypomotility ($p = 0.04$), serositis ($p < 0.001$), secondary antiphospholipid syndrome ($p = 0.039$), and malignancy ($p < 0.001$) was significantly higher in the deceased patients with MCTD.
- anticardiolipin ($p = 0.019$), anti-β2-glycoprotein I ($p = 0.002$), and antiendothelial cell antibodies ($p = 0.002$) increased the risk of mortality.
- Overall, PAH remained the leading cause of death in patients with MCTD.

Haias A et al. J Rheumatol 2013

MCTD: treatment

Adapt treatment to disease severity

- **Skin and joint involvement**
  - hydroxychloroquine
  - NSAID
  - topical corticosteroids
  - low dose oral CS
  - Never use immunosuppressants
- **Pleuritis, pericarditis**
  - hydroxychloroquine (Plaquénil)
  - NSAID
  - CS 0,5 mg/kg
  - No immunosuppressants
- **Visceral involvement**
  - hydroxychloroquine (prevention of relapses)
  - High dose CS (1 mg/kg)
  - Eventually pulse MP
  - Immunosuppressants
  - anti-CD20, plasma exchanges…

Hydroxychloroquine (plaquenil®)

- **Diminue le nombre et l'intensité des poussées de LES**
- **Posologie: 200 mg x 2/j**
- **Il n'est pas nécessaire de faire un examen ophtalmologique avant de débuter un traitement par plaquenil, mais dans l'année qui suit le début du traitement**
- **Toxicité rétinienne dose dépendante, survient en règle après plusieurs années de traitement cumulé**
- **Peut être prescrit au cours de la grossesse et/ou de l'allaitement**
- **Intérêt du dosage plasmatique car hautement variable entre les individus et reflet de l'adhésion au traitement+++**

MCTD: Posologie de la corticothérapie orale

- LES cutanéo-articulaire (on peut essayer les AINS si atteinte articulaire isolée peu sévère)
  - 10 à 15 mg/j de prednisone per os dose totale
- Pleuro-péricardites
  - ½ mg/kg/j de prednisone per os
- Glomérulonéphrites, atteintes viscérales, cytopénies périphériques (thrombopénie < 20 000/mm^3, anémie hémolytique auto-immune symptomatique
  - 1 mg/kg/j de prednisone per os

Traitement non codifié

- Corticoides
  - Usage fréquent (80%)
  - Réponse globale 60-80%
  - Facteur de bonne réponse: inflammation histologique
    rémission = 90% si présente vs 38% si absente*

Crise rénale!

- Immunoglobulines Intraveineuses
  - Très bonne réponse initiale (10/11)
  - Fréquentes rechutes (4/10)

- Autres immunosuppresseurs utilisés
  - Cyclophosphamide (si atteinte pulmonaire associée)
  - Méthotrexate
  - Azathioprine, Mycophénolate mofetil

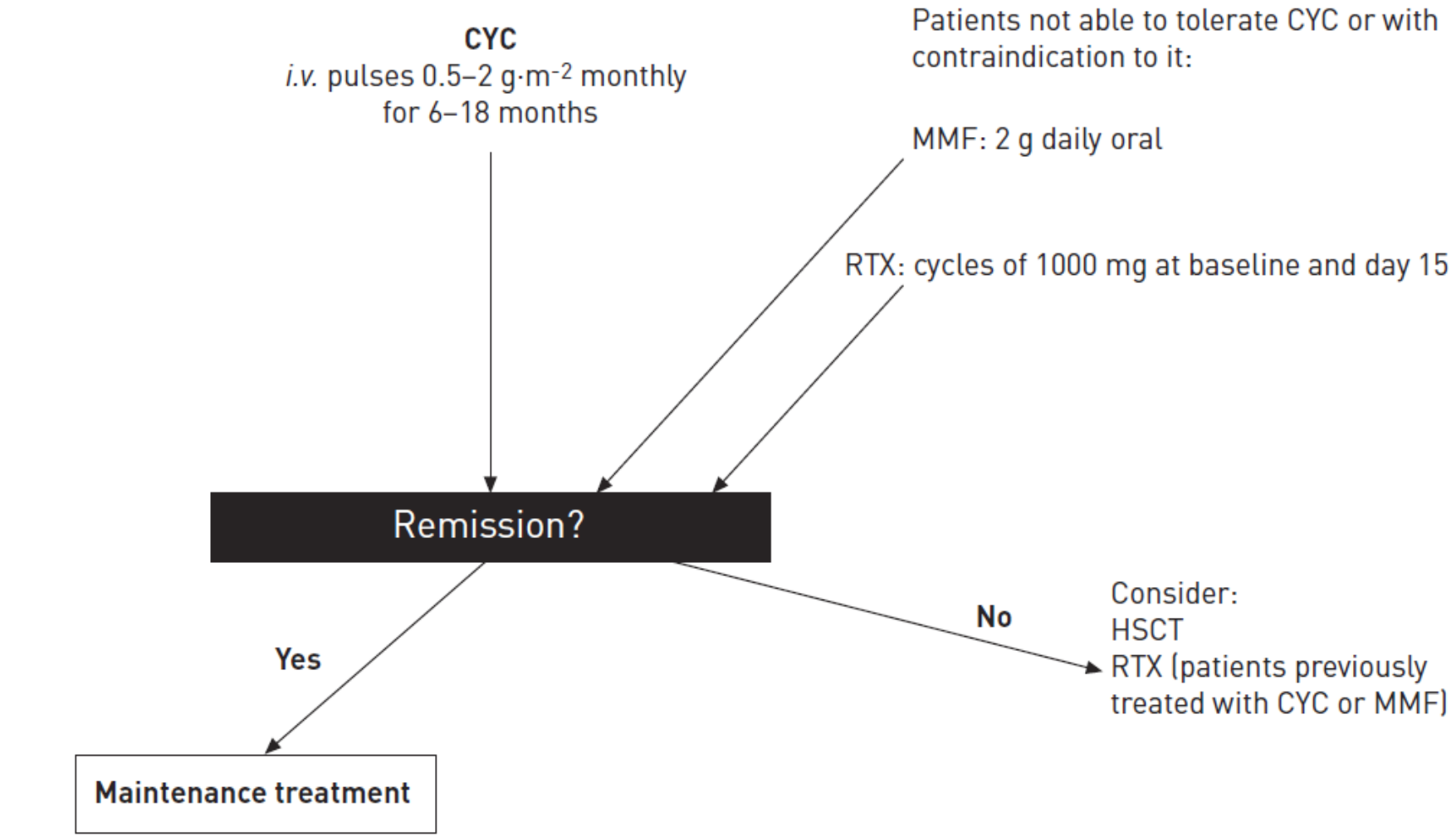
**Ranque et al, ARD 2008*

Treatment of MCTD-ILD: similar to SSc-ILD

- **PPI**
- **Cyclophosphamide**
- **Low dose corticosteroids (10 mg/j)**
- **Oxygen**
- **Lung transplantation**

- **Rehabilitation**

Algorythm for the treatment of SSc-ILD in patients with progressive or extensive disease

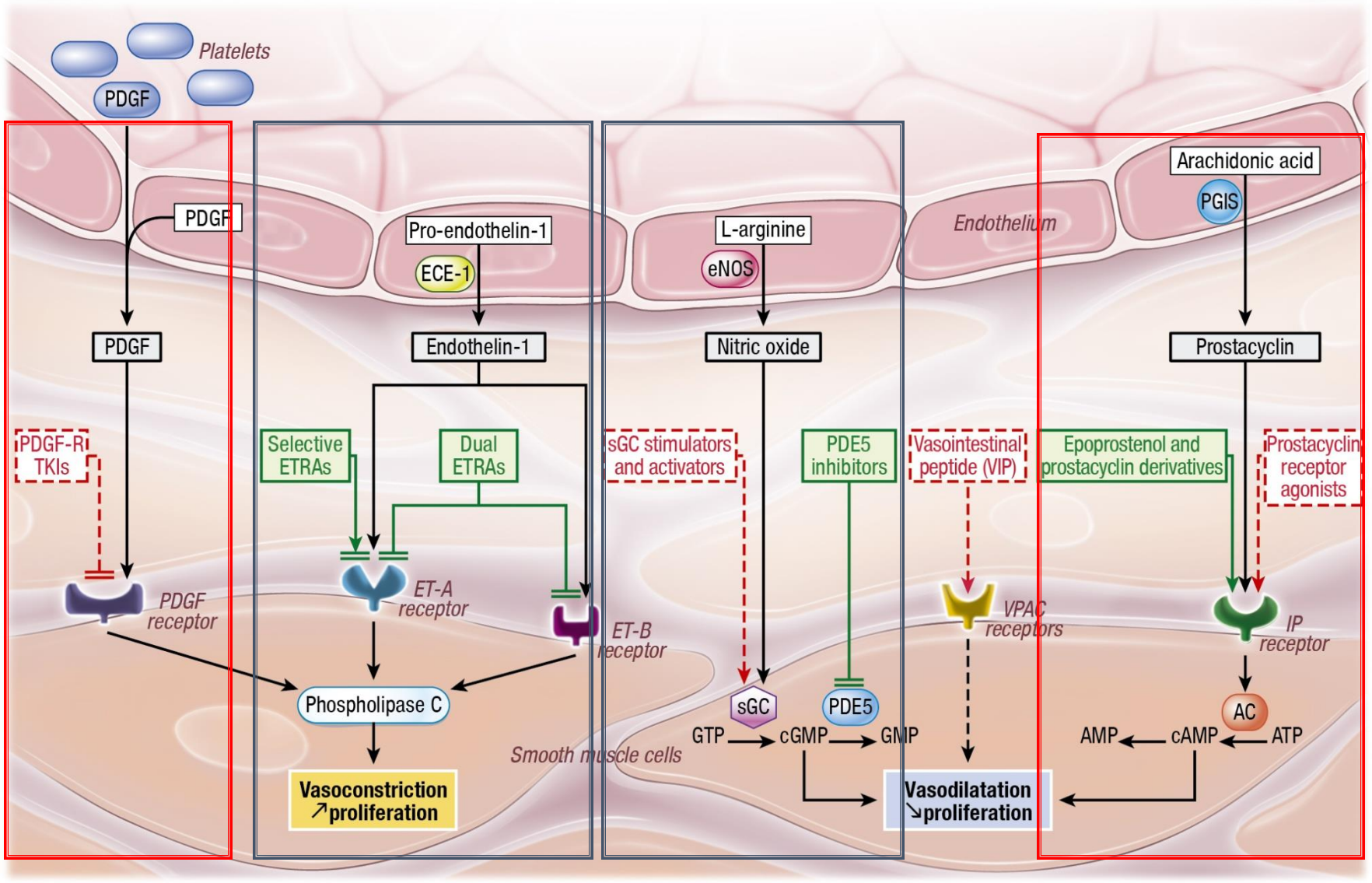


Rare diseases and Orphan Drugs. Cappelli et al. 2013

SSc-MCTD: treatment

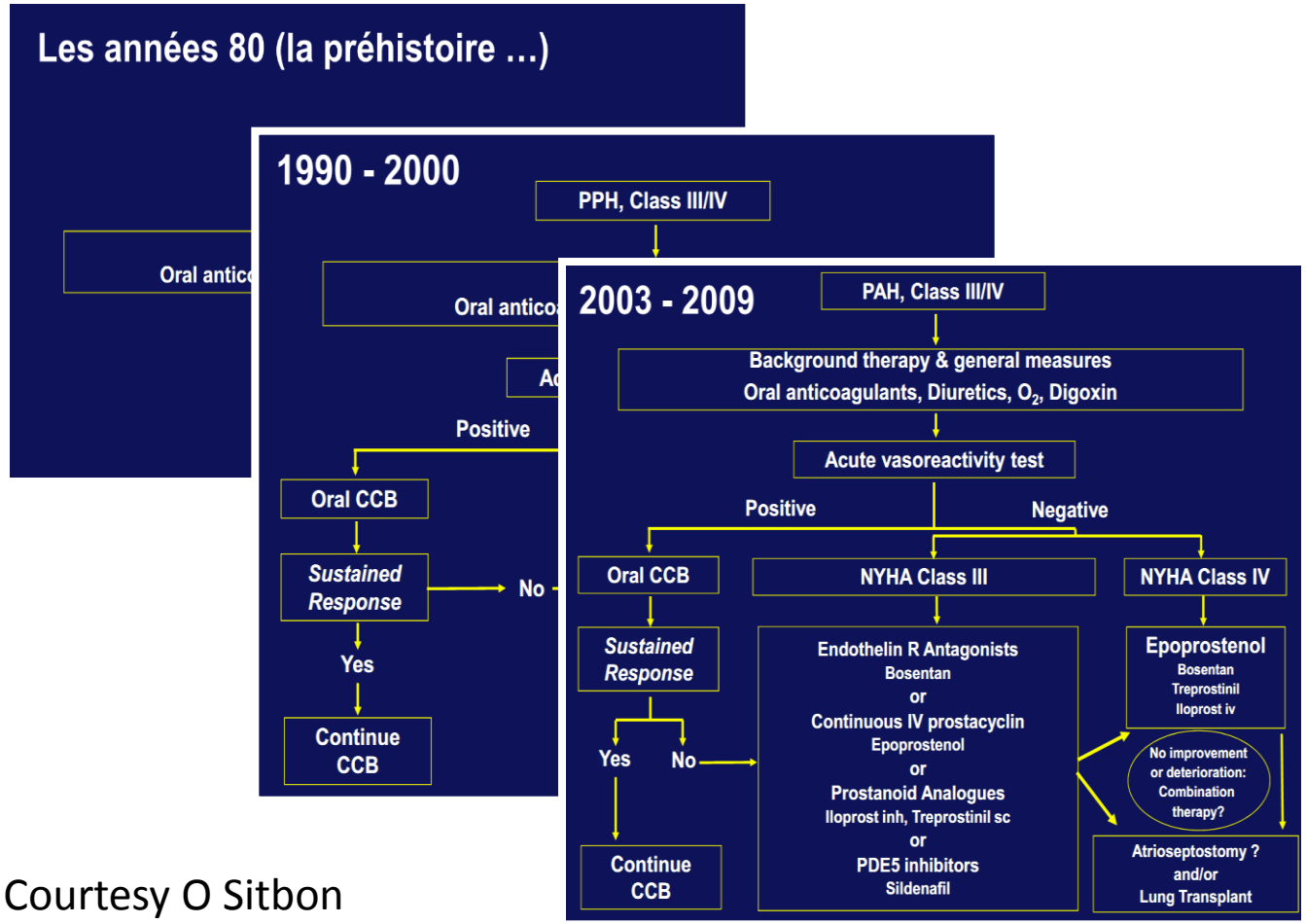
- Preventive measures
- Conventionnal medical treatment (O2 - diuretics - anticoagulants)
- Calcium chanel blockers
- Epoprostenol continuous infusion
- Endothelin receptor antagonists
- PDE-5 inhibitors/GC stimulators
- Combined treatments
- Lung transplantation

Current and Emerging Targets and Therapies in PAH

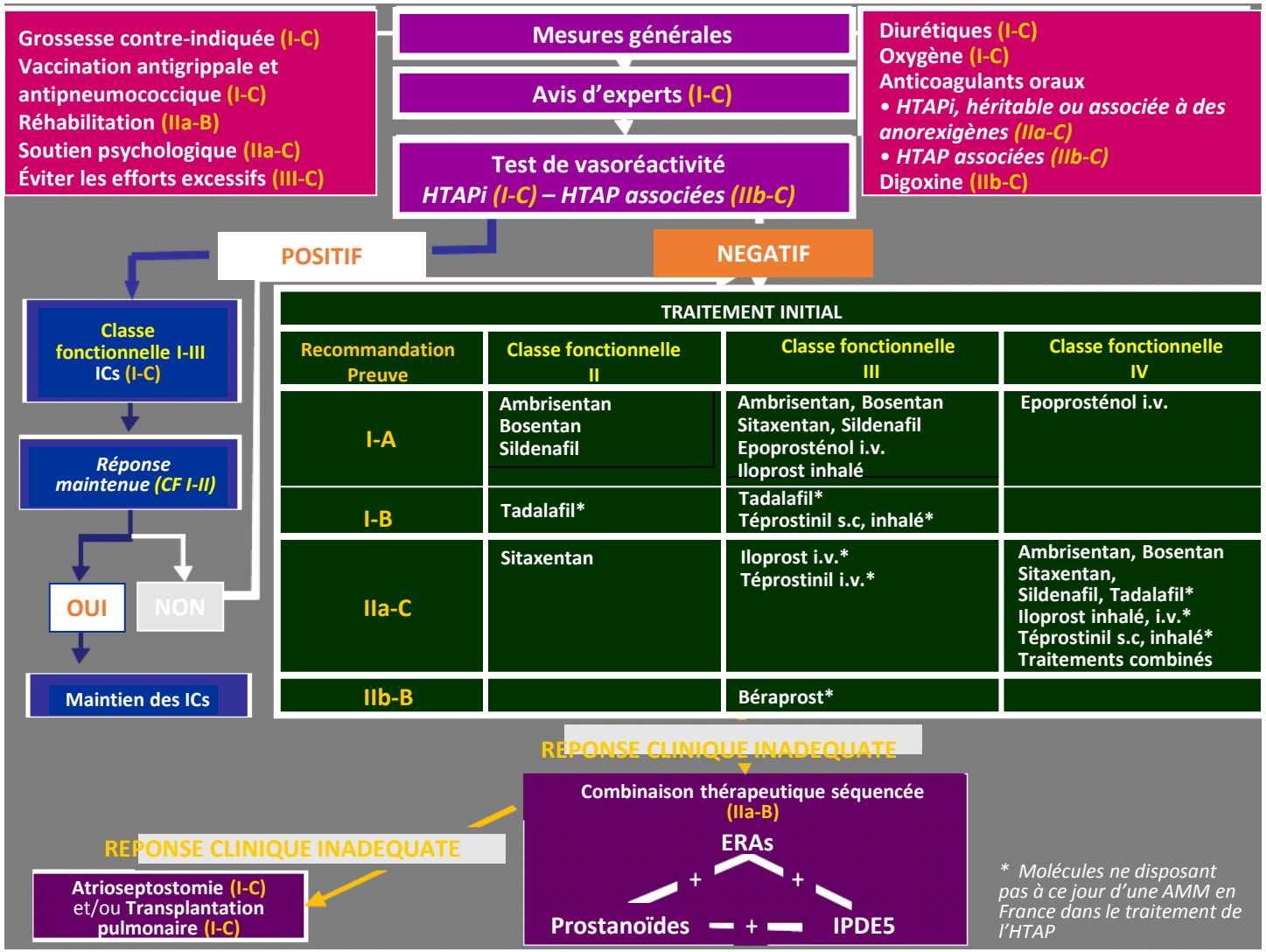


O'Callaghan DS, Savale L, Montani D, Jaïs X, Sitbon O, Simonneau G & Humbert M. Nat Clin Practice Cardiol 2011; 19:526-538

Les algorithmes thérapeutiques dans l'HTAP



Courtesy O Sitbon

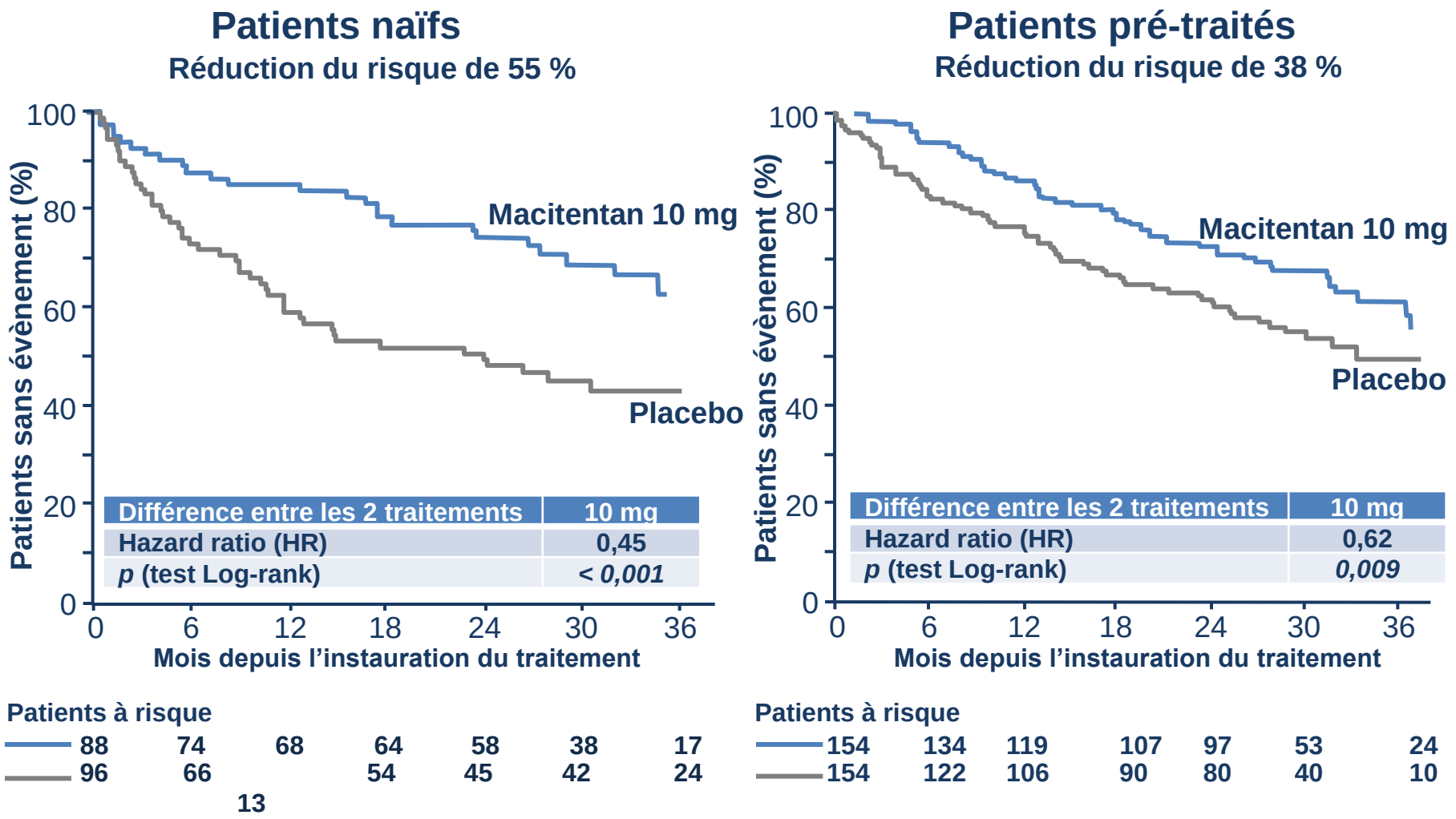

Grossesse contre-indiquée (I-C)
Vaccination antigrippale et antipneumococcique (I-C)
Réhabilitation (IIa-B)
Soutien psychologique (IIa-C)
Éviter les efforts excessifs (III-C)
Mesures générales
Avis d'experts (I-C)
Test de vasoréactivité
HTAPi (I-C) – HTAP associées (IIb-C)
Diurétiques (I-C)
Oxygène (I-C)
Anticoagulants oraux
• HTAPi, héritable ou associée à des anorexigènes (IIa-C)
• HTAP associées (IIb-C)
Digoxine (IIb-C)
POSITIF
NEGATIF
Classe fonctionnelle I-III
ICs (I-C)
Réponse maintenue (CF I-II)
OUI
NON
Maintien des ICs
TRAITEMENT INITIAL
Recommandation Preuve
Classe fonctionnelle II
Classe fonctionnelle III
Classe fonctionnelle IV
I-A
Ambrisentan
Bosentan
Sildenafil
Ambrisentan, Bosentan
Sitaxentan, Sildenafil
Epoprosténol i.v.
Iloprost inhalé
Epoprosténol i.v.
I-B
Tadalafil*
Tadalafil*
Téprostinil s.c, inhalé*
IIa-C
Sitaxentan
Iloprost i.v.*
Téprostinil i.v.*
Ambrisentan, Bosentan
Sitaxentan,
Sildenafil, Tadalafil*
Iloprost inhalé, i.v.*
Téprostinil s.c, inhalé*
Traitements combinés
IIb-B
Béraprost*
REPONSE CLINIQUE INADEQUATE
Combinaison thérapeutique séquencée (IIa-B)
ERAs
+
+
Prostanoïdes
+
IPDE5
REPONSE CLINIQUE INADEQUATE
Atrioseptostomie (I-C)
et/ou Transplantation pulmonaire (I-C)
* Molécules ne disposant pas à ce jour d'une AMM en France dans le traitement de l'HTAP

Nouveaux traitements évalués depuis 2009

	SERAPHIN[1]	PATENT[2]	IMPRES[3]
Molécule	Macitentan	Riociguat	Imatinib
Classe thérapeutique	ERA à forte affinité tissulaire	Stimulateur GC soluble	Inhibiteur de tyrosine kinase
Critère principal de jugement	Morbi-mortalité	TM6	TM6
Durée	~ 96 semaines	12 semaines	24 semaines
Patients, n	742	443	202
Traitement antérieur	Naïf ou monothérapie (PDE5i)	Naïf ou monothérapie (ERA)	Association (≥ bithérapie)
Résultat principal	Réduction de 45 % des évènements de morbi-mortalité (10 mg)	TM6 +36 m	TM6 +32 m, mais > 30 % sorties d'essai groupe imatinib
Tolérance	Elévation enzymes hépatiques : pas de différence avec placebo. Diminution Hb	Vasodilatation systémique, hypotension (Hémoptysies)	Effets secondaires ++, Hématomes sous-duraux, Rapport bénéfice/risque discutable

1. Rubin LJ, *et al.* Presented at CHEST 2012. 2. Ghofrani HA, *et al.* Presented at CHEST 2012. 3. Hoeper MM, *et al.* Presented at CHEST 2011.

SERAPHIN : Critère principal de jugement selon le traitement à l'inclusion



Pulido T, *et al. N Engl J Med* 2013; 369:809-18.

Recent « morbidity and mortality » trials in PAH
Components of primary end-point

Trial Event Driven	All-cause death	Lung transplantation	Atrial septostomy	Initiation of IV or SC prostanoids	Hospitalization for PAH worsening	Worsening of PAH*
Investigating the effect of a new drug						
SERAPHIN (macitentan)	✓	✓	✓	✓		✓
GRIPHON (selexipag)	✓	✓	✓	✓	✓	✓
Investigating a treatment strategy						
COMPASS-2 (bosentan)	✓	✓	✓	✓	✓	✓
AMBITION** Ambrisentan + taladafil	✓	✓	✓	✓	✓	✓

All events adjudicated by a blinded clinical events committee

* Definition of “worsening of PAH” varies between studies

** Additional component: “unsatisfactory long-term response”

Some PAH patients with associated CTD may improve with anti-inflammatory agents

- Retrospective analysis of clinical and haemodynamic effects of immunosuppressants given 1st therapy to 28 patients with PAH-CTD
- All patients received monthly intravenous pulse cyclophosphamide (600 mg/m^2) during at least 3 months and 22 out of 28 patients received oral prednisone
- 9 (32%) patients were responders (SLE 6/12 and MCTD (3/8). None of the 8 patients with SSc responded
- At 1 year of therapy, “responders” to immunosuppressive therapy were those who could be reclassified in New York Heart Association (NYHA) functional class I or II

Sanchez et al. Chest 2006

French Vasculitis Study Group

GFRS Groupe Francophone de Recherche sur la Sclérodermie

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