Sclérodermie systémique: prise en charge thérapeutique

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Conflicts of interest

- **Consultant**: Actelion, CSL Behring, LFB Biotechnologies, Lilly, Pfizer, Octapharma
  - Financial support to ARMIIC
- **Investigator**: Actelion, CSL Behring, Pfizer
- **Financial support (grants to ARMIIC)**: Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer
- **Invited conference**: SOBI, Roche, Actelion, CSL Behring, Octapharma, GSK, LFB Biotechnologies, Pfizer, Lilly, UCB pharma

SSc: prognosis

KEY POINTS

- Patients with SSc are almost four times more likely to die than age-matched and sex-matched peers, and on average lose 16–34 years of life expectancy.
- Although PAH and ILD are the major causes of SSc-related deaths, other SSc organ involvement such as GI, cardiac, renal or extensive skin disease is a major contributing factor to mortality in most patients.
- Although advanced PAH therapies have improved the prognosis of SSc-PAH, the lack of highly effective therapies for ILD, GI and severe skin involvement has impeded progress in improving overall survival in SSc.

Kipour and Baron Current Op Rheumatol 2014

Prise en charge thérapeutique de la sclérodermie systémique

Traitement de fond

- Aucun n'a fait la preuve de son efficacité: ce n'est plus vrai !

Traitement spécifique d'une atteinte d'organe

- Inhibiteurs du remodelage dans l'HTAP
- IEC dans la crise rénale

Traitements symptomatiques:

- Constituent la majorité de nos ressources thérapeutiques

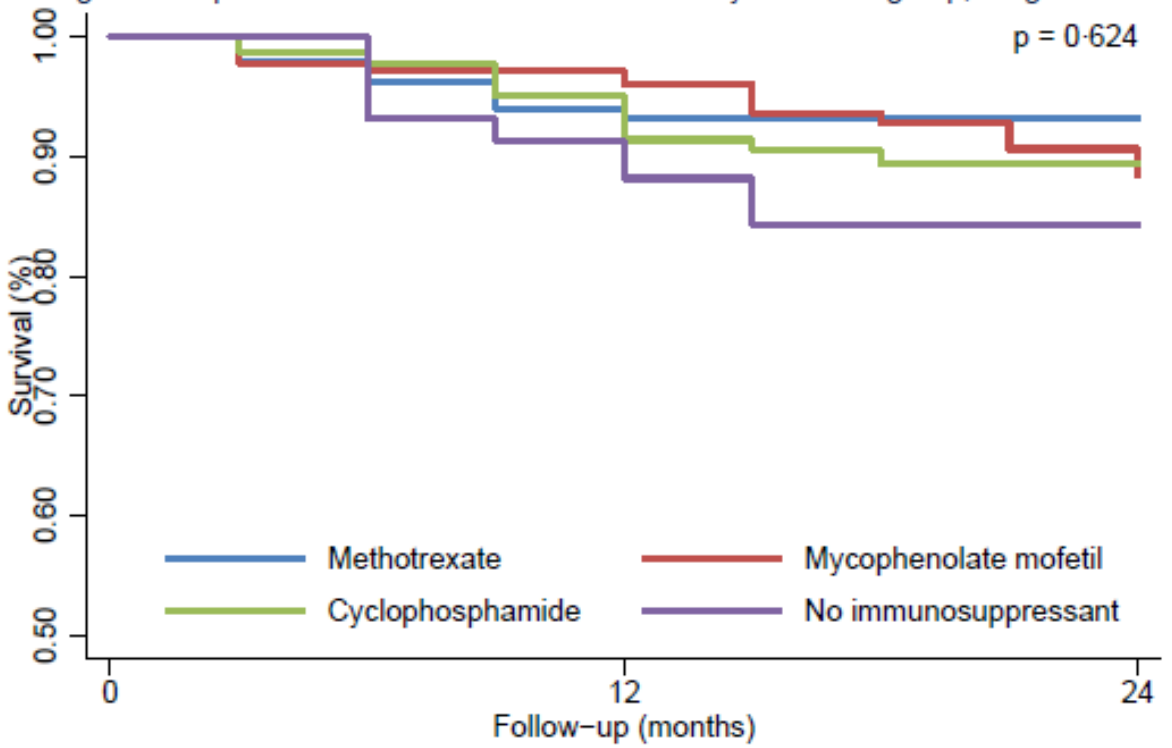
Atteinte cutanée diffuse

Treatment of early diffuse SSc

- Low dose prednisone: only if arthritis/myositis
- Methotrexate: if polyarthritis/myositis
- Cyclophosphamide: if worsening ILD
- Mycophenolate mofetyl: no major visceral involvement
- Plus classical support
- Expert rec: early rehabilitation

AN OBSERVATIONAL STUDY OF TREATMENT OUTCOME IN EARLY DIFFUSE CUTANEOUS SSc - EUROPEAN SCLERODERMA OBSERVATIONAL STUDY [ESOS]

Figure 3. Kaplan–Meier estimated survival curves by treatment group, weighted model.



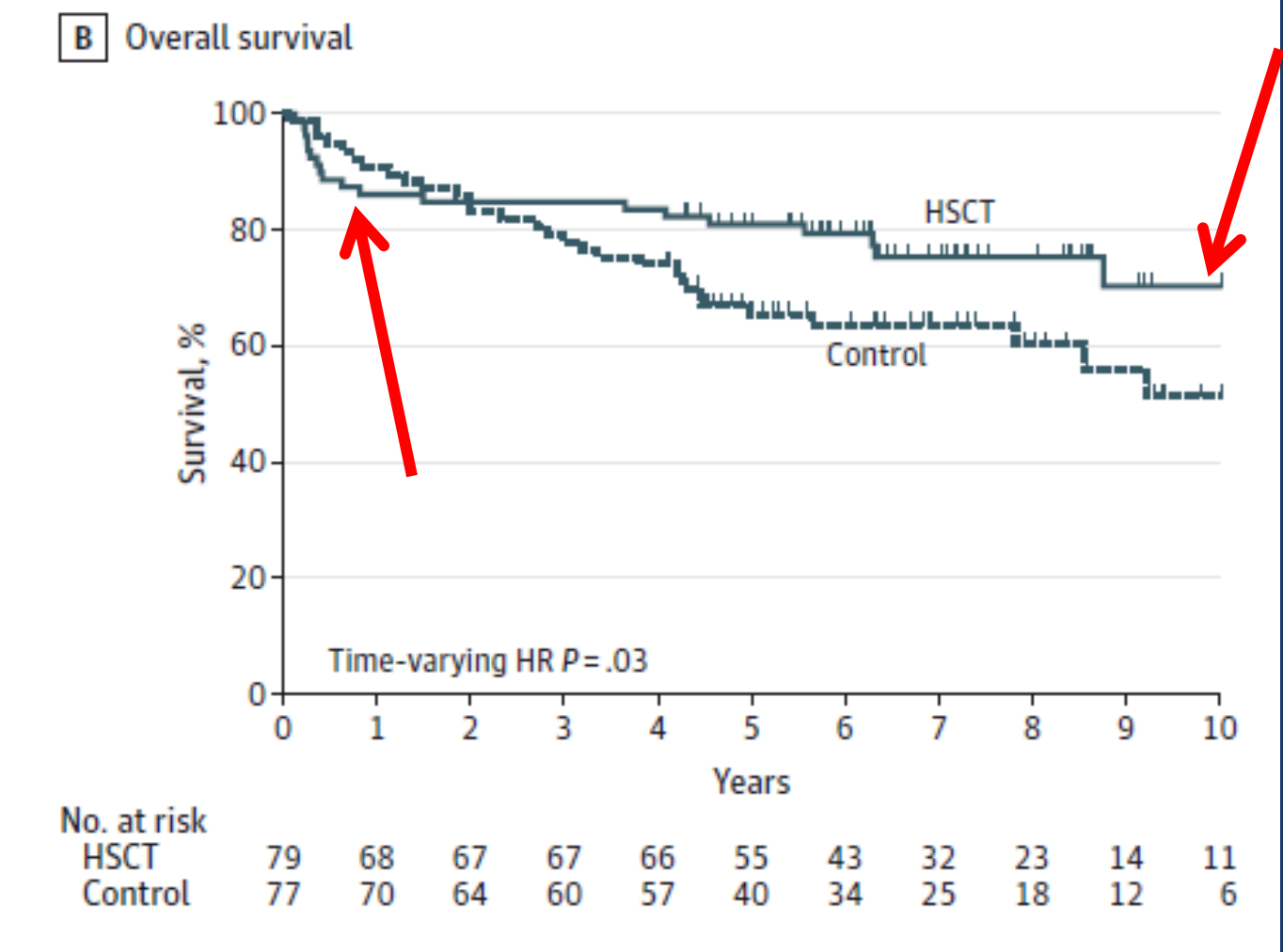
Number at risk

Methotrexate	65	55	46
Mycophenolate mofetil	118	108	83
Cyclophosphamide	87	75	55
No immunosuppressant	56	50	32

Number of patients at risk displayed were derived from the unweighted model.

EULAR 2016; FRI0261 – A. Herrick

Stem cell transplantation: The ASTIS Trial



van Laar JM, *et al. JAMA* 2014; 311:2490-98.

The updated EULAR recommendations for treatment of systemic sclerosis, according to the organ involvement: Skin and lung disease

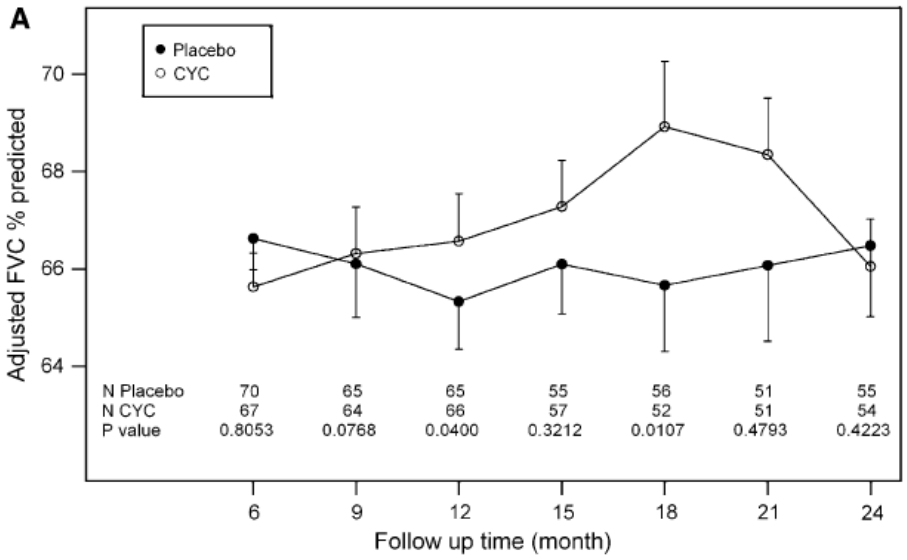
Two RCTs and their re-analysis have shown that *methotrexate* improves skin score in early diffuse SSc. Positive effects on other organ manifestations have not been established. Methotrexate may be considered for treatment of skin manifestations of early diffuse SSc.	A
In view of the results from two high-quality RCTs and despite its known toxicity, *cyclophosphamide* should be considered for treatment of SSc-ILD, in particular for patients with SSc with progressive ILD.	A
Regarding *HSCT*, two RCTs have shown improvement of skin involvement and stabilisation of lung function in patients with SSc and one large RCT reports improvement in event-free survival in patients with SSc as compared with cyclophosphamide in both trials. HSCT should be considered for treatment of selected patients with rapidly progressive SSc at risk of organ failure. In view of the high risk of treatment-related side effects and of early treatment-related mortality, careful selection of patients with SSc for this kind of treatment and the experience of the medical team are of key importance.	A

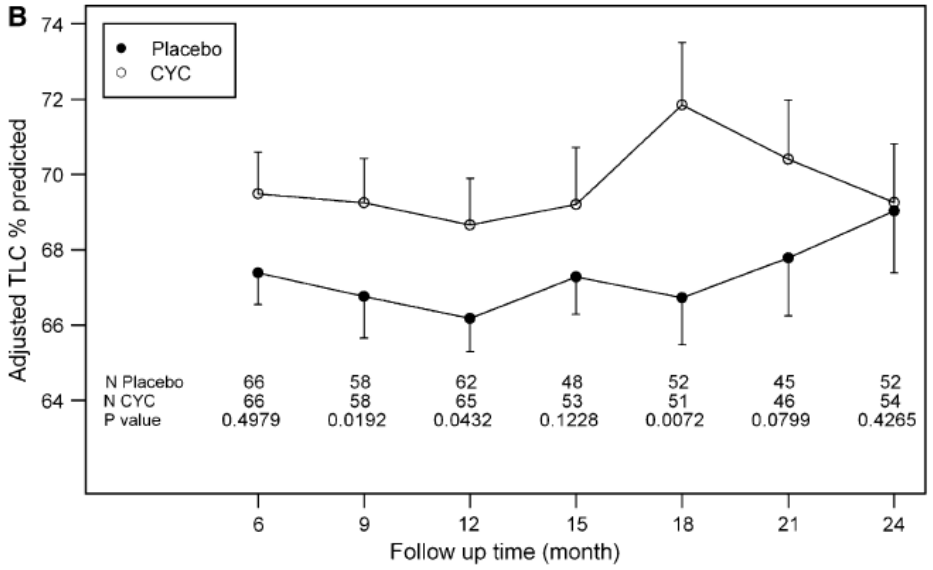
Kowal-Bielecka O, *et al*. *Ann Rheum Dis* 2017;**76**:1327–1339.

Atteinte interstitielle pulmonaire

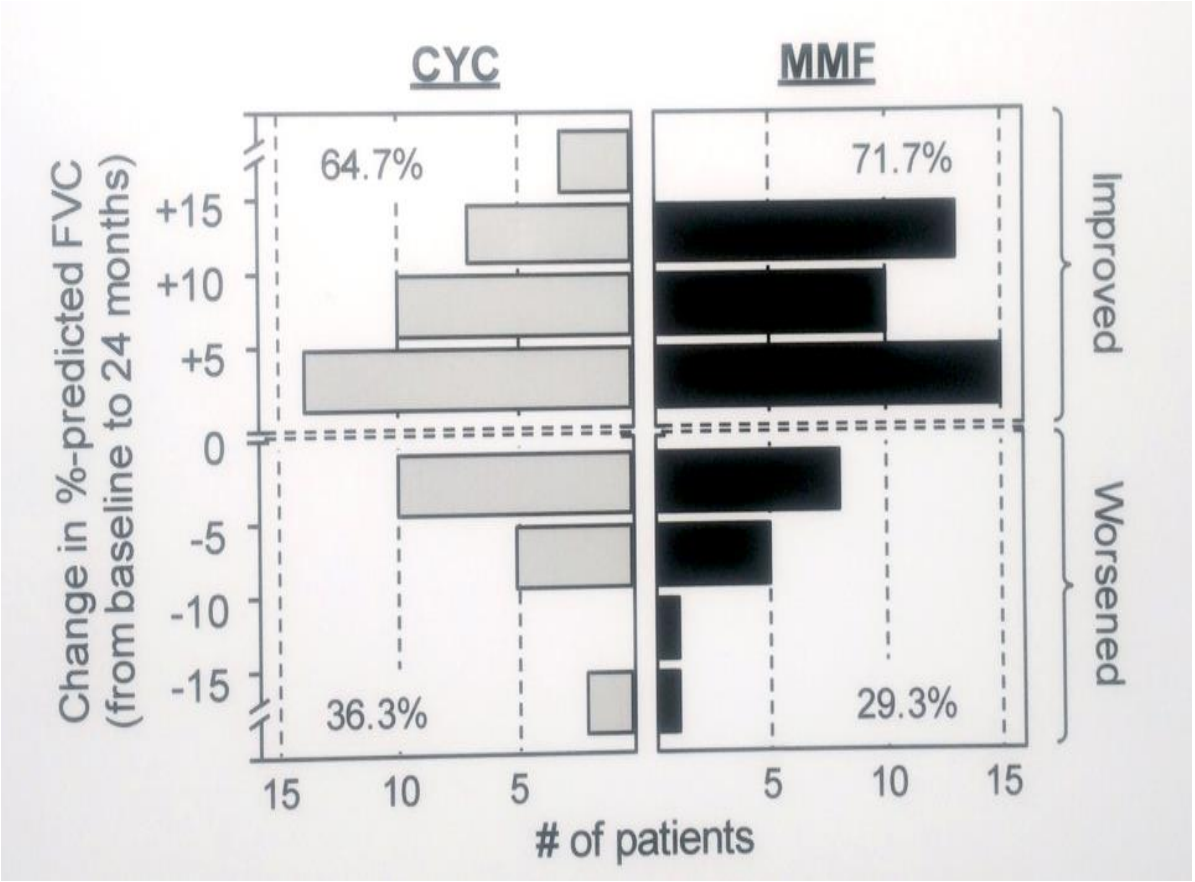
Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

Donald P. Tashkin[1], Robert Elashoff[2], Philip J. Clements[1], Michael D. Roth[1], Daniel E. Furst[1], Richard M. Silver[3], Jonathan Goldin[4], Edgar Arriola[5], Charlie Strange[3], Marcy B. Bolster[2], James R. Seibold[6], David J. Riley[6], Vivien M. Hsu[6], John Varga[7], Dean Schraufnagel[7], Arthur Theodore[8], Robert Simms[8], Robert Wise[9], Fred Wigley[9], Barbara White[9], Virginia Steen[10], Charles Read[10], Maureen Mayes[11], Ed Parsley[11], Kamal Mubarak[12], M. Kari Connolly[13], Jeffrey Golden[13], Mitchell Olman[14], Barri Fessler[14], Naomi Rothfield[15], Mark Metersky[15], Dinesh Khanna[1], Ning Li[2], and Gang Li[2], for the Scleroderma Lung Study Research Group*





SCLERODERMA LUNG STUDY II



142 patients with SSc-ILD were randomized in the SLS II
Patients received MMF (≤3 g daily) for two years or oral CYC (≤2 mg /kg

EULAR 2016; FRI0252 - D. Khanna

Treatment of SSc-ILD

- **PPI (± prokinetics)**
- **MMF**
- **MMF Cyclophosphamide/MMF (if worsening)**
- **Low dose corticosteroids (10 mg/j)**
- **Oxygen**
- **Rituximab**
- **Lung transplantation**

- **Rehabilitation**

Qui ne pas traiter (I) ?

Les grands classiques (I)

I. Insuffisance ventriculaire gauche:

- Scanner thoracique en décubitus ventral/discret épanchement pleural
- Si non disponible: échographie cardiaque avec etude de la relaxation en diastole
- Si nécessaire/réalisable: épreuve d'effort

II. Embolie pulmonaire:

- Angio-scanner thoracique >> scintigraphie de ventilation perfusion

Qui ne pas traiter (II) ?

Les grands classiques (II)

III. Surinfection bronchique/pulmonaire:
Si doute pneumopathie opportuniste: LBA
Au moindre sur une surinfection bronchique, répéter les EFR après trois semaines

IV. Atteinte musculaire:
Si myopathie inflammatoire associée/syndrome de chevauchement

V. EFR « douteuses »
Discuter avec le collègues des EFR
Répéter les EFR au moindre doute

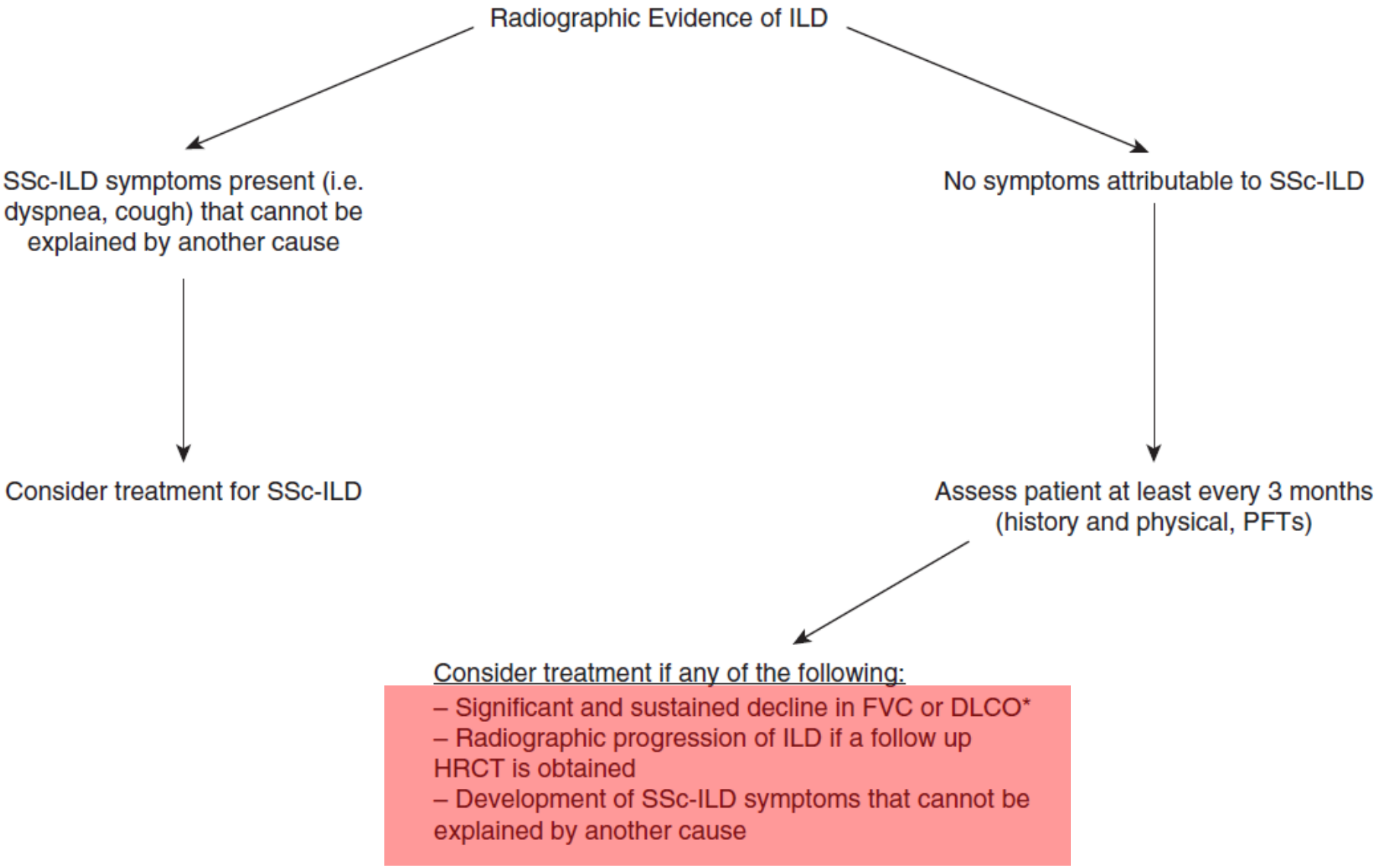
Qui ne pas traiter (III) ?

Avant d'envisager un traitement spécifique de la PID associée à la ScS: rechercher certaines atteintes qui peuvent altérer la fonction respiratoire des patients et qui ne relèveraient pas du traitement spécifique de la fibrose

Situations particulières conditionnant le pronostic de la PID-ScS:

- Obésité morbide (surestimation de la perte des volumes).
- Syndrome d'apnées obstructives du sommeil.
- Syndrome emphysème et fibrose: peut sous-estimer le syndrome restrictif (DLCO plus abaissée, besoins en oxygène plus importants).
- Hypertension pulmonaire (HTP) associée

Proposed algorythm for the initiation of SSc-ILD targeted therapy



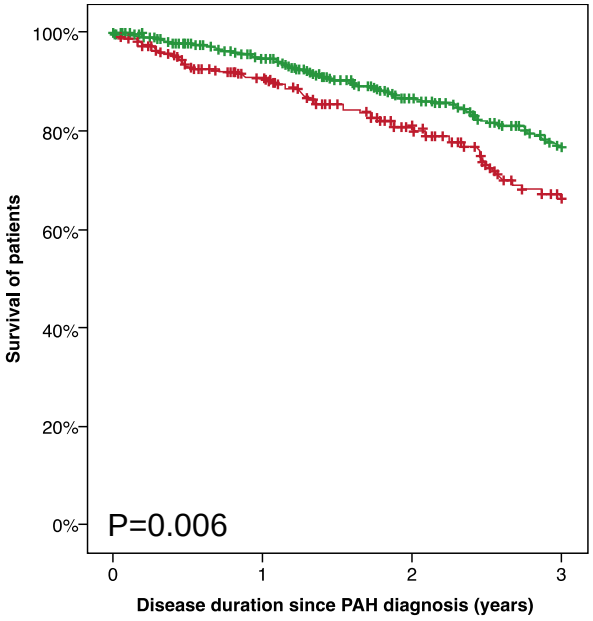
Volkmann & Tashkin, Ann Am Thorac Soc 2016

Hypertension artérielle pulmonaire

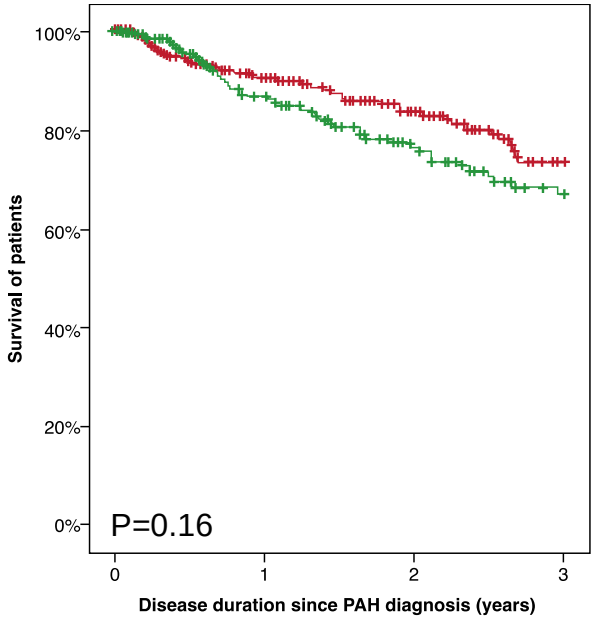
Any place for oral anticoagulants ?

EU COMPERA Registry: 2414 PAH, incl. 1283 incident cases
800 idiopathic PAH: Oral AC in 66%
483 other forms of PAH (incl. 208 PAH-SSc): Oral AC in 43%

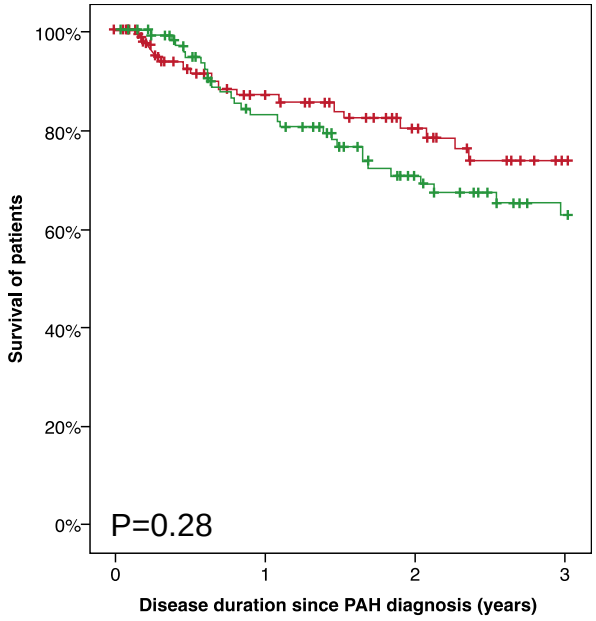
Idiopathic PAH



Non-idiopathic PAH



PAH-SSc

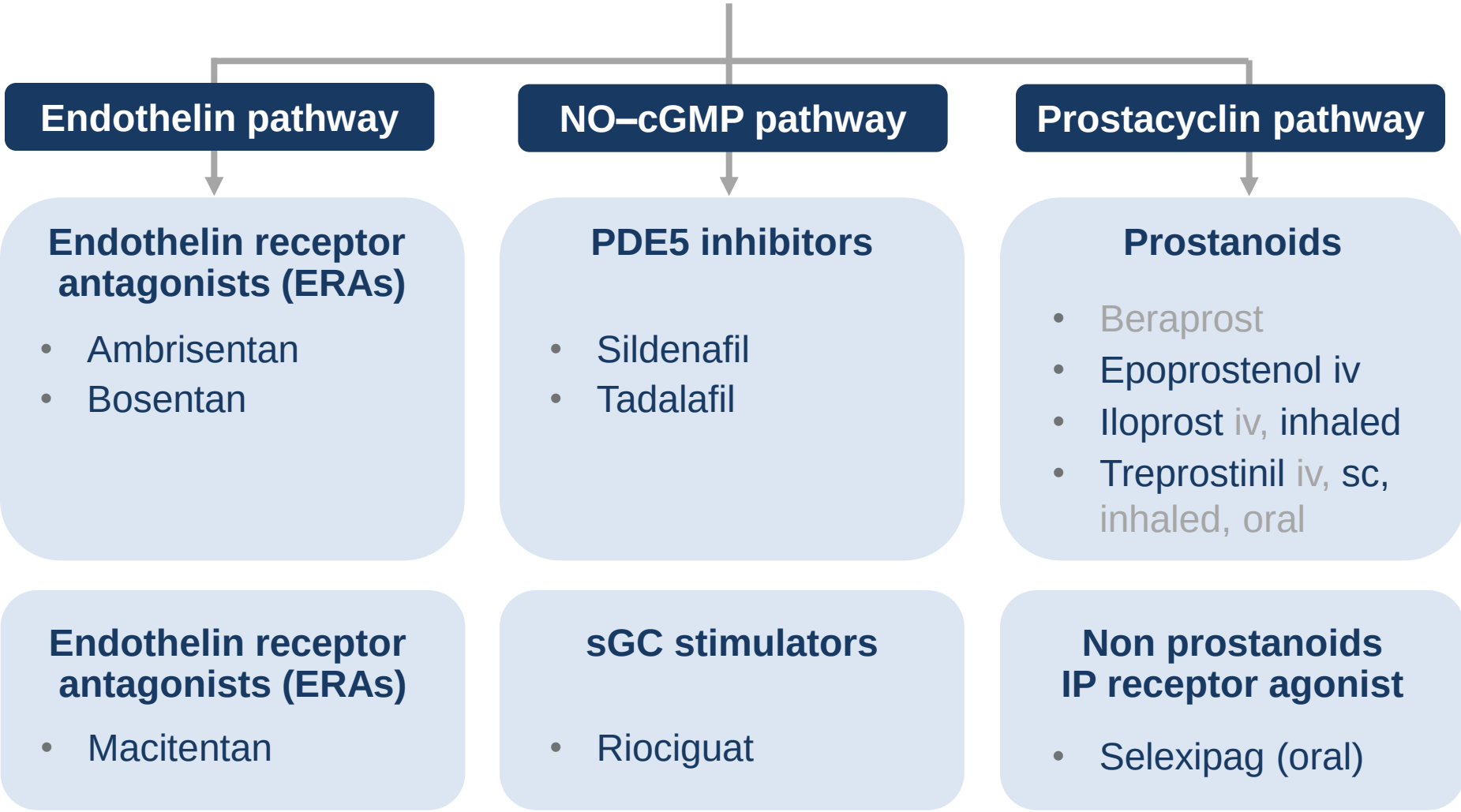


no anticoagulation

anticoagulation

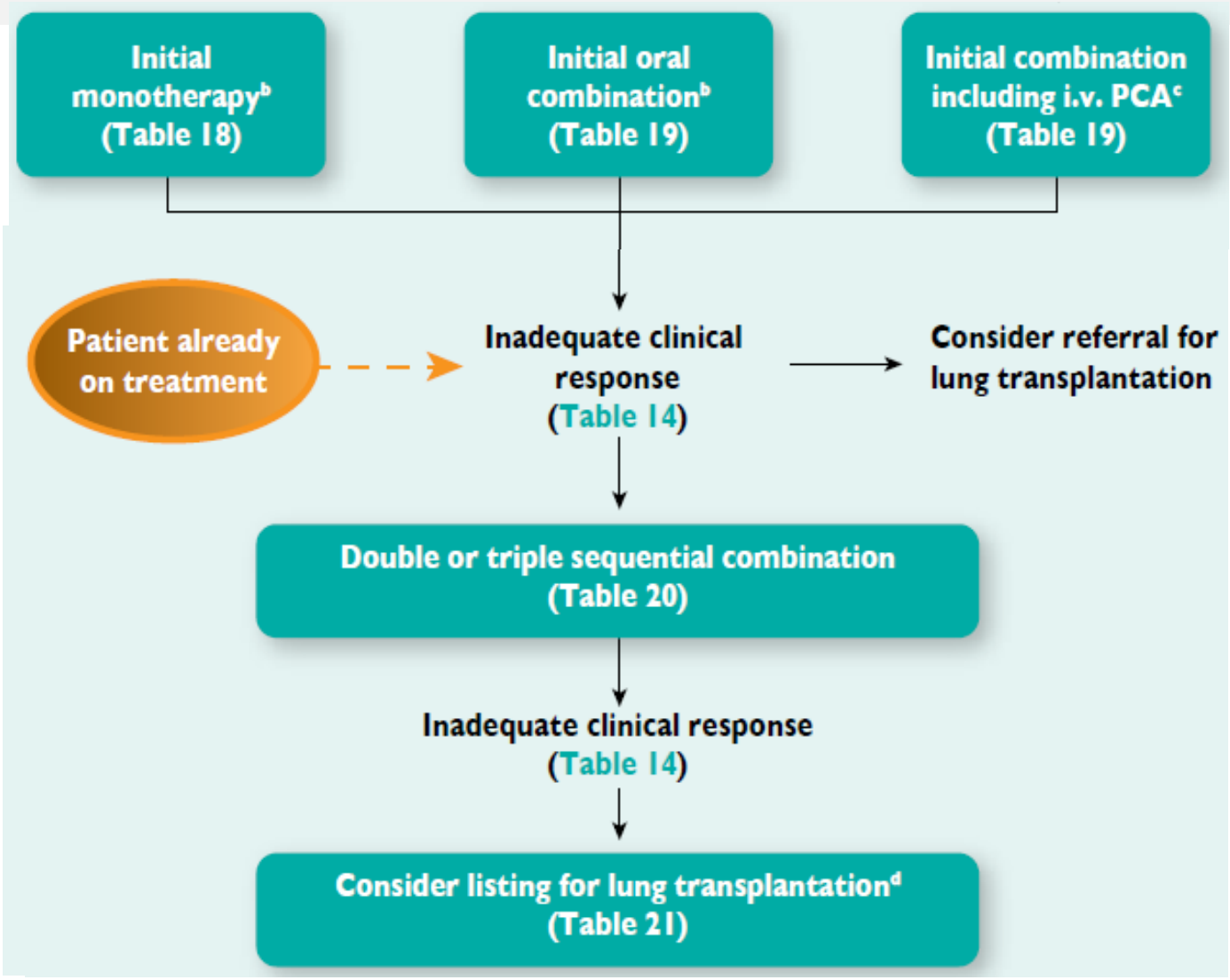
Olsson KM, et al. Circulation. 2014;129:57-65.

PAH-specific therapies target the 3 signaling pathways involved in PAH



Adapted from Galiè N et al. J Am Coll Cardiol 2013;62:D60–72.

Treatment Algorithm for PAH



Galiè N, *et al*. ESC/ERS Guidelines. *Eur Heart J* 2015 & *Eur Respir J* 2015.

Crise rénale sclérodermique

Treatment of SRC

Early diffuse SSc
Hypertension (diastolic blood pressure > 100 mmHg)

↓

Initiate captopril at 6.25-12.5 mg every 8 hours, then increase dose to 50 mg tid

↓

Insufficient results at 72 h: Continue ACEi and add calcium channel blockers

↓

Insufficient results: Continue ACE inhibitors and calcium channel blockers and add minoxidil/central antihypertensive agent

↓

Oliguric renal insufficiency: Early dialysis

↓

Continue ACE inhibitors, maintain normal blood pressure (120-140/70-90 mmHg)

↓

If improvement of renal function, stop dialysis
If dialysis is still necessary after two years, then put the patient on a waiting list for renal transplantation

Bussone G et al. Current Rheumatol Report 2011

Traitement de la CRS

- **Pas d'efficacité démontrée:**
  - [illegible]rost
  - [illegible]matiques
  - [illegible]

- Traitements en cours d'évaluation
  - Bosentan
    - Pilot study (n=6) (Penn H, et al. QJM. 2013)

Bosentan bien toléré, pas de SAE, evolution à long terme favorable.
Rebond hypertensive chez 3 patients à l'arrêt du BOSENTAN.

    - Open study (Reinbo) (N=16)

Ulcères digitaux

Management of DU: Multidisciplinary approach

Prevention of complications
Including patient education

Pharmacological treatment
Prevention of new DU
Healing pre-existing DU

Antibiotics

Pain relief

Non-pharmacological treatment: rehabilitation

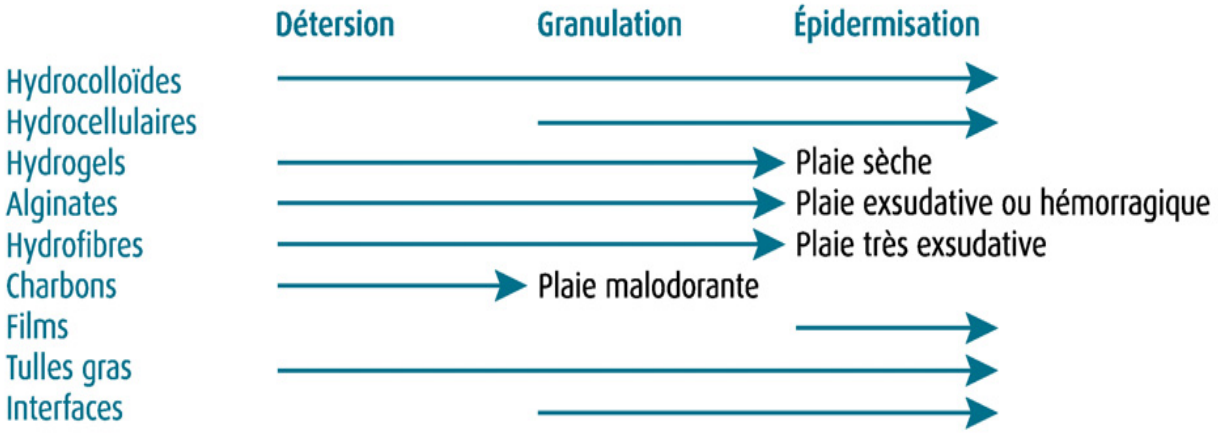
Local treatment & wound care

Surgery
only when necessary

Traitement local de l'ulcère

- diminuer les douleurs, de favoriser la cicatrisation, et de lutter contre le risque d'infection
- **Laver, Rincer, Sécher** +/- antiseptique
- **Détersion mécanique**:
  - éliminer la nécrose et la fibrine avec un grattoir, curette de Brocq, ou bistouri
  - Accélérer l'épidermisation
  - Antalgiques locaux (Emla® à 5% ou xylocaïne gel®)

- **Pansement primaire au contact de la plaie:** Hydratent et favorisent la détersion de la fibrine et de la nécrose



Francès C et al, Presse Med. 2008

EULAR/EUSTAR recommendations for healing of DU

- Two RCTs indicate that i.v. prostanoids (particularly i.v. iloprost) are efficacious in healing DU in patients with SSc
  - i.v. prostanoids (in particular iloprost) should be considered in the treatment of active DU in SSc patients
- Bosentan has no proven efficacy in the treatment of active DU in SSc patients

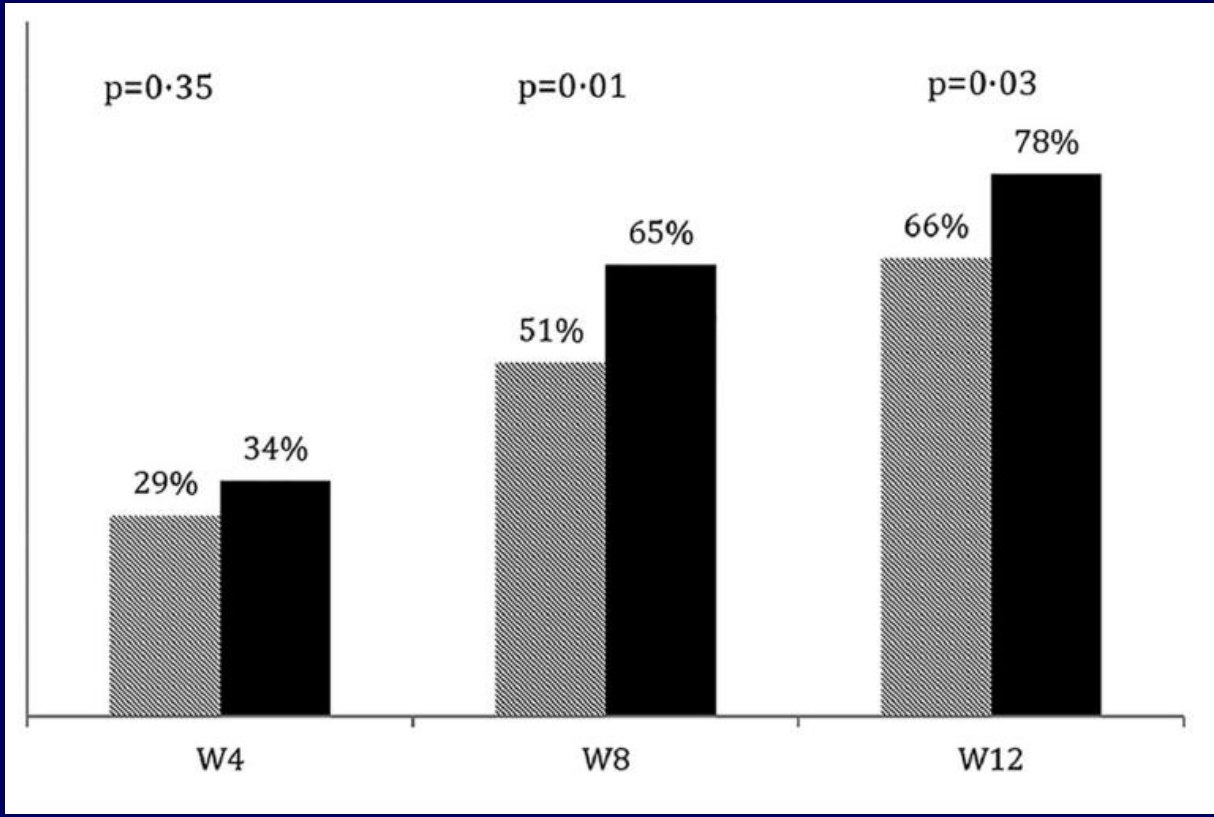
Kowal-Bielecka O, *et al. Ann Rheum Dis* 2009; 68:620-8.

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study



The primary end point was not reached in intention-to-treat, partly because of an unexpectedly high healing rate in the placebo group. We found a significant decrease in the number of DUs in favour of sildenafil compared with placebo at W8 and W12, confirming a sildenafil benefit.

Hachulla et al. ARD 2016

Surgical treatment

Rarely proposed in SSc patients (2 to 4%)

1. **Debridement**
2. **Removal of calcinosis**
   - **Complete removal is rarely feasible; conventional surgery or laser**
3. **Surgery of ischaemia**
   - **Digital sympathectomy (transient improvement, absence of demonstrated beneficial effect)**

Prophylactic measures

A. Cold

- Reduce cold exposure by wearing long and warm clothes, mittens
- Reduce professional cold exposure

B. Drugs

C. Vasoconstrictive agents

- Withdrawal of tobacco, cannabis, cocaine

D. Injuries

- Avoid hand injury, avoid repeated microtrauma
- Work-related trauma
- Occlusion

Francès C, *et al. Presse Med* 2008; 37:271-85.

Prevention in the occurrence of new DU

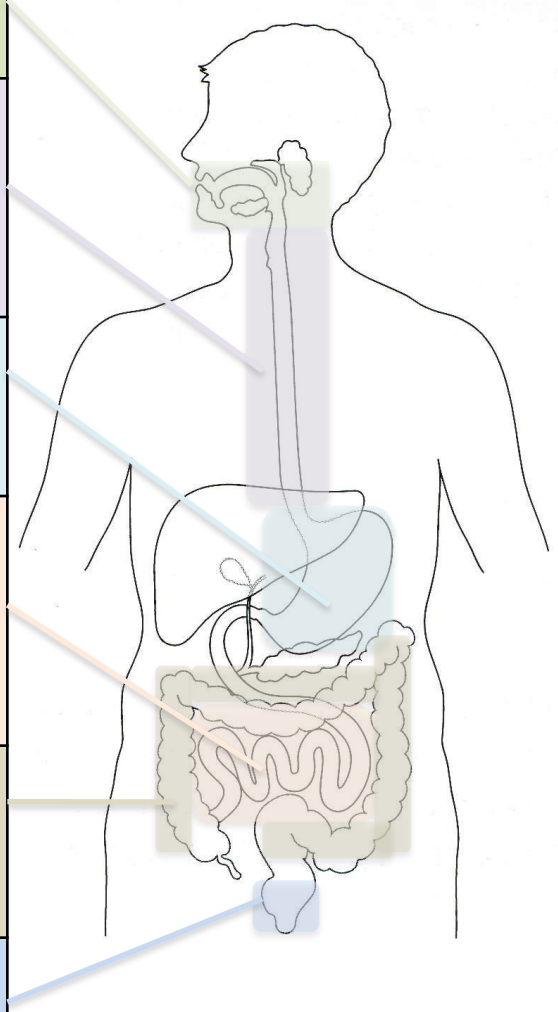
- **Calcium channel blockers (CCBs)**
  - **The preventive role of CCBss has never been evaluated**
- **Prostacyclin**
  - **No evidence from literature that iloprost can prevent DU**
  - **Heterogeneity among clinicians regarding duration and frequency of infusions**
  - **Recommended dose: 0.5 to 2 ng/kg/mn for 6 to 8 h/d during 5 days; minimum six weeks between 2 infusions**
- **Bosentan[1,2]**
  - **Two prospective randomised studies demonstrated the efficacy of bosentan in preventing the occurrence of DU in SSc**
- **Atorvastatin[3]**
  - **84 pts double-blind RCT – 40 mg atorvastatin vs placebo**

1. Korn JH, *et al*. *Arthritis Rheum* 2004; 50:3985-93.
2. Matucci Cerinic M, *et al. Ann Rheum Dis* 2011; 70:32-38.
3. Abou-Raya A, *et al*. *J Rheumatol* 2008; 35:1801-8..

Manifestations digestives

Atteinte digestive de la sclérodermie : traitement

Bouche	-Limitation ouverture buccale -Syndrome sec	-Pilocarpine (si Sjögren)
Oesophage	-RGO -Oesophagite, EBO -Apéristaltisme	-IPP -Prokinétiques (Motilium/primperan)
Estomac	-Gastroparésie (Bezoard) -Estomac pastèque	-Prokinétiques (Erythromycine/acide clavulanique)
Grêle	-POIC -Pullulation microbienne -Télangiectasies -Malabsorption	-Sandostatine -Antibiothérapie -Plasma argon -Correction carences
Colon	-Constipation -Syndrome occlusif -Télangiectasies	-Laxatifs, Lavements
Anus	-Incontinence anale -Prolapsus	-Rééducation



Atteinte digestive: les éléments clés

- Ouverture buccale < 20 mm: alimentation mixée
- Traitement RGO: IPP + prokinétique
- FOGD dans les 5 ans suivant le diagnostic de ScS/si possible sous AG
- Vomissements tardifs = gastroparésie
- Prokinétique estomac ≠ prokinétique œsophage
- Prokinétique estomac et grêle: faible dose+++
- Constipation tenace/occlusion: scanner abdominal
- Diarrhée ++++: traitement épreuve pullulation

Atteinte cardiaque

Management of cardiac complications in SSc

- Management of SSc cardiac complications depends upon the nature of the complication:
  - Administration of the agents **nifedipine** (CCB), **captopril** (ACE inhibitor) and **i.v. dipyridamole** can improve myocardial perfusion, but not all myocardial perfusion abnormalities are reversible
  - **ACE inhibitors, β-adrenoceptor blockade**, ICD and CRT can be used for left ventricular dysfunction
  - Tight control of systemic hypertension and aggressive management of PH are needed to prevent secondary cardiac damage
  - Severe diastolic heart failure can be treated with **diuretics**
  - Patients with active myocarditis can benefit from **aggressive cytotoxic therapy**

ACE: angiotensin converting enzyme; CCB: calcium channel blocker; CRT: cardiac resynchronisation therapy; DPD: dipyridamole; ICD: implantable cardioverter defibrillator

Kahan A, *et al. Rheumatology* 2009; 48:Suppl iii45-iii48.

Appareil locomoteur

Joint/muscle involvement in systemic sclerosis: Treatment

Joints

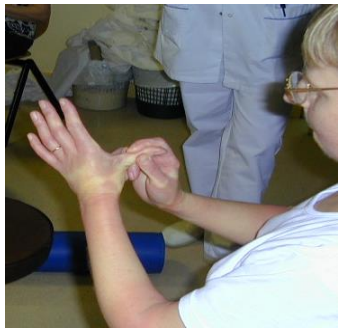
- ✓ Colchicine
- ✓ Low dose prednisone
- ✓ Methotrexate
- ✓ Biologics
  - ✓ Rituximab
  - ✓ Tocilizumab
  - ✓ Abatacept
- ✓ Surgical procedures
- ✓ Physiotherapy
- ✓ Occupational therapy

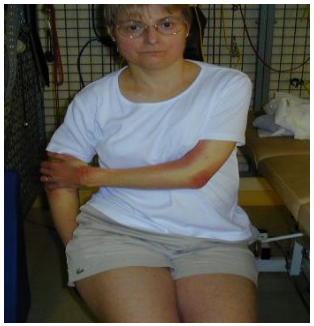
Myositis

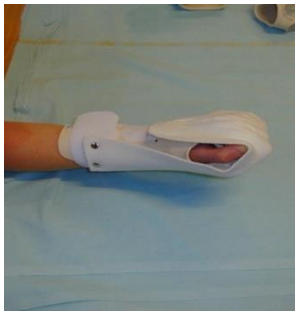
- ✓ Low dose prednisone
- ✓ Methotrexate
- ✓ Intravenous immunoglobulins
- ✓ Physiotherapy

Rehabilitation and systemic sclerosis

– **Multicenter randomized controlled study**
  - **Randomization: Zelen method**
  - **220 patients**
  - **Primary criteria : HAQ**
  - **12 supervised rehabilitation sessions**
  - **Daily non supervised rehabilitation sessions**
  - **Analysis of qualitative and quantitative observance**







Rannou F et al. ARD 2016

Manifestations	Traitement
Pneumopathie interstitielle diffuse	Oxygénothérapie IPP Prednisone 10 mg/j Cyclophosphamide IV (si aggravation) Mycophenolate mofetil Rituximab Transplantation bi-pulmonaire
Hypertension artérielle pulmonaire	Oxygènothérapie Diurétiques Anticoagulation discutée ERA-1 IPDE-5 Analogues de prostacyclines Traitements combinés Atrio-septotomie Transplantation pulmonaire
Atteinte cardiaque	Inhibiteurs calciques IEC Diurétiques Anti-arythmiques (verapamil, amiodarone) Pace maker

Benmostefa N, Legendre P, Mouthon L traité de Médecine 2017

Manifestations	Traitement
Crise rénale sclérodermique	IEC (ne pas utiliser en prévention) Inhibiteurs calciques par voie IV Epuration extra-rénale Transplantation rénale
Atteinte vasculaire périphérique	Inhibiteurs calciques Analogues de la prostacycline Bosentan (prévention des UD)
Atteinte digestive	Œsophage : IPP et prokinétiques Estomac : érythrocine 125 mg x 2/j Grêle : ocréotide, antibiotiques (pullulation microbienne)
Atteinte articulaire	AINS Prednisone à faible dose (7,5 mg/j) Methotrexate
Myopathie inflammatoire	Prednisone < 15 mg/j. Methotrexate

Benmostefa N, Legendre P, Mouthon L traité de Médecine 2017

Comment aggraver un patient sclérodermique en dix leçons (I)

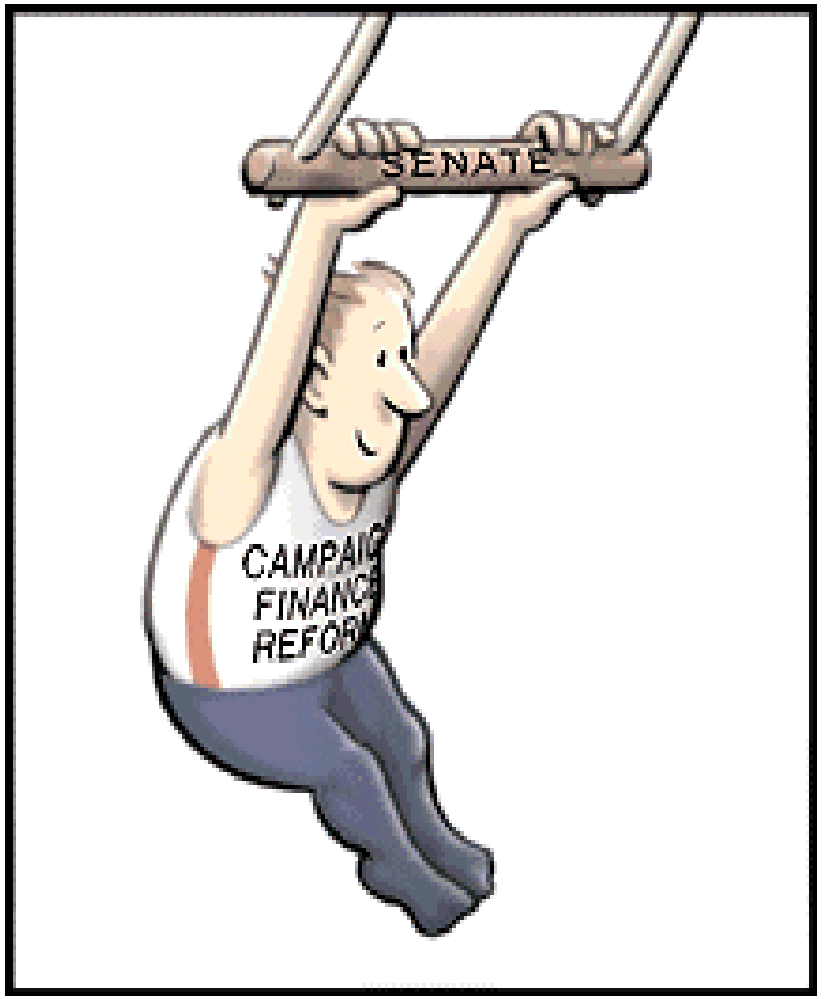
1. Ne pas prescrire de traitement inhibiteur calcique
2. Ne pas sevrer le tabagisme (Rayaud/UD)
3. Faire un gaz du sang par ponction radiale sans manœuvre d'Allen préalable (perméabilité de l'ulnaire)
4. Prescrire une corticothérapie à forte dose (même pour une sinusite/risque de crise rénale)
5. Prescrire de l'érythrocine à plus de 500 mg/j/de l'octréotide a plus de 200 µg/j (perte effet prokinétique)
6. Opérer un patient sclérodermique en occlusion intestinale (occlusion fonctionnelle/bride)

Comment aggraver un patient sclérodermique en dix leçons (II)

7. Prescrire un traitement spécifique de l'HTAP sans apporter la preuve de l'HTAP par un cathétérisme droit (aggravation IVG)
8. Prescrire un traitement antiagrégant/anticoagulant sans preuve d'un bénéfice attendu
9. Prescrire un traitement bêta bloquant (en dehors du post IDM immédiat) / anti-migraineux / collutoires…. (aggravation Raynaud/UD)
10. Ne pas prescrire d'IEC à un patient ScS hypertendu sans explication évidente (CRS)

Prise en charge thérapeutique des patients sclérodermiques

- Bien interroger…. Ajuster …. Plus que tatonner
- Beaucoup d'humilité
- De la disponibilité
- De la gentillesse
- Ne pas dire qu'il n'y a pas de traitement dans la sclérodermie



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Rare Systemic and
Autoimmune Diseases