Systemic sclerosis: new treatments

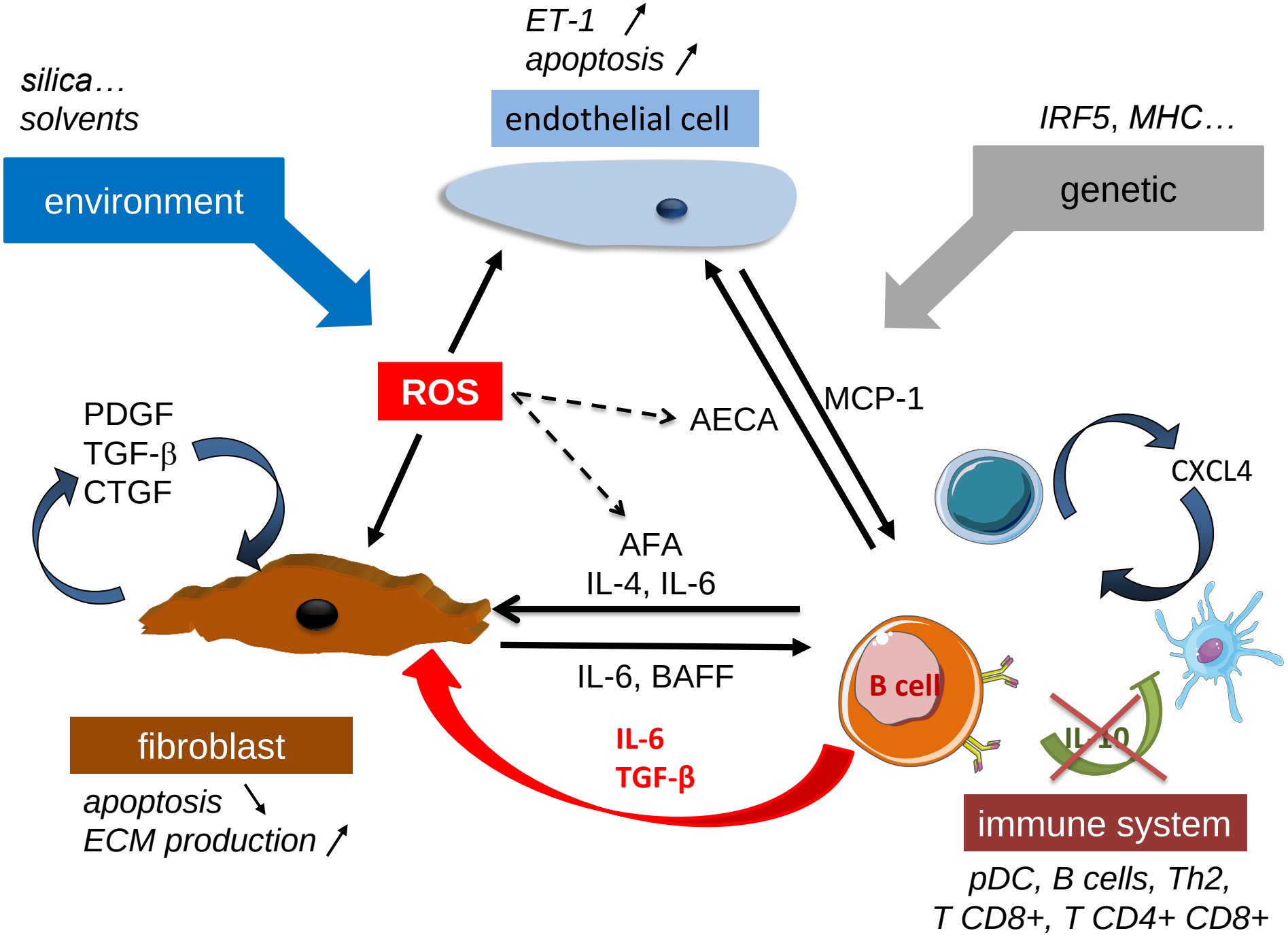
Luc Mouthon

Service de Médecine Interne, hôpital Cochin,

Centre de Référence Vascularites nécrosantes et sclérodermie systémique

Assistance publique-Hôpitaux de Paris, Paris

Université Paris Descartes, Inserm U1016, Institut Cochin, Paris


ET-1 ↗
apoptosis ↗
endothelial cell
silica…
solvents
environment
IRF5, MHC…
genetic
ROS
PDGF
TGF-β
CTGF
AECA
MCP-1
CXCL4
AFA
IL-4, IL-6
IL-6, BAFF
B cell
IL-6
TGF-β
IL-10
fibroblast
apoptosis ↘
ECM production ↗
immune system
pDC, B cells, Th2,
T CD8+, T CD4+ CD8+

Proposed recommendations for future randomised trials

- Limited or diffuse SSc
- 1-year RCT
- Placebo (or active) controlled RCT
- ILD defined on HRCT
- Rigorous quality control of PFT
- Dyspnea not required as an inclusion criteria
- Primary goal: prevent disease progression
- Progression free survival is an important secondary end point
- Enhance sensitivity
  - Cohort enrichment
  - Observed progression
- Composite indices
- Biomarker signal

Khanna D Clin Exp Rheum 2010

Cyclophosphamide Systemic Sclerosis Associated Interstitial Lung Disease (SCLEROCYC)

This study is not yet open for participant recruitment.

Verified April 2012 by Assistance Publique - Hôpitaux de Paris

First Received on April 2, 2012. Last Updated on April 12, 2012 History of Changes

Sponsor:	Assistance Publique - Hôpitaux de Paris
Collaborator:	Service de Médecine Interne de l'hôpital Claude-Huriez, Lille, France - Pr David Launay
Information provided by (Responsible Party):	Assistance Publique - Hôpitaux de Paris
ClinicalTrials.gov Identifier:	NCT01570764

Investigateur coordonnateur :
Professeur Luc MOUTHON
Pôle de Médecine Interne
Hôpital Cochin – Paris

Responsable scientifique :
Professeur David LAUNAY
Service de Médecine Interne
Hôpital Claude-Huriez - Lille

Unité de recherche clinique :
URC/CIC Cochin-Necker
ARC : Clément Lebrun
Chef de projet : Séverine Poignant
Hôpitaux Universitaires Paris Centre
Cochin Broca Necker
Site Tarnier - Paris

Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement par cyclophosphamide IV dans les PID-ScS (I)

- Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement associant cyclophosphamide intraveineux (0.7 g/m²/mois) pendant 12 mois et prednisone 15 mg/j comparativement à une traitement par prednisone 15 mg/j et placebo de cyclophosphamide.
- Les patients sous cyclophosphamide recevront du mesna et les patients sous placebo de cyclophosphamide recevront un placebo de mesna (conditionnement pharmacie agréée).
- Seuls les patients abaissant leurs LT CD4+ en dessous de 300/mm3 recevront du triméthoprime sulfamethoxazole.

Essai multicentrique prospectif randomisé contre placebo évaluant l'efficacité d'un traitement par cyclophosphamide IV dans les PID-ScS (II)

- Patients ayant une ScS et PID aggravative (diminution d'au moins 15% de la DLCO et/ou d'au moins 10% de la CVF et/ou de la CPT dans les 12 ± 3 mois précédant l'inclusion).
- 84 patients (42 dans chaque groupe), puissance 80% pour mettre en évidence une augmentation de la fréquence de stabilisation/amélioration des sujets à 12 mois estimée à 15% sous prednisone et placebo de cyclophosphamide et à 50% sous cyclophosphamide et prednisone (au risque alpha conventionnel de 5%).

Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

Khanna D et al.

- Pirfenidone has been shown to be safe and effective in the treatment of IPF.
- The LOTUSS study was designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD.
- **Methods: o**pen-label, 16-week study. Patients randomized to a 2- or 4-week titration to the target dose of 2403 mg/day. Eligibility: diagnosis of SSc ≤7 years from first non-Raynaud's symptom, HRCT-confirmed ILD, FVC ≥50%, DLco ≥40%, absence of clinically significant PH or severe GERD. Stable treatment with MMF or oral CYC was permitted.

Abstract Number: 3134

- **Results:** 63 patients, mean (SD) age 50.6 (12.3) yrs; female (82.5%); mean (SD) SSc duration: 38.3 (26.0) months.

Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

Khanna D et al.

- 40 patients (63.5%) on MMF and others (36.5%): no immunosuppressant. Mean (SD) mRSS, %FVC and %DL_{CO} at baseline: 11.4 (9.6), 76.0 (14.2) and 59.7 (16.5), respectively.
- Frequency and type of TEAEs were similar for both titration groups.
- No clinically significant changes in vital signs, ECGs, or laboratory tests.
- At week 16, the median change from baseline in %FVC was -0.5% (range -42% to 12%); the median change from baseline in %DL_{CO} was 1.5% (range -24.0% to 40.0%); minor changes (mean±SD) were observed in Mahler TDI (1.0±3.41) and mRSS (-0.4±3.71).
- **Conclusion:** pirfenidone was safe and generally well-tolerated in SSc-ILD patients, despite pre-existing co-morbidities, and concomitant use of MMF.

Abstract Number: 3134

The Scleroderma Lung Study II (SLS II) Shows That Both Oral CYC and MMF Are Efficacious in Treating Progressive ILD in Patients with SSc

Clements PJ et al.

Methods:

- Entry criteria: 1980 ACR criteria for SSc; disease duration of =< 7 years from 1st non-Raynaud sign or symptom; moderate dyspnea (Level 2); %FVC between 45% and 80%; and any ground-glass opacification on chest HRCT.
- At baseline and every 3 months during the 2-year trial, physical exams (MRSS), lung function testing and patient-reported outcomes were completed: HAQDI and 5 100-mm visual analogue scales); SF-36, and TDI.
- Patients were randomized to Arm A (oral CYC 2 mg/kg/day for one year followed by matching placebo for the second year) or Arm B (matching MMF up to 1500 mg BID for 2 years).

Abstract Number: 1075

The Scleroderma Lung Study II (SLS II) Shows That Both Oral CYC and MMF Are Efficacious in Treating Progressive ILD in Patients with SSc

Clements PJ et al.

- **Results:** 142 patients were randomized; 106 completed the 2-year evaluation. With the exception of MRSS, which was higher in the MMF group (15.3 in MMF vs 14.1 in CYC) the baseline characteristics were not different between treatment groups.
- In preliminary analyses, the course of FVC showed comparable improvement in both treatment groups at 24 months.
- Improvements in both treatment groups were noted in TDI (increase of 2.24 in CYC vs 1.86 in MMF,) and in MRSS (decline of 6.1 units in CYC vs 2.9 units in MMF).

Abstract Number: 1075

The Scleroderma Lung Study II (SLS II) Shows That Both Oral CYC and MMF Are Efficacious in Treating Progressive ILD in Patients with SSc

Clements PJ et al.

- **Results**
- More patients in the CYC arm withdrew from study treatment prematurely (36 in CYC and 20 in MMF) ($p=0.019$).
- Of all the subjects with end-point data
  - 23% assigned to CYC received alternative therapy after stopping study treatment (MMF in 8, Rituximab in 1, tocilizimab in 1 and IV-CYC in 2)
  - 4% assigned to MMF received alternative treatment (po CYC in 1 and IV-CYC in 1) after stopping study treatment.
- Weight loss (NS) and leukopenia/thrombocytopenia ($p<0.05$) occurred more frequently in the CYC arm

Abstract Number: 1075

Conclusion

1) At 24 months the improvement in %FVC was comparable in the two treatment groups.

2) The TDI and MRSS improved in both treatment arms but there was a trend favoring improvements in the CYC group.

3) Significantly fewer premature withdrawals were noted in the MMF arm.

4) Leukopenia/thrombocytopenia were noted significantly less frequently in the MMF arm

5) It is unclear how the use of alternative medications in SSc patients who withdrew prematurely from study treatments, particularly in the CYC patients, could have influenced the results.

Abstract Number: 1075

SSc: involvement of B lymphocytes

- Abnormal B cell signalling in TSK/+ mice[1]
- Presence of B cells in skin[2] and in lungs from SSc patients[3]
- Expanded naive B cells and diminished but activated memory B cells[4]
- Presence of serum autoantibodies and elevated serum levels of cytokines such as IL-6 which correlate with skin fibrosis
- Elevated serum BAFF levels correlate with disease severity[5]
- Preliminary results from pilot studies in SSc patients with rituximab[2,6]

1. Saito E, *et al. J Clin Invest* 2002; 109:1453–62.
2. Bosello, *et al. Arthritis Res Ther* 2010; 12:R54.
3. Lafyatis R, *et al. Arthritis Rheum* 2007; 56:3167–8.
4. Sato S, *et al. Arthritis Rheum* 2004; 50:1918–27.
5. Matsushita T, *et al. Arthritis Rheum* 2006; 54:192–201.
6. Lafyatis R, *et al. Arthritis Rheum* 2009, 60:578-83.

RITUXIMAB

- **Small sized randomised study**
  - 14 pts (8 rituximab and 6 conventional treatments)
  - 1 year
  - 2 courses, weeks1 and 24, 375 mg/m2
- **Evaluation**
  - Rodnan
  - Lung function tests
  - CT scann
- **Results**
  - Decrease in FVC (p<0,001)
  - Improvement of CO diffusion 19.4% vs –7.5%
  - Improvement of Rodnan score 13.5 vs 8.7 (p<0,001)

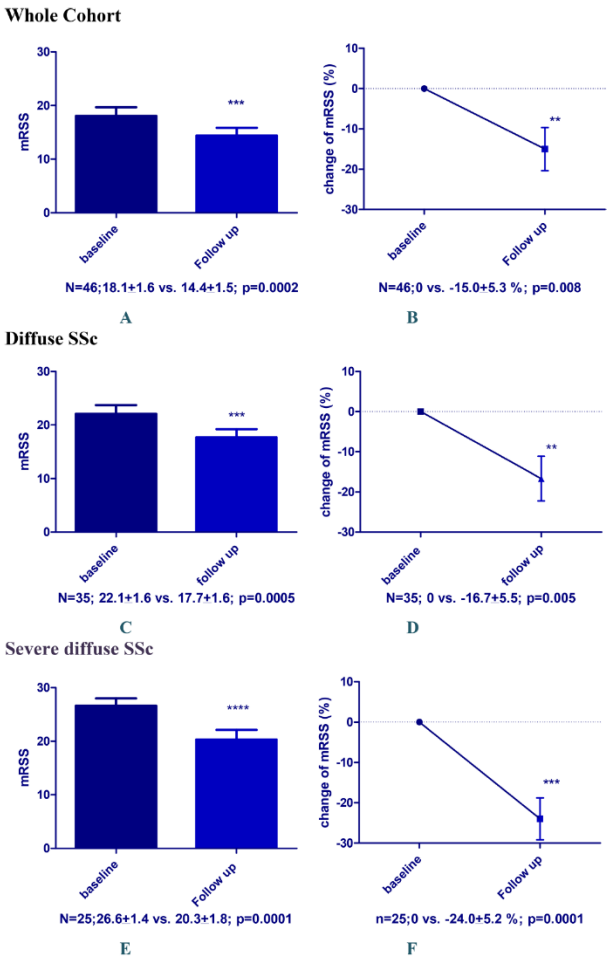
Daoussis Rheumatology 2009

Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group

Suzana Jordan,[1] Jörg H W Distler,[2] Britta Maurer,[1] Dörte Huscher,[3] Jacob M van Laar,[4] Yannick Allanore,[5] Oliver Distler,[1] on behalf of the EUSTAR Rituximab study group

63 patients treated with RTX.
The case-control analysis in patients with severe diffuse SSc showed that mRSS changes were larger in the RTX group versus matched controls (N=25; −24.0±5.2% vs −7.7±4.3%; p=0.03).
In RTX-treated patients, the mean mRSS was significantly reduced at follow-up compared with baseline (26.6±1.4 vs 20.3±1.8; p=0.0001).
In patients with interstitial lung disease, RTX prevented significantly the further decline of FVC compared with matched controls (N=9; 0.4±4.4% vs −7.7±3.6%; p=0.02).
Safety measures showed a good profile.

The comparison of RTX treated vs untreated matched-control SSc patients from the EUSTAR cohort demonstrated improvement of skin fibrosis and prevention of worsening lung fibrosis, supporting the therapeutic concept of B cell inhibition in SSc.



ARD 2013

Rituximab in systemic sclerosis: Interventional studies. ClinicalTrials.gov (10 – 12 – 2014)

- Rituximab in Systemic Sclerosis (RECOVER) (NCT01748084)
  - To determine whether rituximab is effective in the treatment of articular symptoms that occur in systemic sclerosis related **polyarthritis**

- Rituximab for Treatment of Systemic Sclerosis-Associated PAH (SSc-PAH) (NCT01086540)
  - To determine if rituximab has a marked beneficial effect on clinical disease progression, in patients with **SSc-PAH** when compared to placebo
- Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD (RECITAL) (NCT01862926)
  - To evaluate the efficacy of rituximab (compared with standard therapy) in patients with progressive **CTD related ILD**.

Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

Khanna D et al.

- Pirfenidone has been shown to be safe and effective in the treatment of IPF.
- The LOTUSS study was designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD.
- **Methods: o**pen-label, 16-week study. Patients randomized to a 2- or 4-week titration to the target dose of 2403 mg/day. Eligibility: diagnosis of SSc ≤7 years from first non-Raynaud's symptom, HRCT-confirmed ILD, FVC ≥50%, DLco ≥40%, absence of clinically significant PH or severe GERD. Stable treatment with MMF or oral CYC was permitted.
- **Results:** 63 patients, mean (SD) age 50.6 (12.3) yrs; female (82.5%); mean (SD) SSc duration: 38.3 (26.0) months.

Abstract Number: 3134

Safety and Tolerability of Pirfenidone in Patients with SSc Interstitial Lung Disease

Khanna D et al.

- 40 patients (63.5%) on MMF and others (36.5%): no immunosuppressant. Mean (SD) mRSS, %FVC and %DL_{CO} at baseline: 11.4 (9.6), 76.0 (14.2) and 59.7 (16.5), respectively.
- Frequency and type of TEAEs were similar for both titration groups.
- No clinically significant changes in vital signs, ECGs, or laboratory tests.
- At week 16, the median change from baseline in %FVC was -0.5% (range -42% to 12%); the median change from baseline in %DL_{CO} was 1.5% (range -24.0% to 40.0%); minor changes (mean±SD) were observed in Mahler TDI (1.0±3.41) and mRSS (-0.4±3.71).
- **Conclusion:** pirfenidone was safe and generally well-tolerated in SSc-ILD patients, despite pre-existing co-morbidities, and concomitant use of MMF.

Abstract Number: 3134

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

- Cyclophosphamide systemic sclerosis associated ILD
- A trial of Taladafil in ILD of Scleroderma
- Study of pomalidomide in SSc with ILD
- Rituximab Versus Cyclophosphamide in Connective Tissue Disease-ILD
- Safety Evaluation of Dasatinib in Subjects With Scleroderma Pulmonary Fibrosis
- Nintedanib in systemic sclerosis
- Evaluating N-acetylcysteine in CTD-ILD treatment
- Autologous stem cell SSc immune suppression trial

Joint involvement in systemic sclerosis: Treatment

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

Safety and Efficacy of Subcutaneous Tocilizumab in Adults with Systemic Sclerosis: Week 24 Data from a Phase 2/3 Trial

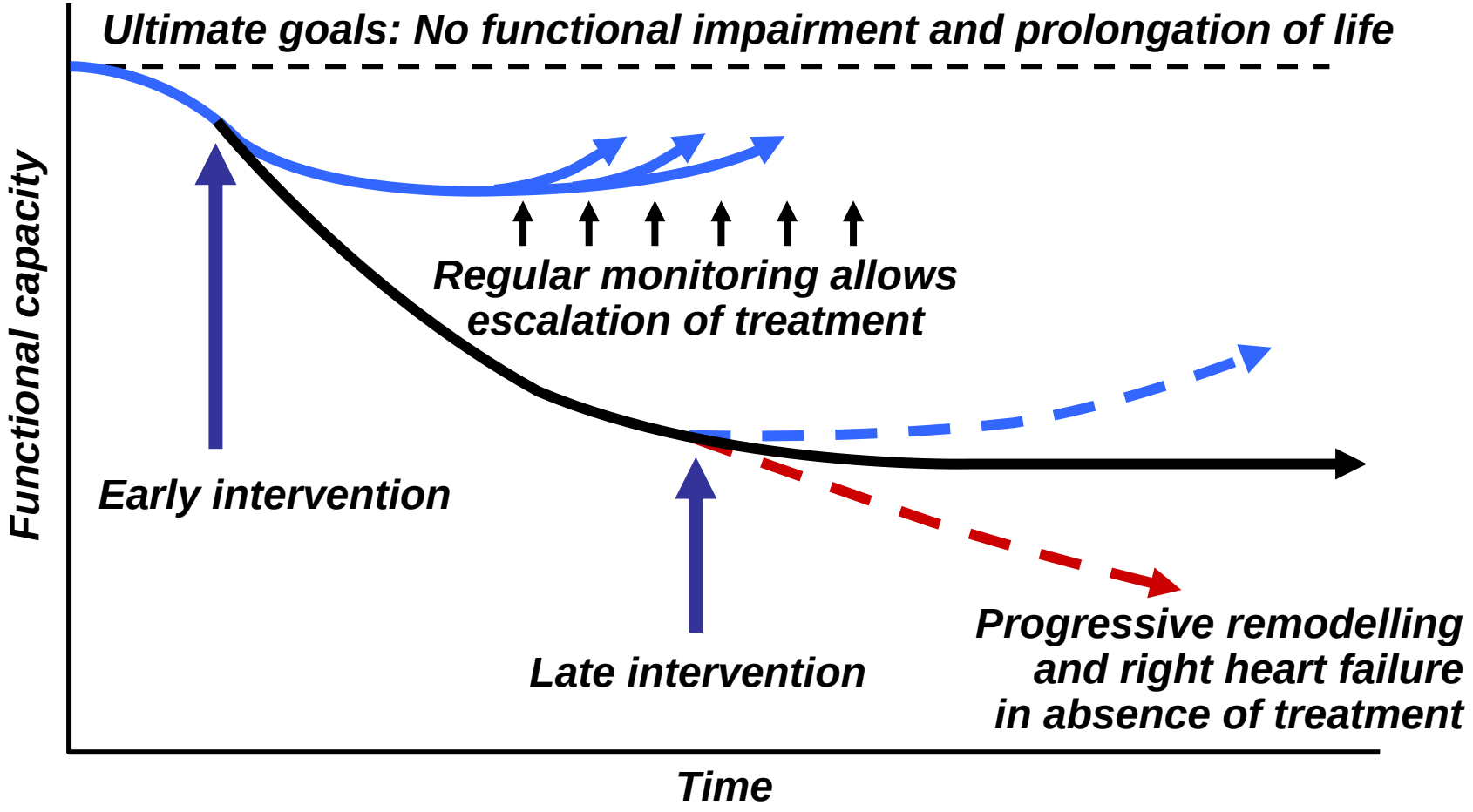
Table. Change From Baseline in mRSS, HAQ-DI, and FVC at Week 24 (ITT population)

	TCZ	PBO	Difference (95% CI)	*p*
mRSS, adjusted[a] mean (SD)	–3.9 n = 41	–1.2 n = 43	–2.70 (–5.85, 0.45)	0.09
HAQ-DI, adjusted[a] mean (SD)	0.14 n = 41	0.12 n = 42	0.02 (–0.19, 0.23)	0.85
FVC (L) change ≤0%, n (%)	15 (50.0) n = 30	30 (81.1) n = 37		
FVC (L) decline ≥10%, n (%)	1 (3.3) n = 30	10 (27.0) n = 37		

HAQ-DI, Health Assessment Questionaire–Disability Index; ITT, intent to treat.
[a]Mixed-model repeated measures analysis that included treatment, visit, joint involvement at baseline, treatment-by-visit interaction, baseline parameter, and baseline parameter-by-visit interaction.

Dinesh Khanna et al. ACR 2015 San Francisco

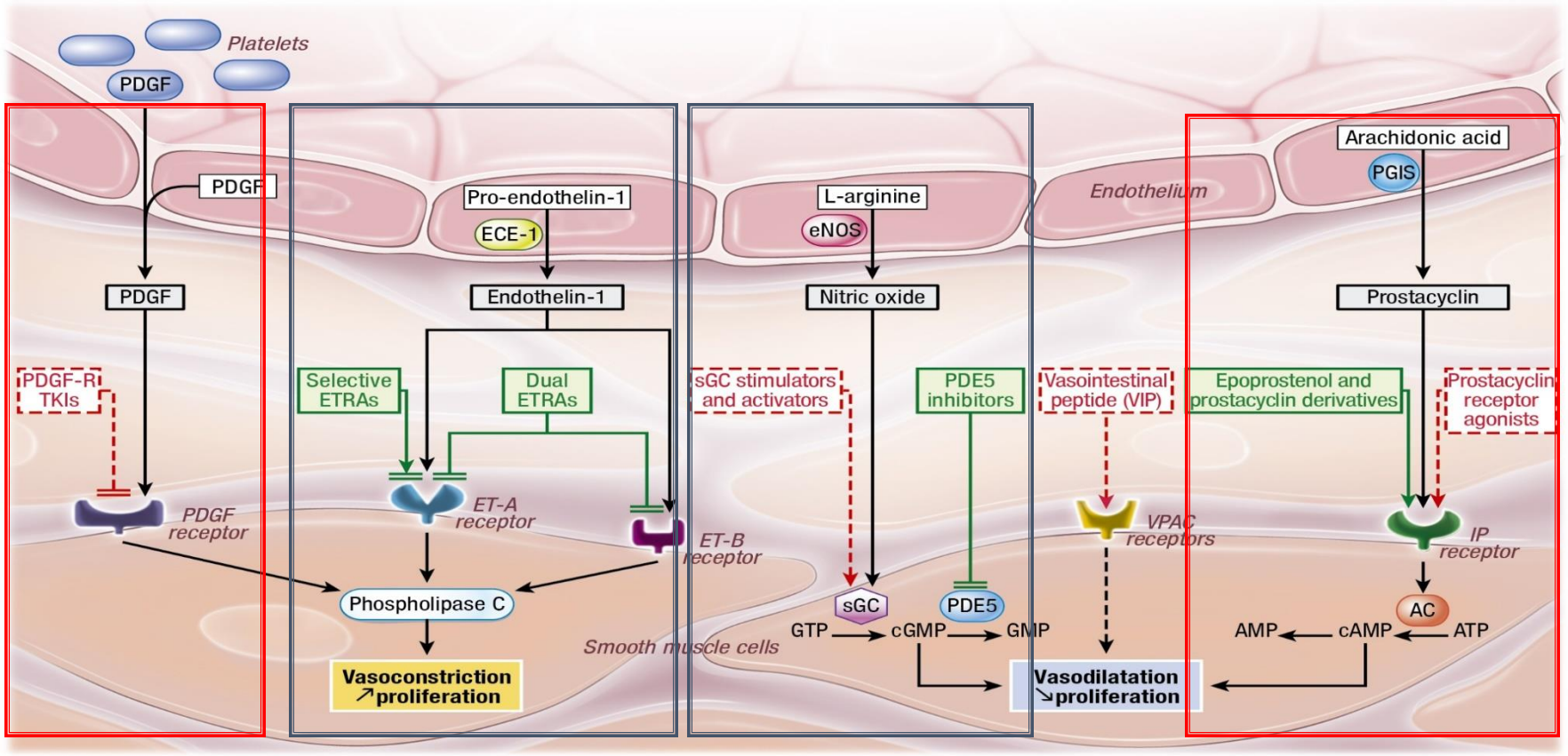
Treat-to-target approach for PAH



Sitbon O and Galiè N. *Eur Respir Rev* 2010.

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

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

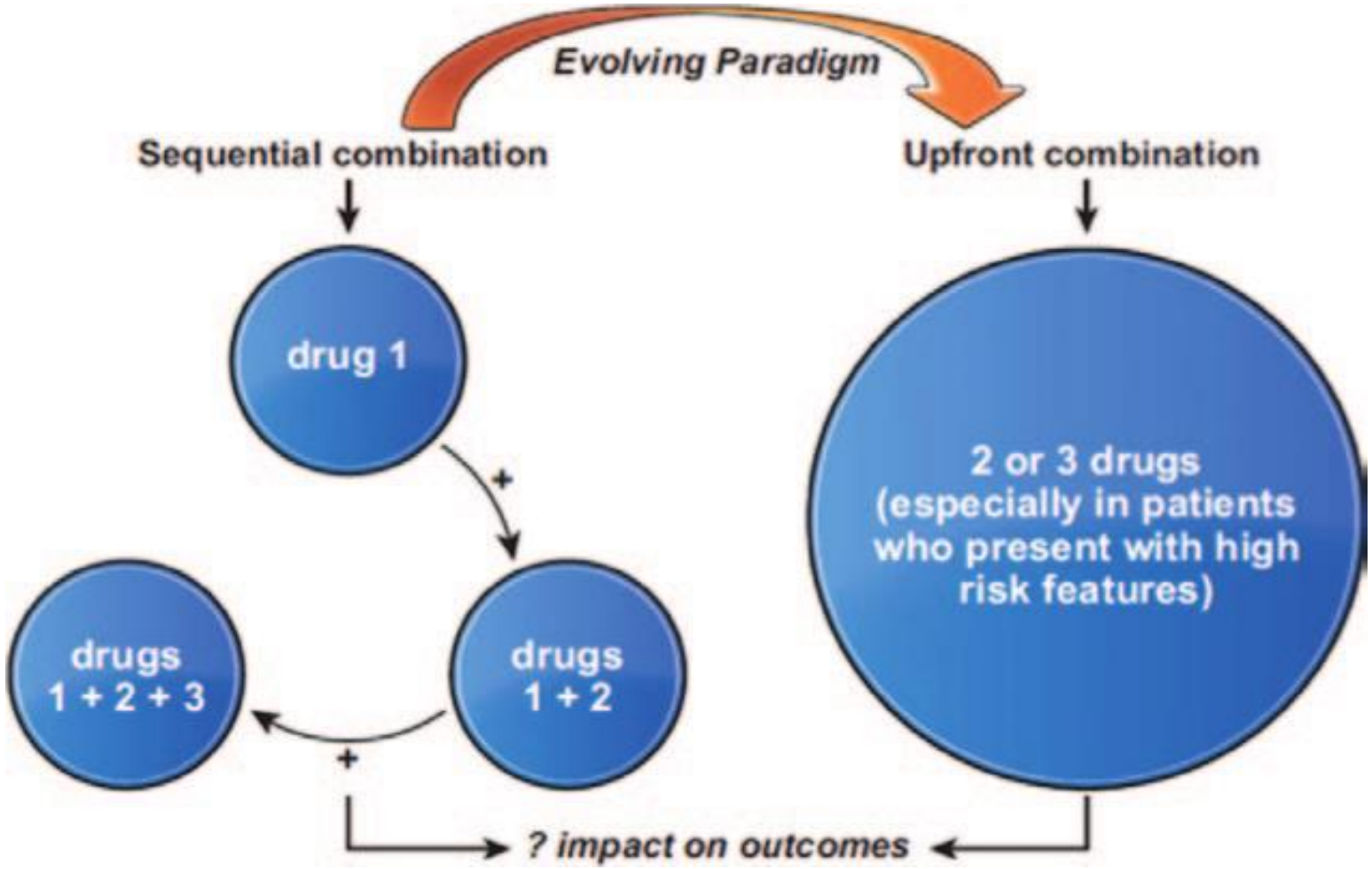
Essais cliniques avec un traitement combiné

	Current therapy	Added therapy	Patients (n)	Study duration	Primary endpoint	Primary EP met	Secondary EP met
BREATHE-2[1]	None	Bosentan & epoprostenol	32	16 weeks	PVR	No	No
STEP[2]	Bosentan	Iloprost	67	12 weeks	6MWD	No	TTCW
PACES[3]	Epoprostenol	Sildenafil	267	16 weeks	6MWD	Yes	TTCW
COMPASS-1[4]	Bosentan	Sildenafil	45	1 day	PVR	Yes	-
PHIRST[5]	Naïve or bosentan	Tadalafil	405 (206)	16 weeks	6MWD	Yes / (No)	TTCW
TRIUMPH-1[6]	Bosentan or sildenafil	Treprostinil (inhaled)	235	12 weeks	6MWD	Yes	No
FREEDOM-C[7]	Bosentan and /or sildenafil	Treprostinil (oral)	354	16 weeks	6MWD	No	No
PATENT[8]	ETRA	Riociguat (oral)	400	12 weeks	6MWD	Yes	Yes
SERAPHIN[9]	PDE5i	Macitentan (oral)	740	≈ 2 years	Morbi-mortality	Yes	Yes

1. Humbert M, et al. Eur Respir J 2004;24:353–9; 2. McLaughlin VV, et al. Am J Respir Crit Care Med 2006;174:1257–63;
3. Simonneau G, et al. Ann Intern Med 2008;149:521–30; 4. Gruenig E, et al. Eur Heart J 2007;28 (Suppl 1): A140;
5. Galiè N et al. Circulation 2009;119:2894–903. 6. McLaughlin V, J Am Coll Cardiol 2010;55:1915–22.;
7. www.clinicaltrials.gov identifier NCT00325442. 8. Ghofrani, NEJM 2013. 9. Pulido, NEJM 2013.

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

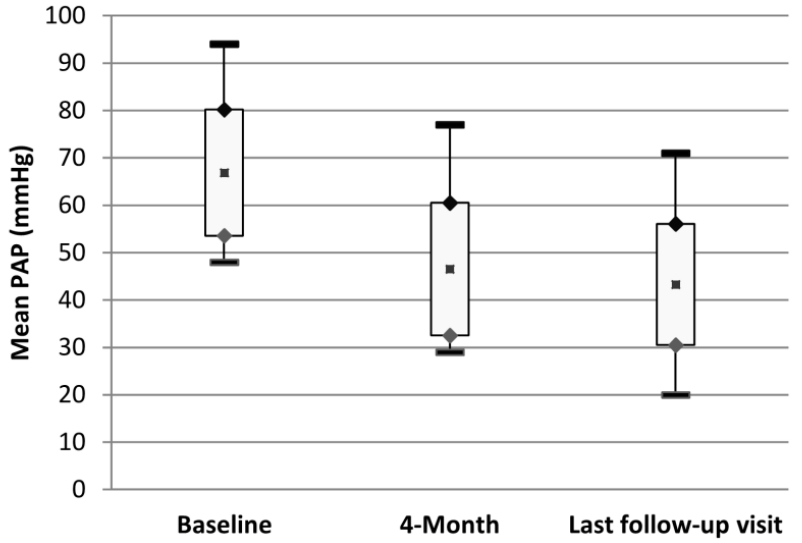
Evolving paradigm: From sequential to initial combination therapy

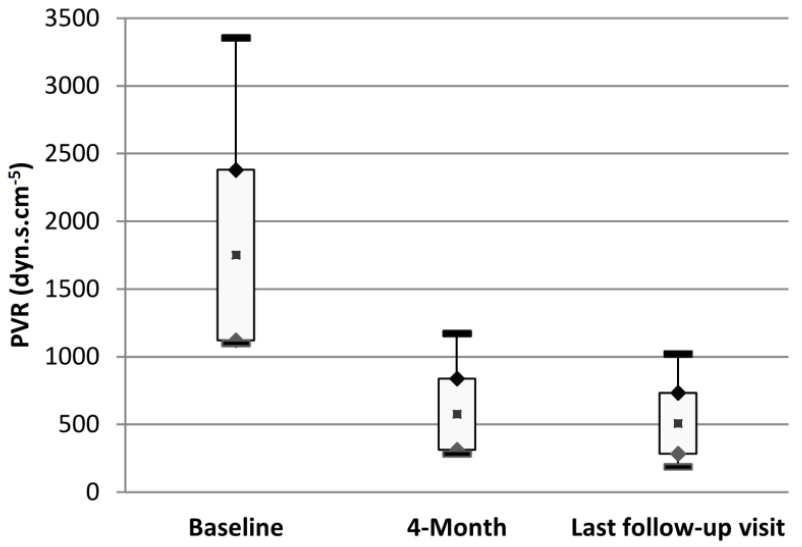


Humbert M, *et al*. *Circulation* 2014.

Traitement combiné triple de première intention

- 18 malades avec HTAP (i ou h) très sévère traités d'emblée par Flolan® + Tracleer ® + Revatio ®
- Après 4 mois
  - Un échec (malade la plus grave): Transplantée en urgence
  - Amélioration majeure chez 17 autres patients
    - Tous en classe NYHA I-II
    - TM6 468±62 m (*vs* 254±153 m)
    - Amélioration majeure des paramètres mesurés au KT droit
- Amélioration maintenue après en moyenne 2,5 ans (1-5 ans)

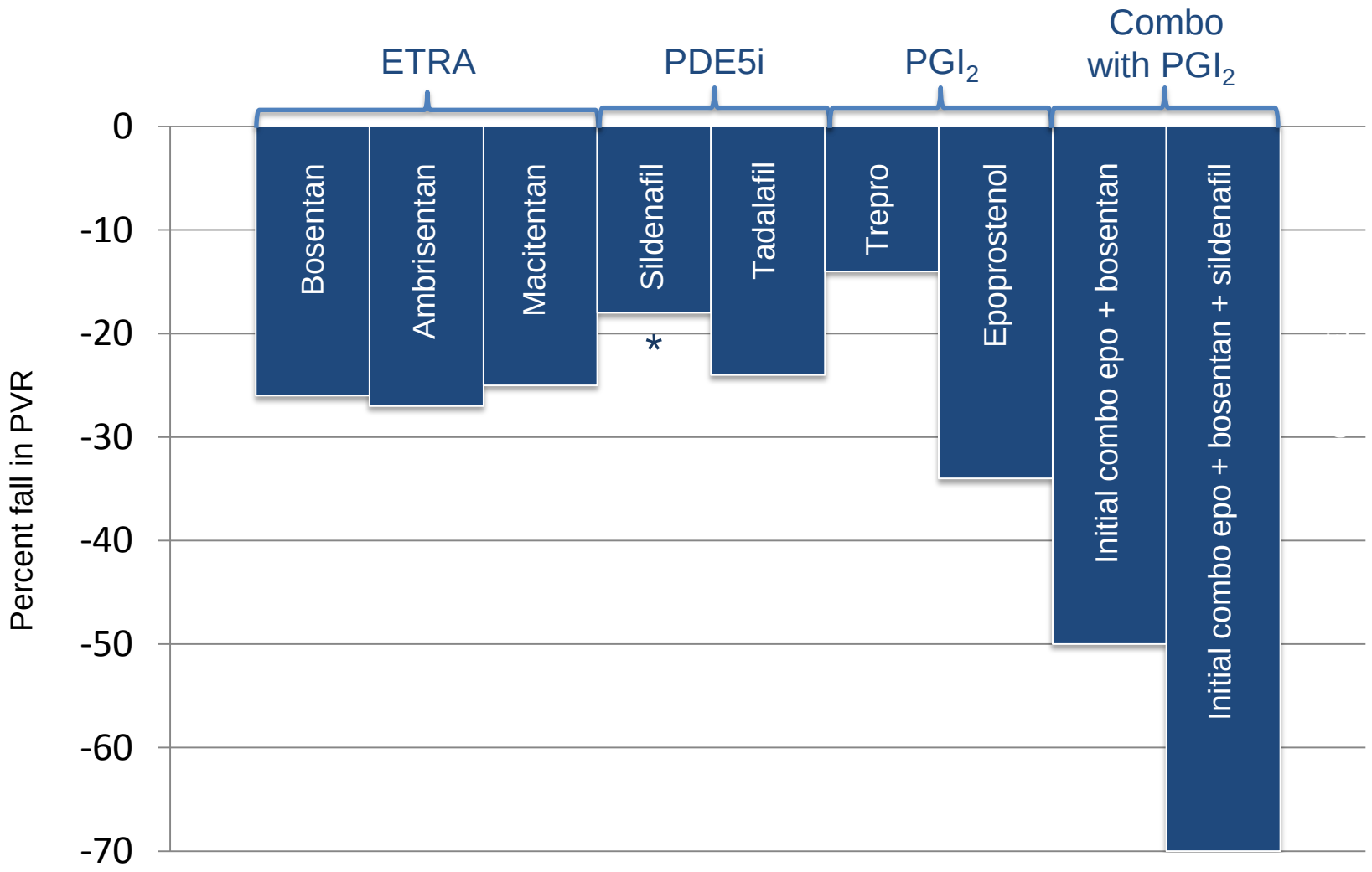




Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

Effect of PAH-specific therapies on PVR after 3-6 months



* Sildenafil: -12% to -28% according to dose

Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

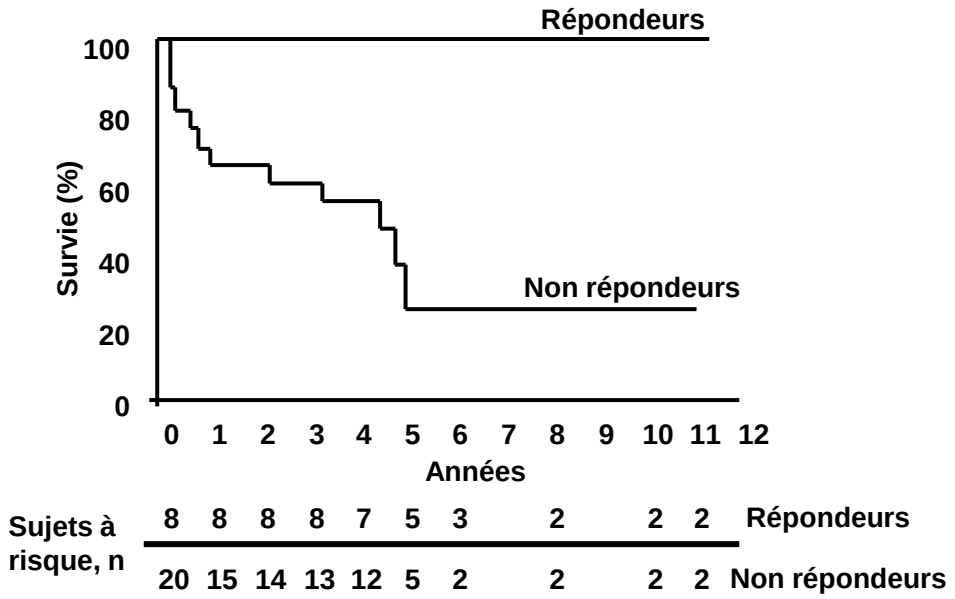
The AMBITION trial

- Event-driven study
- Initial combo AMB+TADA vs monotherapy AMB or TADA
- N=500 treatment-naïve patients with PAH (50% FC II)
- Initial combo of AMB 10 mg + TADA 40 mg **reduced the risk of clinical failure by 50%** compared to pooled AMB and TADA monotherapy arm (HR = 0.502; p=0.0002).
- Hospitalisation for worsening of PAH was the main component of the primary endpoint
- Main AE: peripheral oedema (≈50%) in combo Rx arm

GSK Press Release – 8 September 2014

IMMUNOSUPPRESSIVE THERAPY IN CTD-PAH

- First line immunosuppressive therapy
  - Monthly IV cyclophosphamide pulses (600 mg/m^2)
  - Steroids (prednisone 0.5 - 1 mg/kg/j)
- Eight out of 28 patients (32%) were “responders” (NYHA I-II after 1 yr)
- No patient with systemic sclerosis responded
- 38% of SLE and MCTD patients responded after 7 ± 6 CYC pulses
  - SLE n = 5 / 13
  - MCTD n = 3 / 8
  - SSc n = 0 / 6

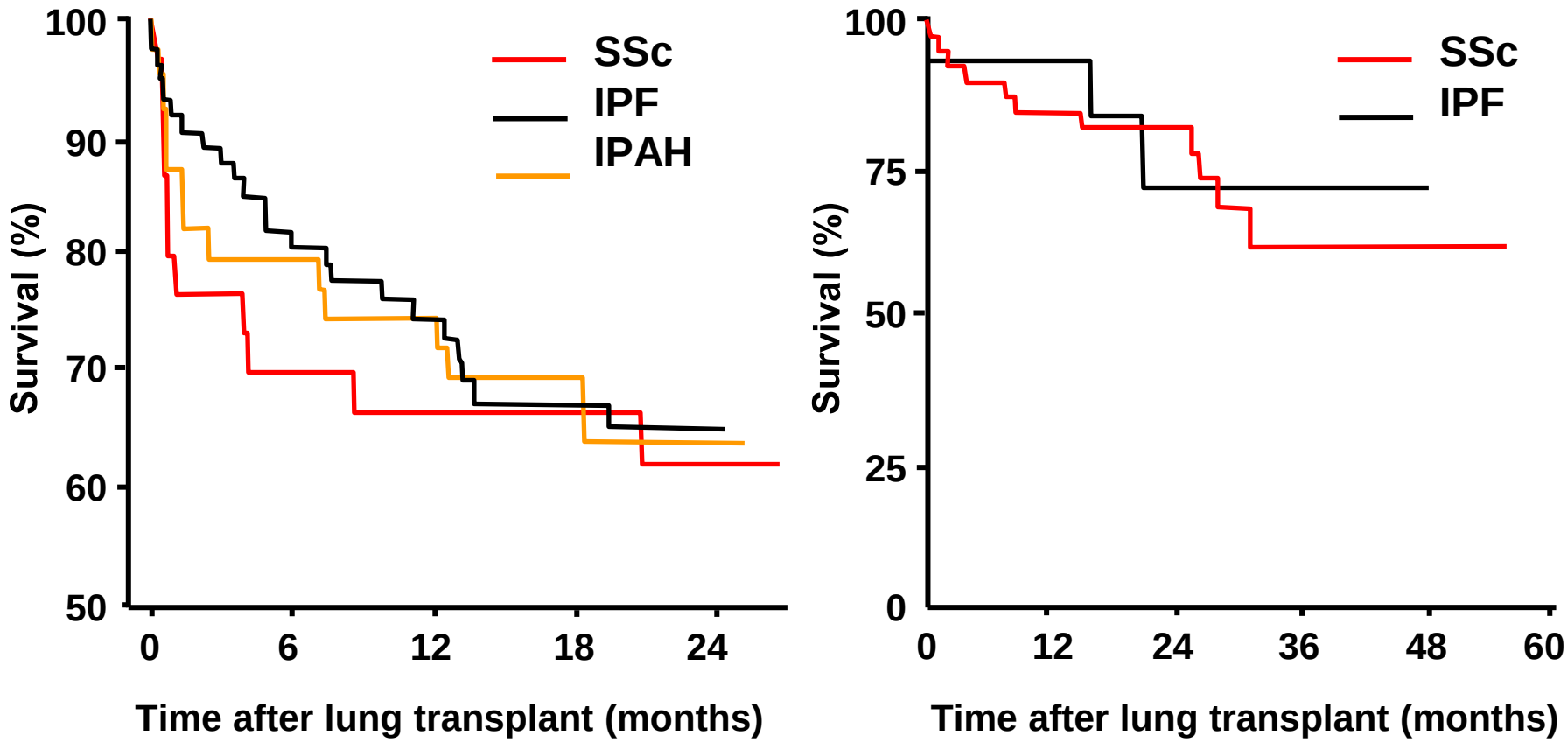


Sanchez O, *et al*. *CHEST* 2006;130;182-9.

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

HTAP-SSc : Place de la transplantation pulmonaire

Transplantation pulmonaire dans le SSc : réticence des chirurgiens
(Maladie systémique, Raynaud, Ulcères digitaux, RGO…)



Schachna L, *et al. Arthritis Rheum* 2006; 54:3954-61.
Saggar R, *et al. Eur Respir J* 2010; 36:893-900.

Hôpitaux universitaires Paris-Sud
Antoine-Béclère Bicêtre Paul-Brousse

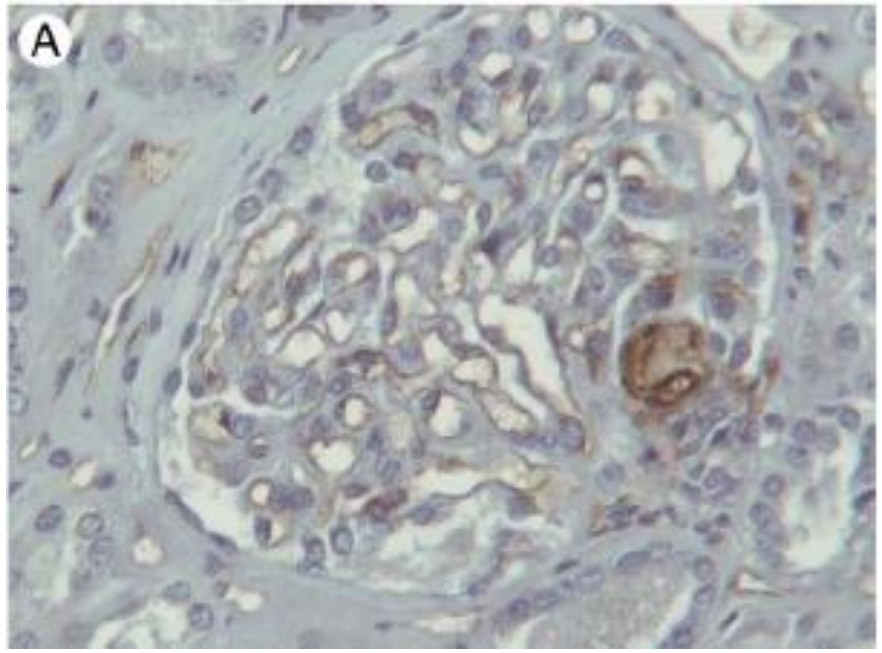
Ongoing / recent studies in DU-SSc

- Seduce: sildenafil vs placebo
- Dual: macitentan vs placebo
- Selexipag vs placebo

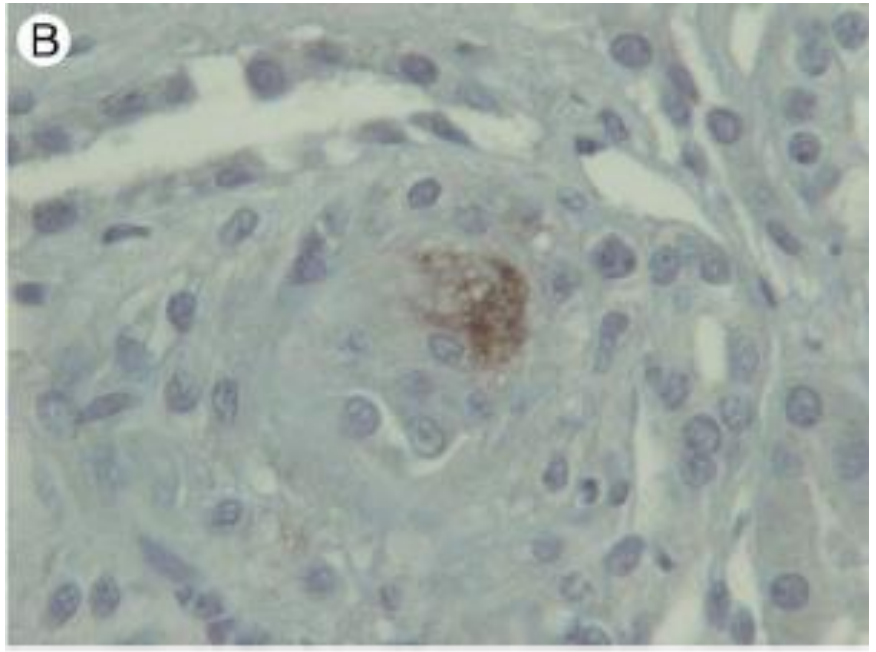
Endothelin 1 expression in scleroderma renal crisis

Table 3 Immunoperoxidase staining of ET-1 and vWF in kidney biopsies of selected groups with nephropathic abnormalities

Condition	No. of patients	Glomeruli		Arterioles		Interlobular arteries	
		ET-1	vWF	ET-1	vWF	ET-1	vWF
Negative controls	5	−	+/− (3)	+/− (1)	+/−(2)	+/−(3)	+/− (5)
SRC	14	6+/8−	++ (12)	++ (12)	++ (14)	++ (10)	++ 13)
HUS	5	+ (4)	+++ (5)	−	++(5)	−	++ (5)
APLN	6	−	++ (4)	+/− (3)	++ (6)	+/− (2)	++ (5)
Cyclosporine A toxicity	5	−	+/− (1)	+(1)	++(4)	−	++(4)
Nephroangiosclerosis	5	−	+ (4)	+/−(1)	++(3)	+/−(3)	++(5)
Diabetic nephropathy	5	−	++ (3)	+(2)	++(4)	+(3)	++(4)



ET-1 in glomerular thrombosis and along glomerular basement membranes



ET-1 in arteriolar thrombosis

Mouthon et al. Human Pathol 2010

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 intravenous α-/β-blockers and/or minoxidil

↓

Oliguric renal insufficiency: Early dialysis

↓

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

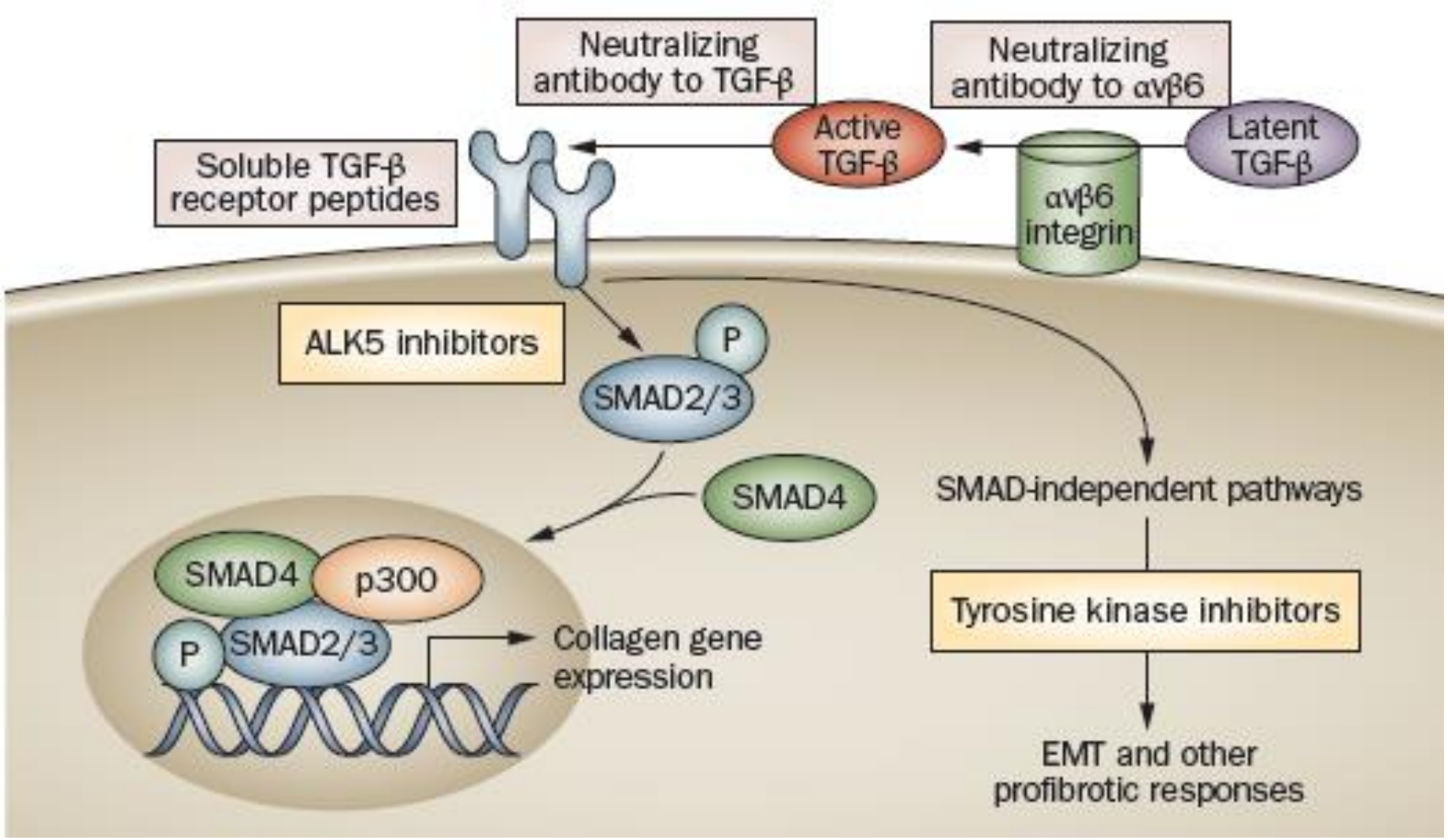
↓

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

Add anti-endothelin 1 receptor antagonists ?

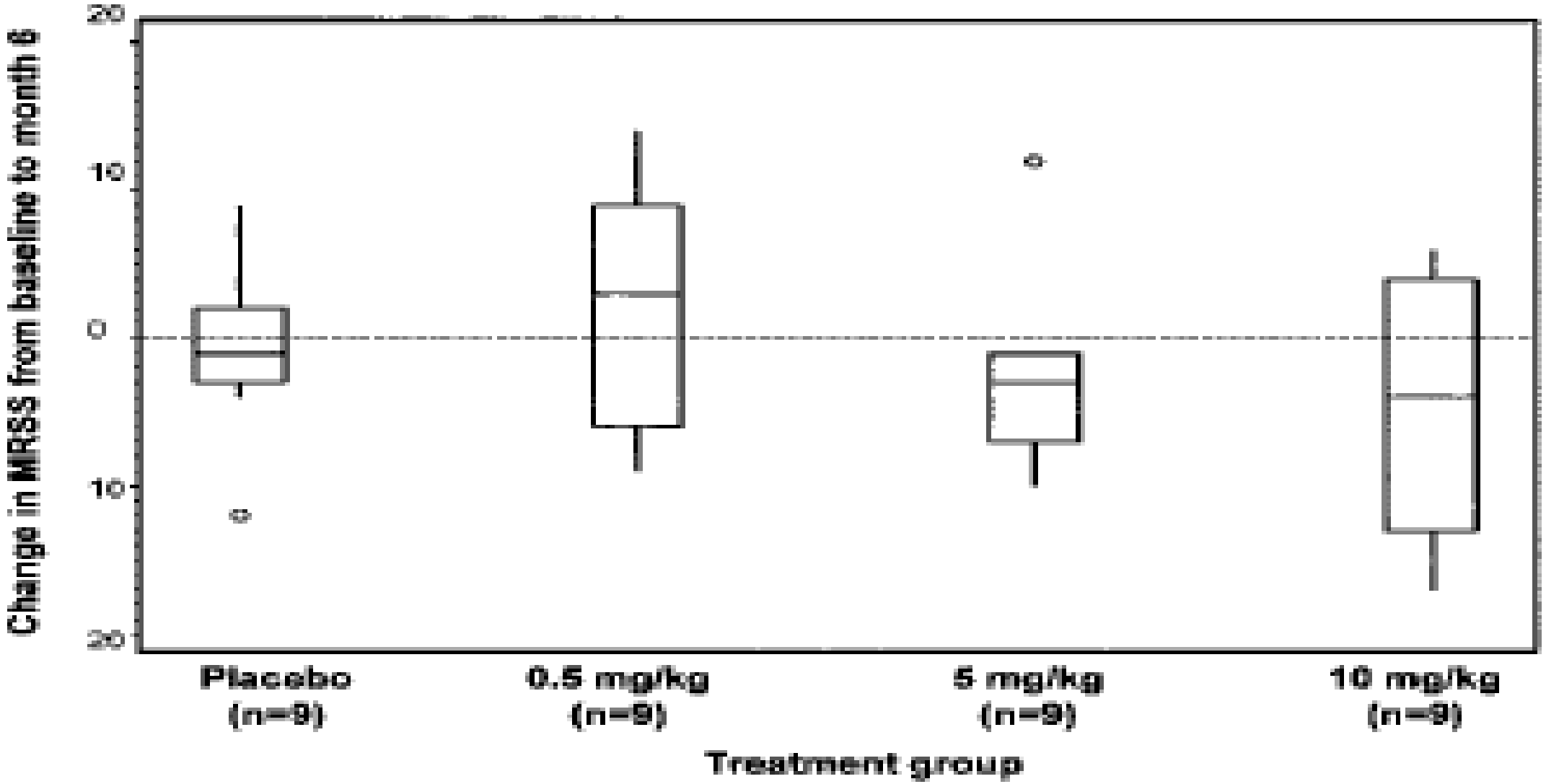
Teixeira et al 2007 Ann N Y Acad Sci;
Mouthon et al. Clin Rev Allerg Immunol 2009
Penn et al. QJM 2012

Proposed therapeutic strategies to block TGF-β



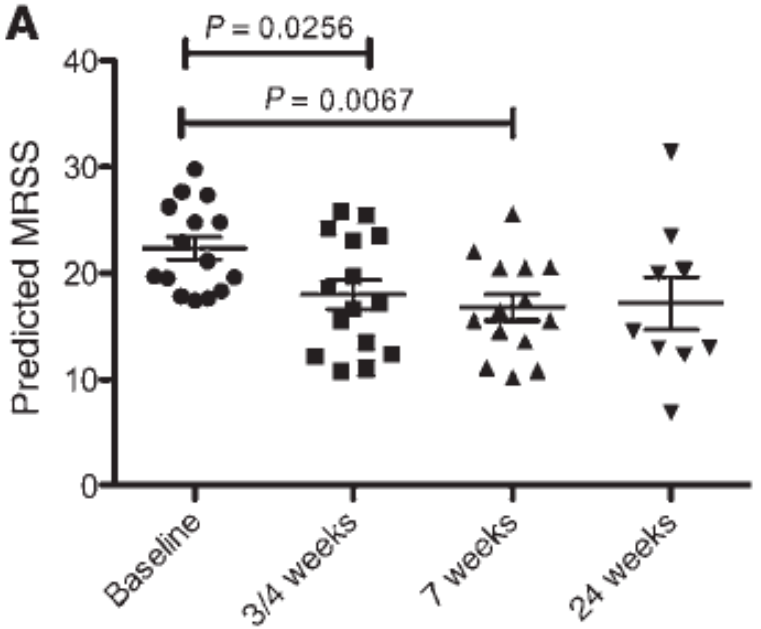
varga, J. & Pasche, B. Nat. Rev. Rheumatol. 5, 200–206 (2009)

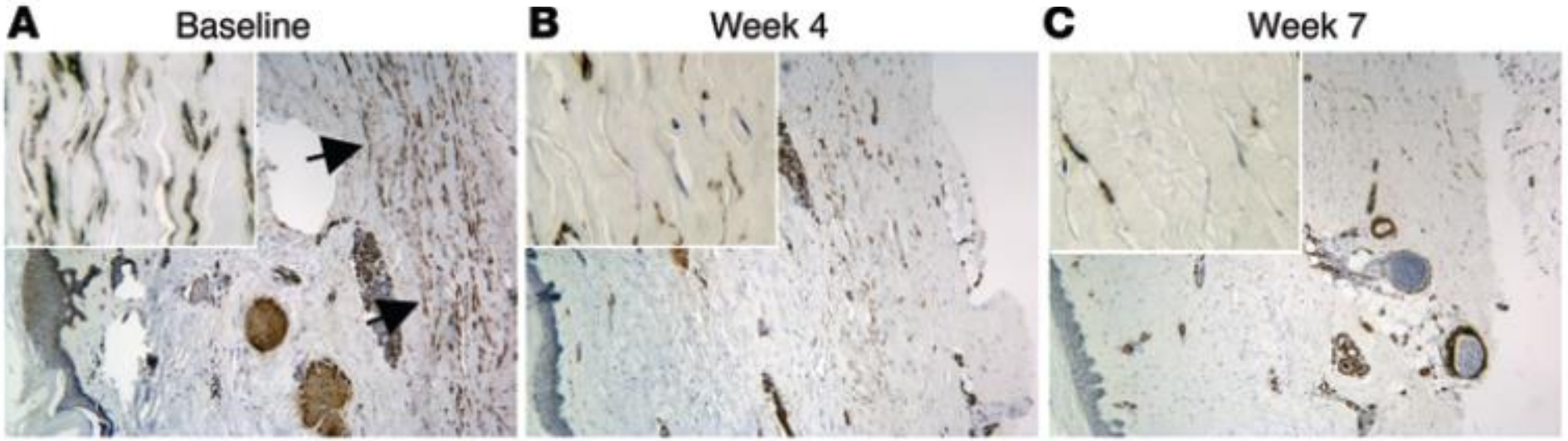
Change in the modified Rodnan skin score from baseline to month 6 in patients with diffuse cutaneous SSc treated with placebo or with 3 different doses (0.5, 5, or 10 mg/kg) of CAT-192.



Denton CP et al, A & R 2007

Fresolimumab treatment decreases biomarkers and improves clinical symptoms in SSc patients





Rice et al. 2015 J Clin Invest

Fresolimumab treatment decreases biomarkers and improves clinical symptoms in SSc patients

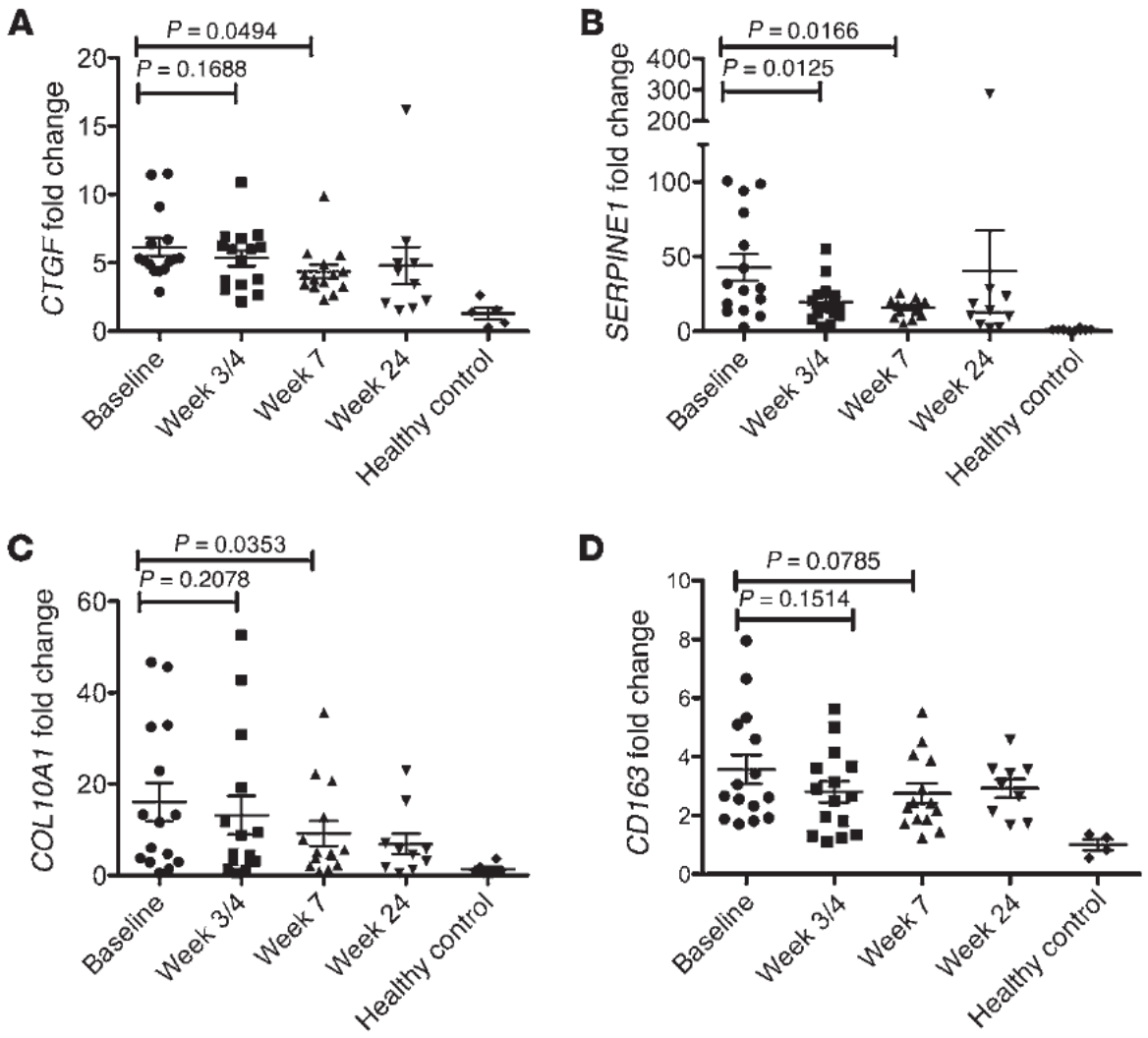


Figure 5. Changes in gene expression before and after fresolimumab treatment. Skin biopsy RNAs were analyzed for expression of TGF-β–regulated genes, (**A**) *CTGF*, (**B**) *SERPINE1*, (**C**) and *COL10A1*, and a macrophage marker, (**D**) *CD163*, at baseline and after fresolimumab treatment. Levels from 5 healthy controls skin samples are also shown. *CTGF*, *SERPINE1*, and *COL10A1* mRNA expression was assayed by RT-PCR; *CD163* expression was assayed by NanoString. Statistical significance was assessed by Wilcoxon signed-rank. Error bars indicate SEM.

Rice et al. J Clin Invest 2015

Unanswered questions

- Disease susceptibility:
  - rôle of environnemental factors
  - Why females
- Epigenetics
- Identify the « ideal » experimental model
- Mechanisms underlying:
  - vascular hyperreactivity
  - ROS production
  - Increased ECM production
- Why anti-fibrotic agents fail to improve patients in SSc
- Identify new targets for developing new molecules

CMR
CENTRE MALADIES RARES
VASCULARITES I SCLÉRODERMIES
GOUGEROT-SJÖGREN I LUPUS

GFRS

Hôpital Cochin
Paris

www.vascularites.org

Luc.mouthon@cch.aphp.fr

Referral Center for
Rare Systemic and
Autoimmune Diseases