Yverdon 29 mars 2018

Traitement inhalé pour maladies rares

JD Aubert

Pneumologie CHUV

Quelles maladies rares ?

- Hypertension artérielle pulmonaire
- Protéinose alvéolaire
- Fibrose pulmonaire

The New England Journal of Medicine

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

HORST OLSCHEWSKI, M.D., GERALD SIMONNEAU, M.D., NAZZARENO GALIÈ, M.D., TIMOTHY HIGENBOTTAM, M.D., ROBERT NAEIJE, M.D., LEWIS J. RUBIN, M.D., SYLVIA NIKKHO, M.D., RUDOLF SPEICH, M.D., MARIUS M. HOEPER, M.D., JÜRGEN BEHR, M.D., JÖRG WINKLER, M.D., OLIVIER SITBON, M.D., WLADIMIR POPOV, M.D., H. ARDESCHIR GHOFRANI, M.D., ALESSANDRA MANES, M.D., DAVID G. KIELY, M.D., RALPH EWERT, M.D., ANDREAS MEYER, M.D., PAUL A. CORRIS, F.R.C.P., MARION DELCROIX, M.D., MIGUEL GOMEZ-SANCHEZ, M.D., HARALD SIEDENTOP, DIPL.STAT., AND WERNER SEEGER, M.D., FOR THE AEROSOLIZED ILOPROST RANDOMIZED STUDY GROUP*

N Engl J Med, Vol. 347, No. 5 · August 1, 2002 · www.nejm.org

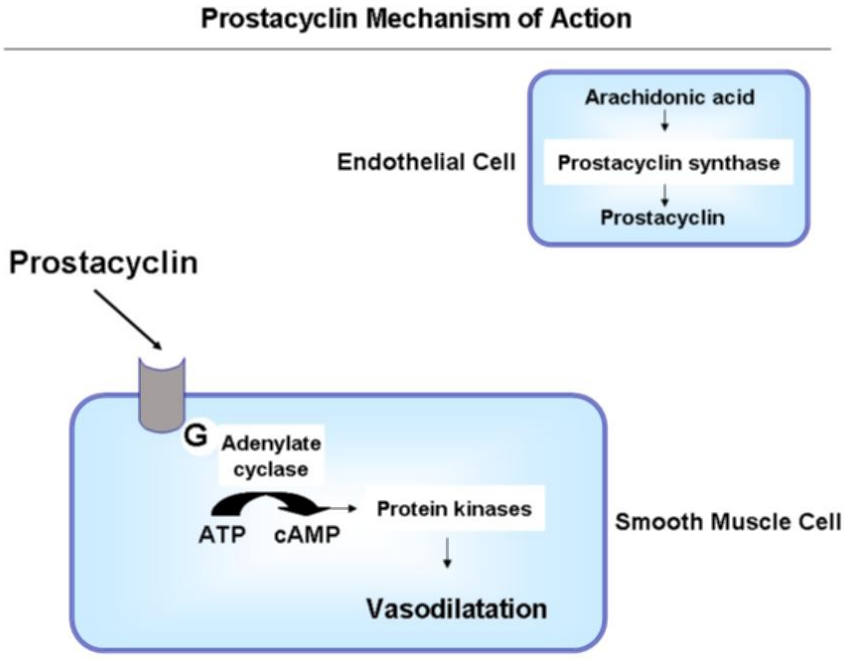


TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)
Age — yr	51.2±13.2	52.8±12.0
Weight — kg	71.3±14.6	72.6±13.9
Sex — %		
Male	31.7	33.3
Female	68.3	66.7
Underlying disease — no. (%)		
Primary pulmonary hypertension	51 (50.5)	51 (50.0)
Nonprimary pulmonary hypertension	50 (49.5)	51 (50.0)
Appetite suppressants	4 (4.0)	5 (4.9)
Collagen vascular disease	13 (12.9)	22 (21.6)
Chronic thromboembolic pulmonary hypertension	33 (32.7)	24 (23.5)
Oral vasodilator therapy — no. (%)	52 (51.5)	58 (56.9)
NYHA functional class — no. (%)		
III	60 (59.4)	59 (57.8)
IV	41 (40.6)	43 (42.2)

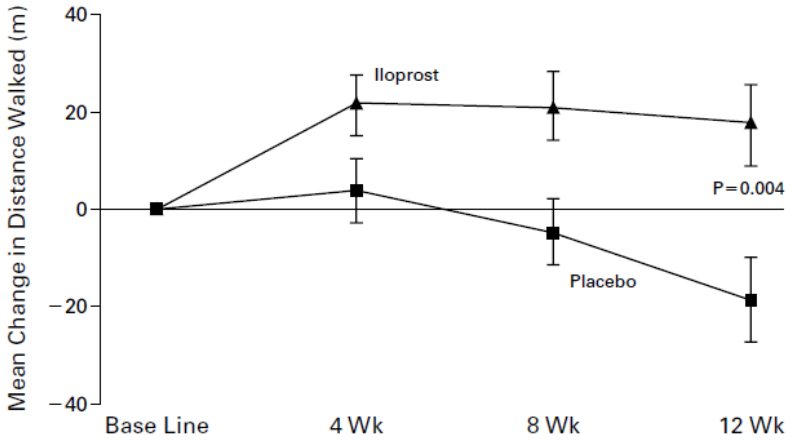


Figure 1. Effect of Inhaled Iloprost and Placebo on the Mean (±SE) Change from Base Line in the Distance Walked in Six Minutes, According to an Intention-to-Treat Analysis.
The P value was obtained with Wilcoxon's test for two independent samples.

For inhalation, iloprost or placebo was diluted with saline to a concentration of 10 μg per milliliter, and 2 ml was added to a nebulizer (HaloLite, MedicAid). This device delivered short pulses of aerosolized particles (geometric median [±SD] aerodynamic diameter of particles, 4.3±0.05 μm)[23] during the first part of each inspiration until a predefined total inhaled dose of 2.5 μg had been dispensed. The inhalation was then stopped or repeated once, to achieve a total dose of 5.0 μg, depending on how well the patient tolerated the treatment. After each inhalation, the residual volume in the nebulizer was discarded. This maneuver was repeated six or nine times daily, with an overnight break. The frequency of inhalation and the dose were individually determined within the first eight days of therapy according to a predefined dosing algorithm.

Current Marketed Prostanoids for Pulmonary Arterial Hypertension

Drug	Dosing	Pros	Cons
Flolan, Veletri (epoprostinil)	Intravenous via continuous infusion	Continuous drug level	▪ Intravenous – central line infection ▪ Requires infusion pump
Ventavis (iloprost)	Inhaled with 6-9x daily dosing	Less invasive than infusion	▪ Swings in peak/trough plasma levels ▪ Lack of drug overnight ▪ Inconvenient 6-9x/day dosing
Remodulin (treprostinil)	Subcutaneous / Intravenous via continuous infusion	Continuous drug level	▪ Subcutaneous -- site pain ▪ Intravenous – central line infection ▪ Requires infusion pump
Tyvaso (treprostinil)	Inhaled with 4x daily dosing	Less invasive than infusion	▪ Swings in peak/trough plasma levels ▪ Lack of drug overnight ▪ Inconvenient 4x daily dosing
Orinetram (treprostinil)	Oral with BID/TID dosing	Convenient dosage form	▪ Swings in peak/trough plasma levels ▪ Lack of drug overnight

Le cas du treprostinil

- 4 formes disponibles:
- iv
- sc
- oral (pas disponible en Suisse)
- Inhalé

Treprostinil route[a]	Risks [9–11]	Benefits		Other considerations
		Placebo-corrected Hodges-Lehmann median change in 6MWD after 12 weeks [5, 7, 39]	Survival [6, 24, 38]	
Parenteral treprostinil (Remodulin®)	Indwelling central catheter, bloodstream infection, sepsis (IV) Injection-site pain, occasionally requiring narcotics (SC) Headache Diarrhea, nausea Rash Jaw pain Vasodilation Edema Hypotension	+16 m (as monotherapy)	1 year: 87 % 2 years: 78 % 3 years: 71 % 4 years: 68 %	Device required Continuous infusion Ability to titrate dose
Inhaled (Tyvaso®)	Cough, throat irritation, pharyngolaryngeal pain Headache, flushing Nausea, diarrhea Dizziness Jaw pain	+20 m (with single oral background therapy)	1 year: 97 % 2 years: 91 % 3 years: 82 %	Device required; part replacement and cleaning qid dosing Titrate to a maximum dose (72 µg)
Oral (Orenitram®)	Headache Diarrhea, nausea Flushing Pain in jaw Pain in extremity Hypokalemia Abdominal discomfort	+23 m (as monotherapy)	1 year: 92 % 2 years: 87 %[b] 3 years: 82 %[b]	No device required bid or tid dosing Take with food Ability to titrate dose

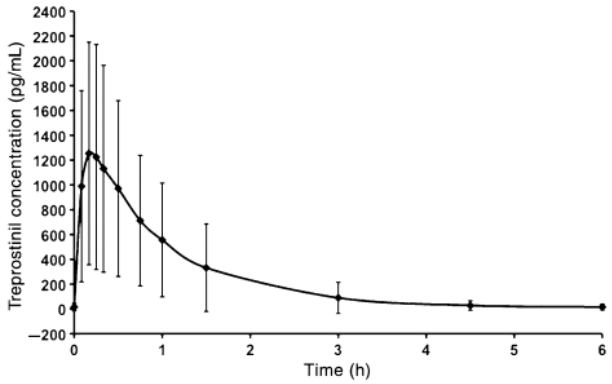


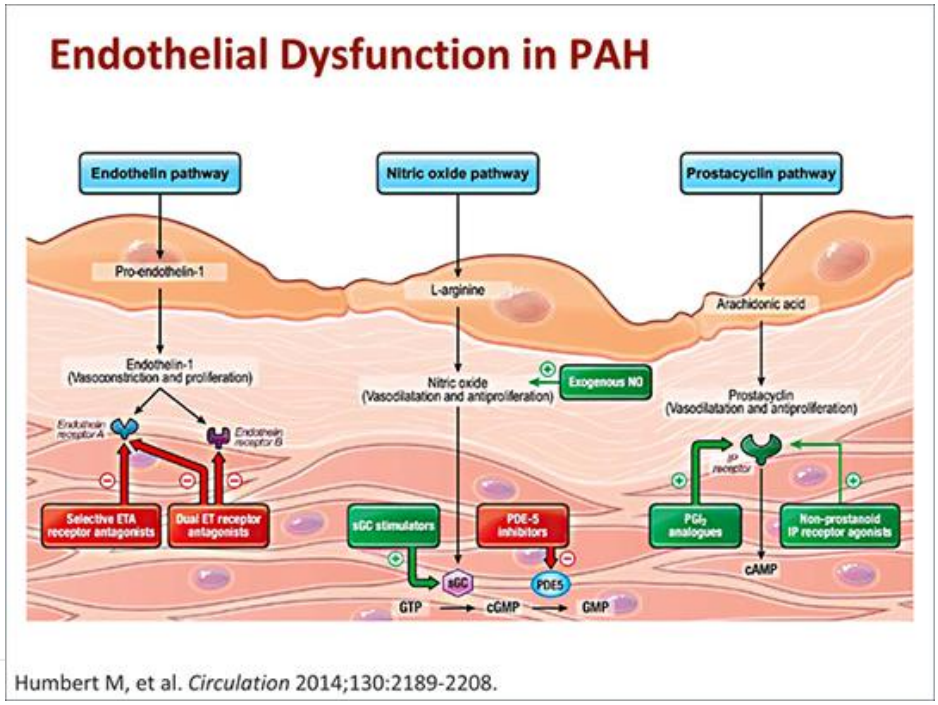
Fig. 2 Mean (±standard deviation) plasma treprostinil concentration vs. time following administration of 54 µg of inhaled treprostinil ($n = 11$) [18]

Tyvaso® (treprostinil sodium)

Pivotal trial	Inhaled	PAH patients	235	12-week, randomized, double-blind, placebo-controlled multicenter trial in clinically stable patients, mostly NYHA class III, receiving background therapy with either bosentan (70 %) or sildenafil (30 %) for at least 3 months prior to study initiation (mean dose 50 µg qid)

Table 2
Functional, echocardiographic and hemodynamic assessments in patient 2.

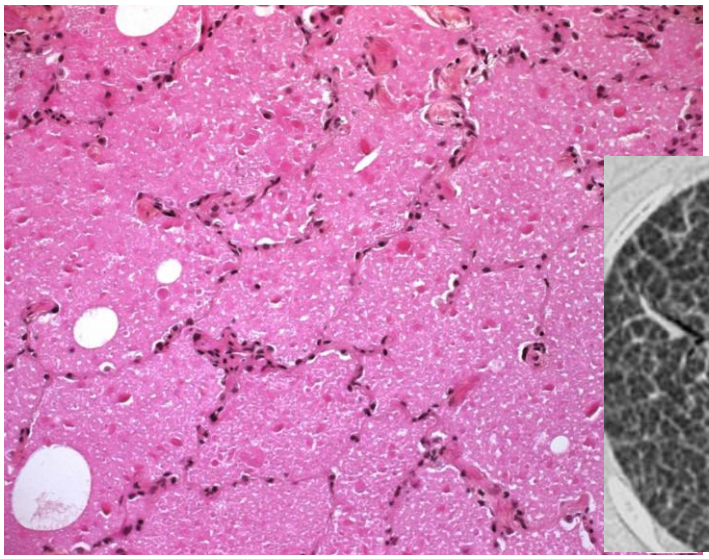
	At time of diagnosis	Before inhaled treprostinil	On inhaled treprostinil	On oral treprostinil	Back on inhaled treprostinil
PAH therapies	Bosentan 62.5 mg every 12 h	Bosentan 125 mg every 12 h & tadalafil 40 mg daily	Bosentan 125 mg every 12 h, tadalafil 40 mg daily & inhaled treprostinil 54 μg 4 times a day	Bosentan 125 mg every 12 h, tadalafil 40 mg daily & selexipag 1400 μg every 12 h	Bosentan 125 mg every 12 h, tadalafil 40 mg daily & inhaled treprostinil 54 μg 4 times a day
NYHA class	III	III	I/II	III	II
6MWT (meters walked & % predicted)	N/A	328 (60%)	379 (69%)	241 (47%)	363 (69%)
Echocardiogram					
TAPSE (mm)	2.3	2.3	3.0	1.3	1.9
RV basal diameter (mm)	3.8	3.1	3.3	4.8	4.3
RVOT notching	Yes	Yes	Yes	Yes	Yes
RVOT AT (ms)	48	72	60	44	55
Tricuspid annular systolic velocity (S') (cm/s)	11	12	14	5	9
RVSP (mmHg)	86	62	38	102	77

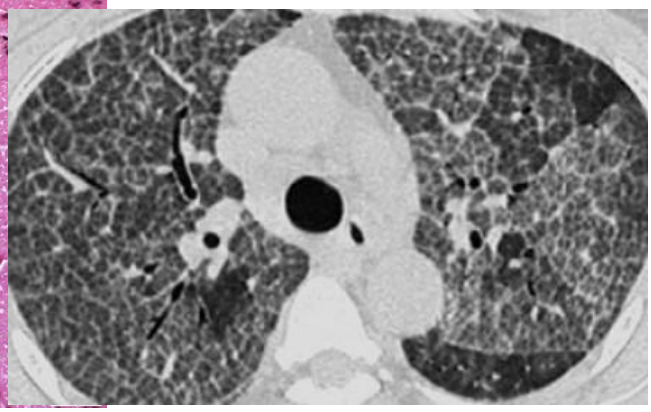


Humbert M, et al. *Circulation* 2014;130:2189-2208.

Figure 1 INOpulse DS-C delivery device and cartridge.
Abbreviation: iNO, inhaled nitric oxide.

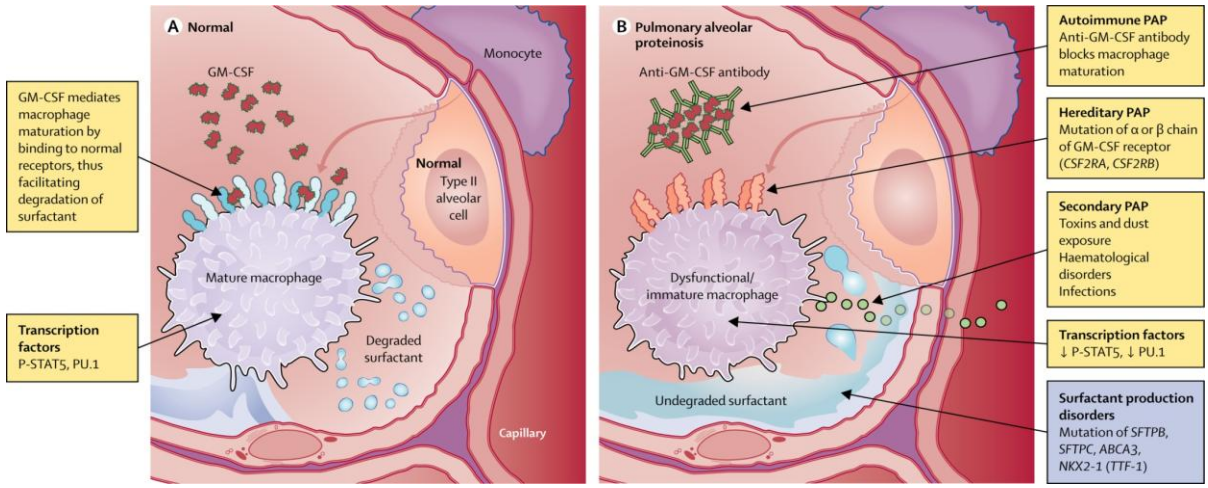
Protéinose alvéolaire





Les différentes formes de PAP

- auto-immune: anti-corps anti GM-CSF
- génétique: mutations des récepteurs CSF2RA and CSF2RB
- congénitales: anomalie du surfactant, plusieurs formes héréditaires ou acquises
- PAP secondaires: toxiques ou hémopathies



Eur Respir J 2006; 27: 585–593
DOI: 10.1183/09031936.06.00058305

Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis

M.E. Wylam, R. Ten, U.B.S. Prakash, H.F. Nadrous, M.L. Clawson and P.M. Anderson

Between 1999 and 2003, 12 patients elected to receive aerosolised GM-CSF (250 microg b.i.d. every other week) in lieu of whole-lung lavage or observation

Of the six patients tested, all had GM-CSF neutralising antibodies

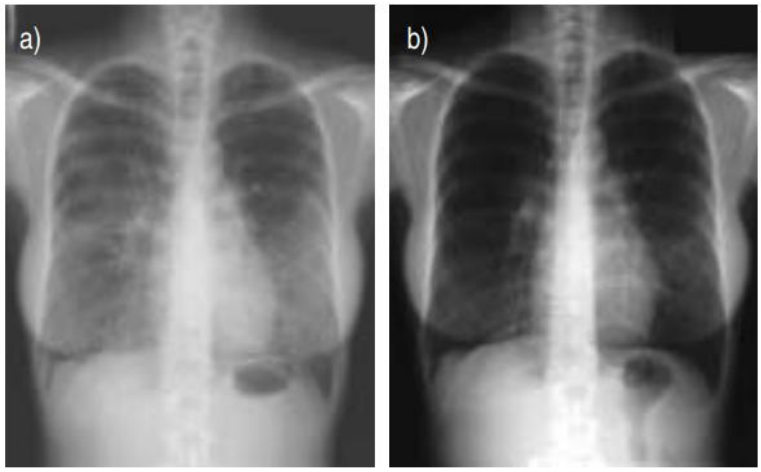
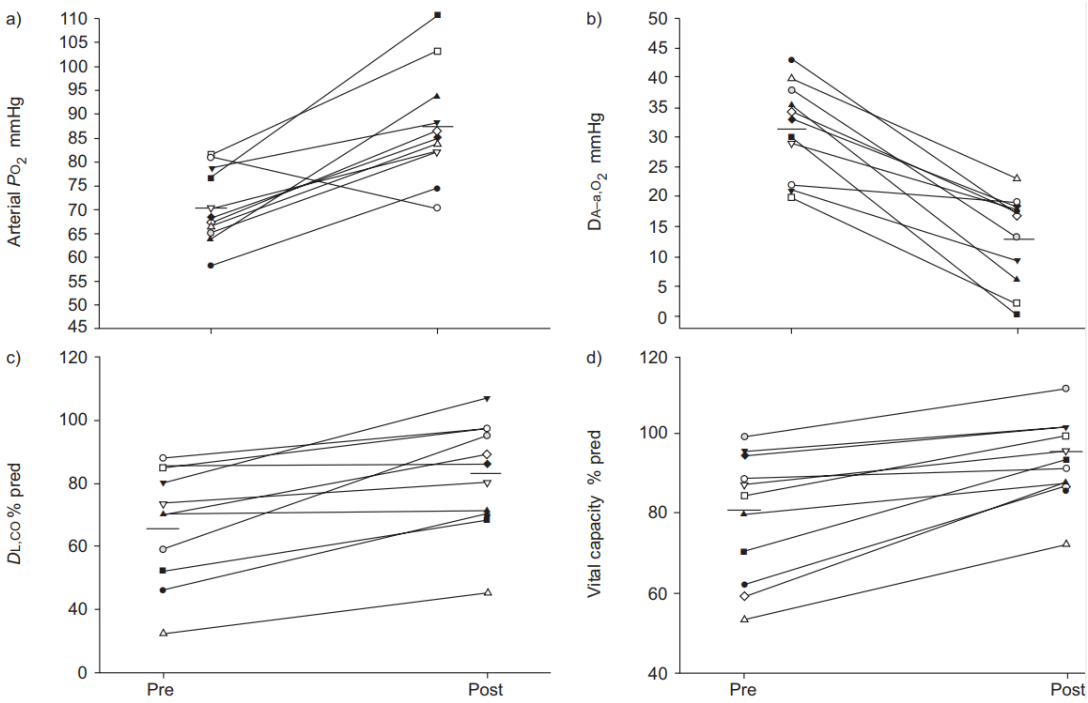
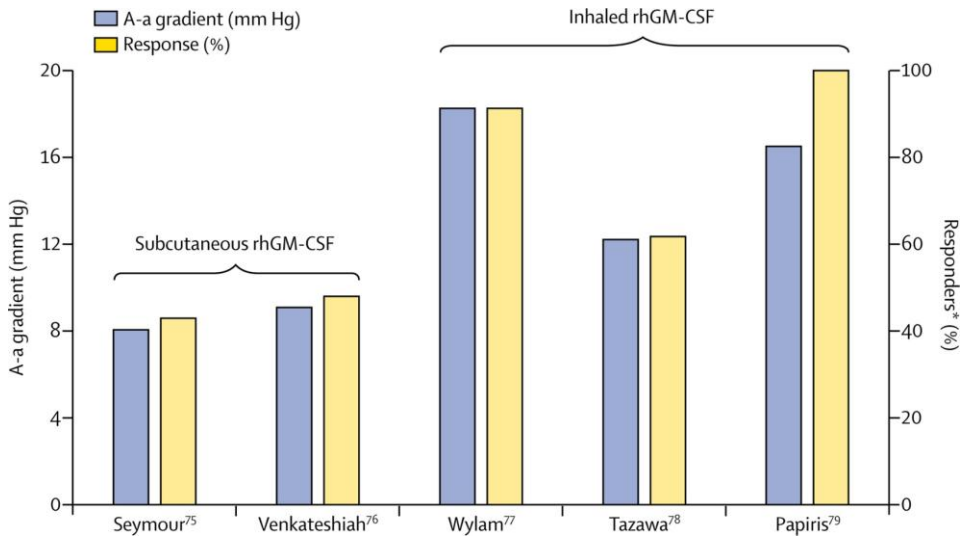
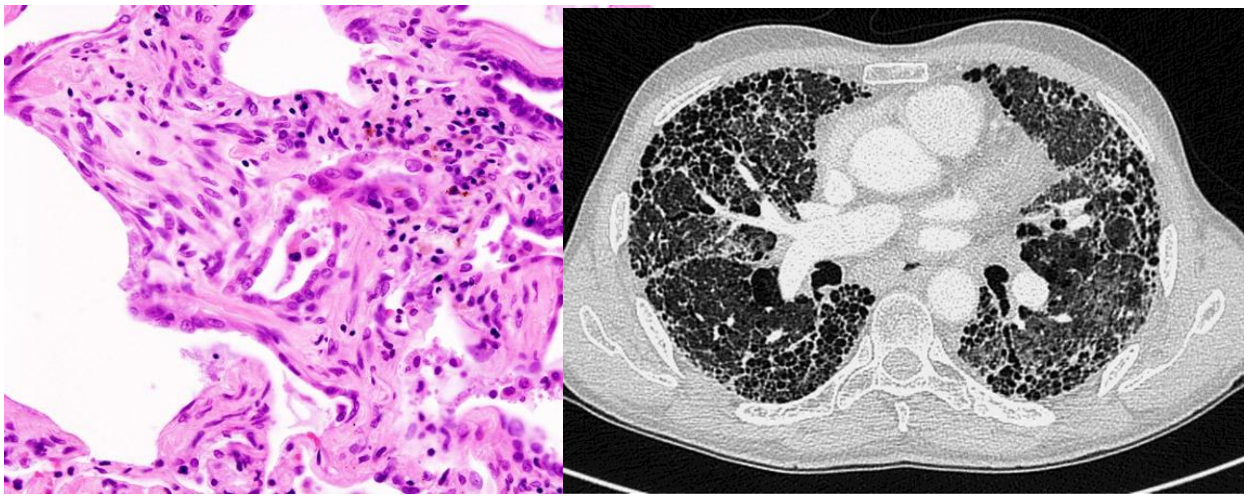


FIGURE 2. Chest radiographs at a) baseline and b) following 12 cycles of aerosolised granulocyte-macrophage colony-stimulating factor (24 weeks) in an index pulmonary alveolar proteinosis case.





Fibrose pulmonaire idiopathique



Traitements inhalés de la fibrose pulmonaire: quel intérêt ?

- Les traitements actuels sont insuffisants et ont des effets secondaires systémiques: troubles digestifs, hépatiques, photosensibilité.
- L'atteinte initiale de la fibrose idiopathique se situe au niveau de l'épithélium alvéolaire-→ accessible aux particules de 1-5 μm

Traitements inhalés de la fibrose pulmonaire

- Traitements validés par voie systémique→ expérimental en inhalation
- Traitements inhalés expérimentaux

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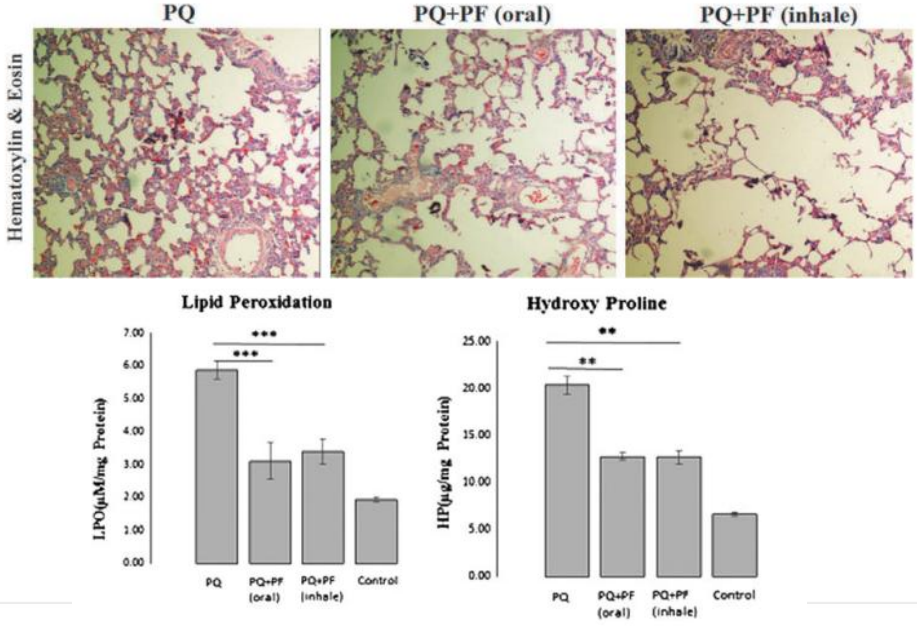
Original Research

Preference of Aerosolized Pirfenidone to Oral Intake: An Experimental Model of Pulmonary Fibrosis by Paraquat

Rokhsana Rasooli, PhD,[1] Hamid Rajaian, PhD,[1] Abbas Pardakhty, PhD,[2] and Ali Mandegary, PhD[2–4]



Fibrose pulmonaire:

Quelques molécules en cours d'investigation

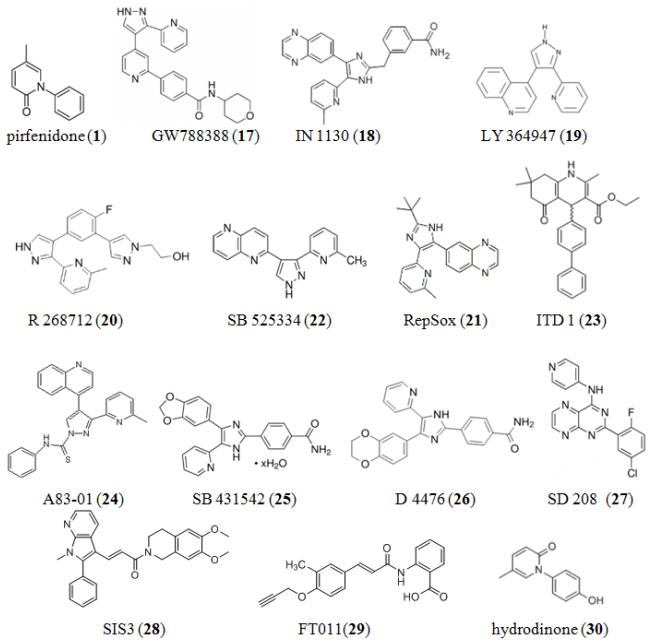
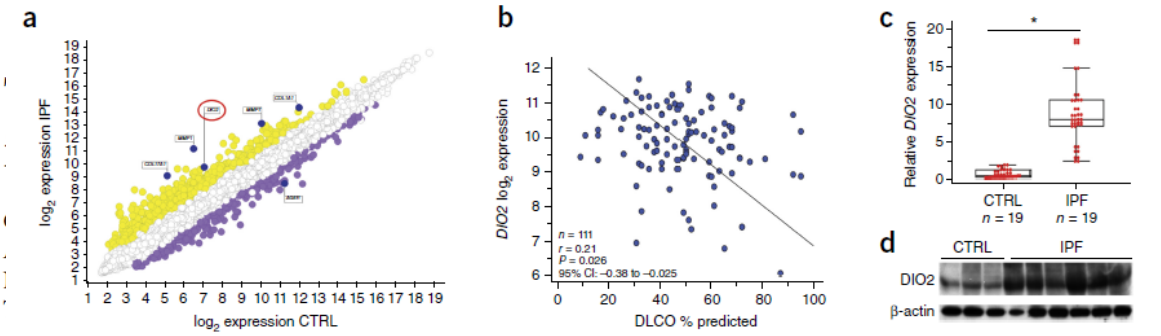


Figure 2. *Examples of inhibitors of the TGF-β signaling.*

Juillerat-Jeanneret L Aubert J-D, Josip M Golshayan D, *submitted*

nature medicine



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Aerosolized T_3 was administered every other day on days 10–20 and mice were sacrificed on day 21

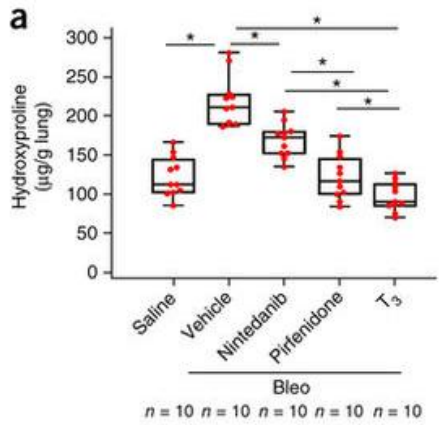
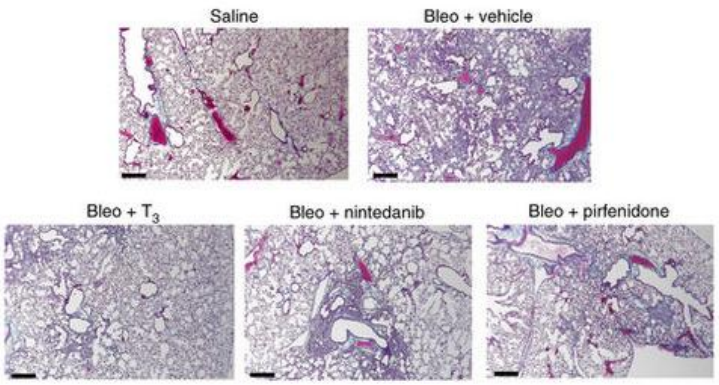


Figure 2 : Aerosolized T_3 blunts established fibrosis in two mouse models of lung fibrosis.

From: Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function



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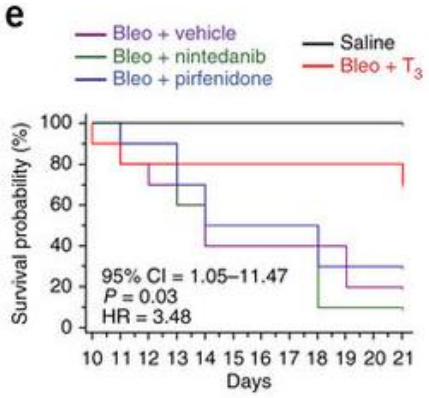

Autres études en cours pour l'IPF

CO inhalé

Inhaled CO is well tolerated and can be safely administered to patients with IPF in the ambulatory setting; however, inhaled CO did not result in significant changes in study end points. Our findings support testing the efficacy of inhaled therapies in future IPF clinical trials.

Galectin-3 Inhibitor :
A Placebo-controlled RCT in HV's Investigating the Safety, Tolerability and PK (Pharmacokinetic) of TD139, a **Galectin-3 Inhibitor**, Followed by an Expansion Cohort Treating Subjects With IPF

Integrin alphaV-beta6 antagonist: GSK3008348 Phase 1

Pour conclure..

- Les pathologies du parenchyme pulmonaire peuvent être une cible pour des traitements en inhalation
- En ce cas les particules doivent être de 1-5 μm
- Le mode d'administration est à considérer si un rapport local/systémique élevé est souhaitable


AeroDawg