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Pirfenidone : l'esperienza italiana

Sergio Harari
U.O. di Pneumologia e UTIR
Servizio di Emodinamica e
Fisiopatologia Respiratoria
Ospedale San Giuseppe - Milano

Safety and efficacy of Pirfenidone in idiopathic pulmonary fibrosis in clinical practice

Studio osservazionale, **monocentrico**, retrospettivo sulla safety e sull'andamento funzionale di 76 pazienti con diagnosi (clinico-radiologica e/o istologica) di IPF prima e dopo terapia con Pirfenidone;

Popolazione e obiettivi dello studio:

Diagnosi clinico-radiologica e/o istologica di IPF;

Malattia di grado lieve-moderato e grave;

Slop di caduta di **FVC** durante 6 mesi di terapia con Pirfenidone, slop di caduta di **DLCO%**, 6MWT (metri), PaO2 e marcatori sierici di IPF (KL-6, SP-D);

Safety del farmaco;

Safety and efficacy of Pirfenidone in idiopathic pulmonary fibrosis in clinical practice, Respiratory Medicine (2013) 107, 1431-1437

Safety and efficacy of Pirfenidone in idiopathic pulmonary fibrosis in clinical practice

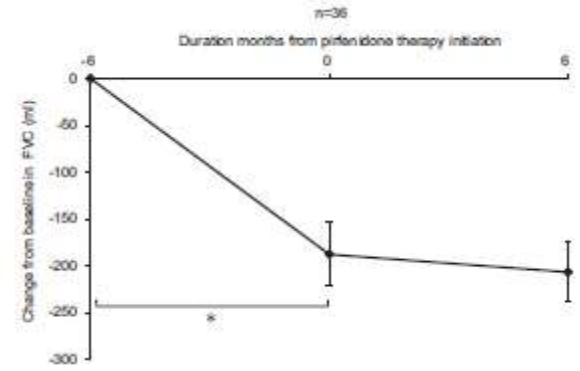

Figure 1 Change from 6 months before therapy in forced vital capacity (FVC). The change in FVC from the baseline value (6 months before initiation of pirfenidone therapy) was −188 mL at initiation of therapy and −207 mL after 6 months of therapy. Paired *t*-test was used. Data are presented as mean ± standard error. •: *p*-value <0.05.

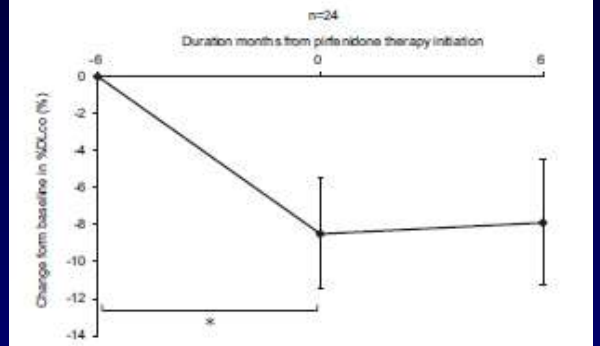

Figure 2 Change in percentage predicted diffusion capacity of the lung for carbon monoxide (%DLco). Change in %DLco from the baseline value (6 months before initiation of pirfenidone therapy) was −8.5% at initiation of therapy and −7.9% after 6 months of pirfenidone therapy. Paired *t*-test was used. Data are presented as mean ± standard error. *: *p*-value <0.05.

Table 6 Comparison of 6-min walk test results.

6MWT	*n*	Initiation of therapy	*n*	6 months after therapy	*p*-Value
Mini SpO_2 (%)	33	86 ± 1	20	88 ± 1	0.399
Distance (m)	29	342 ± 21	13	383 ± 32	0.143

6MWT: 6-min walk test; SpO_2: oxygen saturation measured by pulse oximetry. Data are presented as mean ± standard error.

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Table 4 FVC decline in subpopulations characterized by %FVC and by change in FVC before therapy.

%FVC at initiation of therapy	*n*	Mean change in FVC for 6 months before therapy (ml)	Mean change in FVC for 6 months after therapy (ml)	*p*-Value
%FVC ≥80	4	−60 ± 96	−80 ± 69	0.840
80> %FVC ≥70	11	−130 ± 58	20 ± 70	0.282
70> %FVC ≥60	10	−210 ± 44	−60 ± 63	0.156
60> %FVC	11	−280 ± 72	−80 ± 55	0.074
Decline in FVC for 6 months before therapy	***n***	**Mean change in FVC for 6 months before therapy (ml)**	**Mean change in FVC for 6 months after therapy (ml)**	***p*-Value**
≥150 ml	16	−350 ± 48	30 ± 58	<0.001
<150 mL	20	−60 ± 20	−100 ± 31	0.274

Paired *t*-test was performed. Values are given as mean ± standard error.

Pirfenidone was well-tolerated and had beneficial effects in patients with mild-to-severe and/or progressive IPF.

The degree of disease progression prior to the initiation of pirfenidone therapy had an impact on the response to the therapy.

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Clinical Experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis

Studio osservazionale, prospettico, **monocentrico**;

Popolazione:

- Pazienti (n = 45) con **diagnosi** clinico-radiologica e/o istologica di IPF;
- Paziente con **malattia lieve-moderata**;
- Valutazione di prove funzionali (VC e TLC), DLCO, e emogasanalisi 6 mesi prima dell'introduzione del farmaco e al termine della terapia;

Obiettivi dello studio:

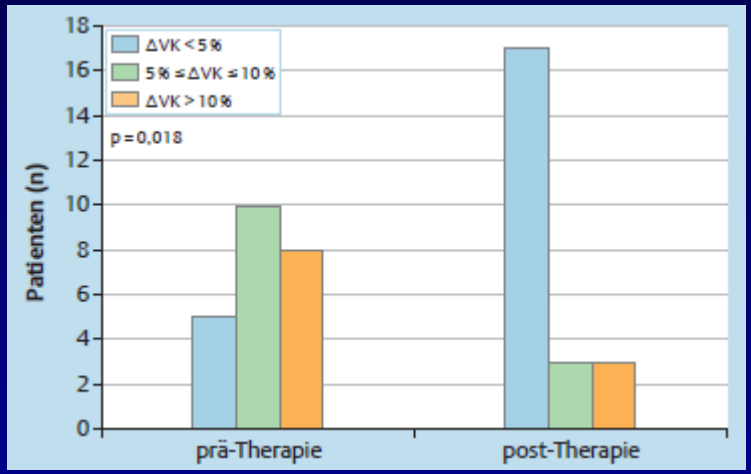
- Valutazione della stabilità di malattia VS progressione (stabilità= riduzione della CV <5% del predetto e della DLCO<10% del predetto in assenza di progressione clinica e radiologica nei 3-6mesi di osservazione successivi all'introduzione del farmaco);
- Valutazione effetti collaterali della terapia;

Clinical Experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis
German Medical weekly, 2013; 138: 518-523

Clinical Experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis

Treatment of idiopathic pulmonary fibrosis (IPF) before the beginning of treatment with pirfenidone (top) and combination treatment with pirfenidone (below).

Treatment of IPF before pirfenidone administration	
None	18 (40%)
Study drug *	5 (11%)
NAC (monotherapy)**	3 (7%)
Steroids (monotherapy)***	4 (9%)
NAC** + steroids ***	4 (9%)
Azathiprine + NAC** + steroids***	11 (24%)
IPF treatment with pirfenidone	
pirfenidone alone	16 (35%)
pirfenidone + steroids***	7 (16%)
pirfenidone + NAC**	6 (13%)
pirfenidone + NAC** + steroids***	16 (35%)
* 3 patients were treated with triple kinase inhibitors, and 2 patients with anti-CCL-2 monoclonal antibodies ** 1800 mg/d *** 5-15 mg/d	



Category reduction in vital capacity (VK) 6 months before and after start of treatment with pirfenidone in 23 patients. Calculation of significance using the McNemar test.

Clinical Experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis German Medical weekly, 2013; 138: 518-523

Clinical Experience with pirfenidone for the treatment of idiopathic pulmonary fibrosis

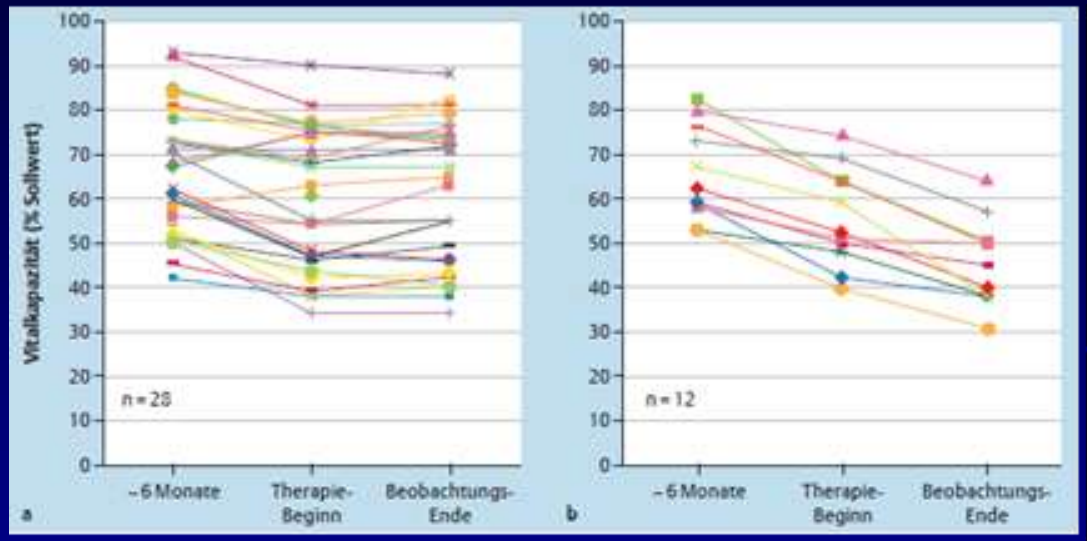


Figure 1. Course of vital capacity (VK) before and after the start of treatment with pirfenidone in patients with a stable status (**a**) and progression (**b**) under pirfenidone

Legend:
Y-axis: Vital capacity (% of target value)
X axis: 6 months, Treatment start, End of observation period (repeated 2 times)

At the end of the observation period, 28 of the 40 patients with treatment duration greater than three months (70%) showed stable findings. Altogether, side effects occurred in 26 patients (58%); the most frequent (n = 17 (38%)) were of a gastrointestinal nature. Pirfenidone was discontinued in 6 patients (13%) due to side effects. The median survival time after the beginning of treatment was 3.8 years.

German Medical weekly, 2013; 138: 518-523

Cosa è e cosa non è NPP
Named Patient Access Program di Pirfenidone

- E' un programma che è stato supportato da InterMune a livello Europeo: Italia, UK, Germania , Spagna ,Grecia, Irlanda, Olanda, Austria, Belgio , Svezia, Repubblica Ceca, Svizzera, Finlandia, Polonia, Malta.

- L'arruolamento di pazienti è stato aperto in Italia nel Settembre 2011 e si è chiuso nel Settembre 2012. Il farmaco è stato però erogato fino al Giugno 2013 ai pazienti che risultavano in trattamento al 30 Settembre 2012

- NPP non è stato uno studio clinico

Cosa è e cosa non è NPP

- Obiettivo dell'NPP Pirfenidone è stato mettere immediatamente a disposizione dei pazienti affetti da IPF il primo farmaco approvato dall'Autorità Regolatoria Europea (EMA) nel trattamento della malattia

- Per essere arruolabili, i pazienti dovevano possedere specifiche caratteristiche cliniche, in linea con l'indicazione approvata da EMA (pazienti adulti, con malattia di grado da lieve a moderato)

- Il farmaco veniva fornito su richiesta dello specialista esperto nella diagnosi e nel trattamento dell'IPF il quale assumeva piena responsabilità nella gestione del paziente

36 CENTRI IN ITALIA HANNO ATTIVATO NPP

Center	PI		Center	PI
Trieste	Confalonieri		Milano	Amaducci
Forlí	Poletti		Foggia	Foschino
Monza	Pesci		Benevento	Del Donno
Catania	Vancheri		Parma	Bertorelli
Padova	Agostini		Pisa	Paggiaro
Modena	Richeldi		Padova	Balestro
Napoli	Sanduzzi		Palermo	Di Gesú
Roma	Saltini		Roma	Valente
Siena	Rottoli		Sassari	Fois
Milano	Harari		Milano	Centanni
Orbassano	Albera		Reggio Emilia	Carbonelli
Palermo	Vitulo		Milano	de Juli
Napoli	Stanziola		Catania	di Maria
Pisa	Palla		Teramo	di Re
L'Aquila	Donati		Busto Arsizio	Berra
Roma	Sebastiani		Ascoli Piceno	Pela
Palermo	Ferrara		Chieti	Marinari
Brescia	Tantucci		Brescia	Tassi

Efficacy of Pirfenidone for Idiopathic Pulmonary Fibrosis: an Italian real life study

Sergio Harari, Valeria Giunta, Carlo Albera, Carlo Vancheri, Venerino Poletti, Alberto Pesci, Fabrizio Luppi, Cesare Saltini, Carlo Agostini, Paola Rottoli, Alfredo Sebastiani, Alessandro Sanduzzi, Antonella Caminati, Rossana Della Porta, Gian Piero Bandelli, Silvia Puglisi, Sara Tomassetti, Alice Biffi, Stefania Cerri, Alessia Mari, Francesco Cinetto, Francesca Tirelli, Gianfranco Farinelli, Marialuisa Bocchino, and Marco Confalonieri

From clinical trial to real life: an italian experience

- Population:
  - Diagnosis: confirmed by HRCT UIP pattern and/or surgical lung biopsy (according to 2011 IPF guidelines);
  - Mild /moderate and severe stage disease
  - Availability of functional follow-up data at least 6 months before and at least 6 months after starting Pirfenidone therapy

Design of the study

- Each subject is control of himself;
- The time (at least six months) before starting pirfenidone have the role of control period;
- Each subject is monitored in a period before the assumption of the drug and in the period after;
- Baseline conditions for each period can be defined using functional evaluation at the beginning of each period, i.e. 6 months before the initiation of the therapy and at the initiation itself.

Periodo di osservazione (in mesi) prima e dopo introduzione di Pirfenidone	N pazienti (%)
Pre compreso fra 6 e 12 mesi e post compreso fra 6 e 12 mesi	28 (21.5)
Pre compreso fra 6 e 12 mesi e post maggiore di 12 mesi	32 (24.6)
Pre maggiore di 12 mesi e post compreso fra 6 e 12 mesi	29 (22.3)
Pre maggiore di 12 mesi e post maggiore di 12 mesi	41 (31.5)

Objectives

- Primary End-point:
  - Evaluation of the slope of decline of FVC before and after starting Pirfenidone therapy;
- Secondary End-points:
  - Distance walked 6MWT;
- Data have been analyzed using a regression statistical model built using available data points

Table 1. Patients' characteristics at baseline – first pirfenidone prescription (N=128)

Variable	Levels	N (%)
Center	Catania	14 (10.9)
	Forlì	13 (10.2)
	Milano	12 (9.4)
	Modena	9 (7.0)
	Monza	9 (7.0)
	Napoli	2 (1.6)
	Padova	7 (5.5)
	Roma Saltini	8 (6.3)
	Roma Sebastiani	5 (3.9)
	Siena	6 (4.7)
	Torino	18 (14.1)
	Trieste	25 (19.5)
Gender	Female	32 (25.0)
	Male	96 (75.0)

Variable	Levels	N (%)
Age at baseline (years)*	<=60	17 (13.3)
	61-65	20 (15.6)
	65+	91 (71.1)
Smoking status	Ex-smoker	97 (75.8)
	Non smoker	27 (21.1)
	Smoker	4 (3.1)
Histological diagnosis	No	96 (75.0)
	Yes	32 (25.0)
Clinical/Radiological diagnosis	Uncertain	20 (15.6)
	No	3 (2.3)
	Yes	105 (82.0)
Cortisone	No	53 (41.4)
	Yes	75 (58.6)
Azathioprine	No	97 (75.8)
	Yes	31 (24.2)
N-Acetylcysteine	No	75 (58.6)
	Yes	53 (41.4)

*Mean age 69 years SD 7 years

Table 1. Patients' characteristics at baseline – first pirfenidone prescription (N=128)

- Population is mainly composed by male patients (75 %);
- Age has been evaluated at baseline, i.e. at starting Pirfenidone (and not at the time of diagnosis of IPF).
- 41 (31 %) pts had more than one year of f.u. before and after starting therapy
- Cortisone, azathioprine, N-acetyl cysteine were the drugs used before pirfenidone therapy . Only cortisone has been, in some cases, associated with Pirfenidone.

Table 2. PFTs and 6MWT distance at baseline (first pirfenidone prescription)

	N	Mean (SD)	Min-Max
FVC	128	2.50 (0.70)	1.02-4.80
FVC %	128	0.75 (0.18)	0.35-1.43
FEV1	119	2.10 (0.57)	0.96-4.87
FEV1 %	119	0.80 (0.18)	0.35-1.31
DLCO	120	11.33 (4.02)	1.52-26.40
DLCO %	120	0.47 (0.15)	0.17-1.20
Distance (m)	93	401 (118)	100-750

Changes in the PFTs -All patients (N=128)

Parameter	Time	Mean* (95% CI)	% change**	Difference in % changes	p-value***
FVC %	1-yr before	0.81 (0.77, 0.84)	-	-	
	baseline	0.75 (0.72, 0.78)	-7.4%	-	
	1-yr after	0.73 (0.70, 0.77)	-2.7%	4.7%	0.049

*based on predicted values at 1-yr before, at baseline and at 1-yr after estimated from a linear mixed model [**here model details**]

** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1yr after-baseline)/(baseline)

*** based on the null hypothesis beta2=0 [**second trend component: here model details**]

Analisi preliminare distanza percorsa al test del cammino

In questa analisi preliminare abbiamo preso in considerazione solo i dati di 23 pazienti che avevano tutti i test del cammino disponibili ai diversi tempi e li avevano effettuati tutti in AA.

Paziente	Dist. Prima visita	Distanza baseline	Dist. ultima visita	Trend pre	Trend post
2005	540	512	510	-5,19%	-0,39%
2006	540	491	533	-9,07%	8,55%
2007	560	544	491	-2,86%	-9,74%
2008	420	386	438	-8,10%	13,47%
2009	524	523	532	-0,19%	1,72%
2012	590	629	598	6,61%	-4,93%
2015	450	460	455	2,22%	-1,09%
2016	470	476	429	1,28%	-9,87%
2021	430	421	466	-2,09%	10,69%
2023	380	380	370	0,00%	-2,63%
2025	630	612	625	-2,86%	2,12%
2026	410	385	460	-6,10%	19,48%
2028	430	415	400	-3,49%	-3,61%
3006	475	445	450	-6,32%	1,12%
5001	450	420	460	-6,67%	9,52%
8002	550	490	520	-10,91%	6,12%
8003	475	350	485	-26,32%	38,57%
8011	400	400	400	0,00%	0,00%
9001	360	360	360	0,00%	0,00%
9007	420	450	520	7,14%	15,56%
9018	450	450	460	0,00%	2,22%
11003	420	400	360	-4,76%	-10,00%
11008	400	320	360	-20,00%	12,50%
23	**468,4347826**	**448,6521739**	**464,4347826**	**-4,25%**	**4,32%**
(conteggio)	(media)	(media)	(media)	(media)	(media)

L’introduzione del farmaco determina una inversione del trend negativo sulla distanza percorsa che migliora

Table 7. Changes in the PFTs, 6MWT distance and GAP index, by stage (I vs II/III) (1/2)

	Predictor	N (%)	Median, (Min-Max)
P - Physiology	FVC %		
	>=0.75	60 (46.9)	
	0.50-0.75	65 (50.8)	
	<0.50	3 (2.3)	
	DLCO %		
	>0.55	26 (20.3)	
	0.36-0.55	75 (58.6)	
	<=0.35	19 (14.8)	
	missing	8 (6.3)	

Further analysis has been performed splitting the population in the following two sub-groups:

- FVC >= 0.75
- FVC <0.75

Changes in the PFTs, 6MWT distance and GAP index, by FVC % group at baseline (>0.75 vs <=0.75)

		FVC% >0.75 at baseline			FVC% <=0.75 at baseline		
Parameter	Time	Mean* (95% CI)	%change**	Difference in % change	Mean* (95% CI)	%change**	Difference in % change
FVC %	1-yr before	0.92 (0.88, 0.96)	-	-	0.71 (0.67, 0.74)	-	-
	baseline	0.91 (0.88, 0.94)	-1.1%	-	0.61 (0.59, 0.64)	-14.1%	-
	1-yr after	0.88 (0.84, 0.91)	-3.3%	-2.2%	0.61 (0.57, 0.64)	0.0%	14.1%
p-value for homegeneity of difference in % changes between strata***							0.002

*based on predicted values at 1yr before, at baseline and at 1yr after estimated from a linear mixed model [**here model details**]
** first % change reported: (baseline-1yr before)/(1yr before); second % change reported: (1yr after-baseline)/(baseline)
*** based on the null hypothesis beta5=0 **[interaction between second trend component and strata: here model details]**

Conclusions

- In the general population:
  - The drug reduces the slope of decrease of FVC% and distance walked during 6MWT
  - The effect was evident in all the population but more evident in pts < 75%
  - Some patients showed improvements in FVC

    (FVC > 10% - n = 20 – 4 biopsy proven)