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Real-life experience of inhaled iloprost for patients with pulmonary arterial hypertension: Insights from the Spanish REHAP registry

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ABSTRACT

Introduction: REHAP is a voluntary, observational Spanish registry of patients with pulmonary arterial hypertension. We analyzed the experience (use and effectiveness) with inhaled iloprost (inh-ILO) in real-life conditions during a 3-year period.
Methods: Patients included were those with PAH ≥14 years recruited during 1998–2016 who had received inh-ILO. Variables were collected at the beginning of treatment (0 ± 3 months) and 12 ± 3/36 ± 6 months follow-up. Effectiveness was assessed in the intent-to-treat population as changes in functional class and/or physical performance and transplant-free survival from the beginning of treatment. Stopping inh-ILO-related survival was also assessed. Subanalyses included treatment strategy (first-line therapy –monotherapy or upfront combination- or sequential therapy) and risk of clinical worsening/death.
Results: Inh-ILO was the most frequently used prostanoid in Spain, rendering 267 patients eligible for analysis. Median age was 54 years; 61% were WHO FC III. Sixty (23%) patients started inh-ILO as monotherapy, 27 (10%) as upfront combination and 180 (67%) sequentially. At 3-year follow-up significant clinical improvements were observed; however, transplant-free survival rate was 54%, being poorer in patients at high risk (63% vs. 85% in low risk patients; $P < 0.001$) and similar in the three treatment strategies. Only 25% patients remained on inh-ILO. Three-year after stopping inh-ILO-related survival rate was 24.7%.
Conclusion: Data from the REHAP collected during 3 years shows that inh-ILO has low effectiveness independently of the treatment strategy used, with a 3-year survival rate of 54% despite significant clinical improvements, probably due to the use in high-risk patients. Discontinuation rate was as high as 75%.

1. Introduction

Patients with pulmonary arterial hypertension (PAH) have been shown to present dysregulation of the prostacyclin metabolic pathway [1]. This prostaglandin, which derives from arachidonic acid, mediates vasodilatory effects on pulmonary arteries as well as the inhibition of

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[1] REHAP: Registro Español de Hipertensión Arterial Pulmonar (Spanish Registry of Pulmonary Arterial Hypertension).
[2] A full list of REHAP investigators is given in the appendix.

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vascular smooth muscle cell proliferation and of platelet aggregation [2]. Given the important role the decrease of prostacyclin plays in the pathogenesis of PAH [2,3], the so-called "prostacyclin pathway" is one of the three main targets of current PAH treatments [2]. To date, the prostanoid epoprostenol or its analogues iloprost and treprostinil –and to a lesser extent beraprost, which is not licensed in all countries- have been the only treatments to target this pathway [1,2]. These drugs are recommended for patients with advanced PAH (functional class [FC] III-IV according to the World Health Organization [WHO] [1]. Despite the clinical evidence supporting their therapeutic potential, the use of these prostanoids in the clinical practice has been limited due to a number of shortcomings, with adverse effects and complications derived from the method of drug delivery being the main concerns [2].

As of mid-2017, three prostanoids with different routes of administration were licensed for the treatment of PAH in Spain: iloprost (inhaled), epoprostenol (intravenous) and treprostinil (subcutaneous). Of these, the inhaled way of delivering iloprost presents inherent advantages over intravenous or subcutaneous administration, such as the potential for selective delivery of the drug to the pulmonary circulation, ease of administration and lack of potential adverse events associated to the administration route, with only limited side effects due to targeted delivery [2,3]. Inhaled iloprost (inh-ILO) has demonstrated to be effective and to have a favourable safety profile in patients with PAH who are World Health Organization (WHO) FC III and IV, either as monotherapy [4] or in combination with endothelin receptor antagonists [ERA] or phosphodiesterase 5 inhibitors [PDE-5i] [5–8]. Long-term (up to 5 years), open-label studies have supported the long-term clinical benefit from continued therapy with inh-ILO as monotherapy in patients with PAH [9–11].

Since it became available in the first years of the 21st century, iloprost has emerged as a major strategy in the treatment of PAH. However, the fact that it has to be inhaled 6–9 times a day owing to its short half-life may affect adherence. There is a paucity of evidence regarding the effectiveness of inh-ILO in clinical practice. This evidence would help to understand the role of inh-ILO in the management of patients with PAH, especially as selexipag, a new orally active, first-in-class, selective prostacyclin I2 receptor agonist, has recently become available.

We collected data from PAH patients included in the REHAP, a voluntary, observational Spanish registry of PAH patients which was created in 2007 [12], with the objective of analyzing the experience with inh-ILO in terms of use and effectiveness in real-life conditions during a 3-year period. Subanalyses were performed to evaluate treatment strategy (first-line therapy –monotherapy or upfront combination therapy concomitantly with an ERA or PDE-5i - or as sequential therapy after an ERA or PDE-5i) and risk of clinical worsening or death of the patients.

2. Methods

2.1. Study subjects

Patients included in this analysis were PAH patients who were enrolled in the REHAP registry between January 1, 1998 and December 31, 2016 and had received inh-ILO as first-line therapy, either monotherapy or as upfront combination therapy (i.e. concomitantly with other PAH treatments such as ERA or PDE-5i), or as sequential therapy (i.e. added-on to treatment with ERA or PDE-5i). Patients diagnosed in the period 1998–2006 were entered retrospectively, and prospectively thereafter. The REHAP registry study design, patient inclusion criteria and data collection have been previously described [12]. Briefly, patients included were those with newly or previously diagnosed pulmonary hypertension (PH) ≥14 years of age. PAH patients had to meet the modified definition of PAH [13] and pre-specified hemodynamic criteria assessed by right heart catheterization (RHC): mean pulmonary artery pressure (mPAP) ≥25 mmHg, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mmHg and pulmonary vascular resistance (PVR) ≥3 units [1]. Patients with evidence of left heart disease or respiratory disease (pulmonary capillary wedge pressure or left ventricular end-diastolic pressure > 15 mmHg), those classified as Group 1′ or for whom there was a lack of data on the beginning of treatment with iloprost were excluded. Diagnosis of PH type and specific PAH subtype was assigned by the investigators. Other types of pre-capillary PH were also excluded on the basis of forced expiratory volume in the 1st second (FEV_1) and forced vital capacity (FVC) (Group III) and ventilation-perfusion (VQ) scan (Group IV). The REHAP registry gathers data on patients from 31 hospitals (both PH-specialized centres and general hospitals who were willing to participate) from 15 of the 17 administrative regions of Spain.

2.2. Information collected

Demographic (age, sex), hemodynamic (cardiac output, PVR, mPAP and right atrial pressure [RAP]) and clinical variables (WHO FC and the 6-minute walking test [6MWT]) were collected during routine clinical practice at the beginning of the treatment with inh-ILO (0 ± 3 months), at 12 ± 3 months and 36 ± 6 months follow-up. Variables were subjected to quality testing prior to analysis.

2.3. Outcome variables

Effectiveness was assessed in the intention-to-treat (ITT) population as changes in FC and/or physical performance and as transplant-free survival (defined as non-occurrence of death or transplantation). Stop inh-ILO-related survival (defined as non-occurrence of inh-ILO withdrawal for any reason, including death or transplantation) was also assessed.

2.4. Statistical analysis

Continuous variables are expressed as mean (standard deviation [SD]) / median (first and third quartiles [Q1;Q3]) and compared using the paired *t*-test or the Kruskal-Wallis test. Categorical variables are expressed as n (%) and compared using the Chi-square test or Fisher's exact test. Patients undergoing transplantation or lost for follow-up were censored, the latter at the date of their last visit. The study entry date was defined as the date on which treatment with inh-ILO was started. Patients were followed-up until the censoring date, June 1, 2017 or the date of transplantation or death.

Overall change (delta value) was calculated for the WHO FC and the 6MWT. Kaplan-Meier survival curves were constructed to assess cumulative transplant-free and stop inh-ILO-related survival rates from the beginning of treatment in the ITT population. Two subanalyses were performed according to the place of iloprost in the treatment sequence (first-line, either as monotherapy or as upfront combination with ERAs and/or PDE-5i, or sequential, on top of these treatments) and the risk for clinical worsening or patient's death ("high risk" defined as WHO FC IV or 6MWT <165 m and "low risk" defined as WHO FC ≤ III and 6MWT >165 m) [1]. A value of 50 m was assigned to those patients who were unable to perform the 6MWD test. The log-rank test was used to compare the transplant-free survival rates. All statistics were performed using SPSS v.17 (SPSS Inc., Chicago, IL, USA). A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Study population

As of December 31, 2016 there were 2829 patients with PH enrolled in the REHAP registry. Of these, 664 (34.1%) had received a prostanoid, of which inh-ILO was the most frequent (58%, n = 376). A total of 267 patients with PAH who had been treated with inh-ILO were eligible for analysis (see Fig. 1 at the Supplemental Materials section, available at the online version). The most common PAH etiologies were idiopathic (34%) and associated with connective tissue disease (25%) followed by congenital heart disease (14%), portal hypertension (14%), human immunodeficiency virus (HIV) (7%), the combination of portal hypertension and HIV (6%) and toxic oil syndrome (2%). Median (Q1;Q3) time between diagnosis and treatment with inh-ILO was 8 (0.5;25.7) months.

Patients' characteristics at the time of starting treatment with inh-ILO are shown in Table 1. Median (Q1;Q3) age was 54 (43;67) years and 71% were women. The most frequent functional class was WHO FC III (61%). Median (Q1;Q3) values of hemodynamic parameters were: cardiac output 4.0 (3.1;5.2) L/min, PVR 11.3 (7.3;15.6) Wood units, mPAP 55 (46;64) mmHg and RAP 10 (6;16) mmHg. Inh-ILO was started as first-line treatment in 87 (33%) patients –as monotherapy in 60 (23%) and as upfront combination therapy in 27 (10%)- and introduced sequentially in 180 (67%) patients (Table 1). Most frequent upfront combination was inh-ILO + PDE-5i, while inh-ILO + PDE-5i + ERA was the most common combination treatment when inh-ILO was added sequentially (Table 2). One hundred forty-seven patients (55%) received standard therapy with diuretics and 100 (38%) with oxygen.

3.2. Clinical and hemodynamic changes and transplant-free survival in the overall population

At 12 months, 63 patients (24%) died, 4 (2%) underwent pulmonary transplantation, 39 (15%) lacked a WHO FC and 6MWT follow-up registration at this time and 4 (2%) were lost for follow-up. Data was thus available for 157 (58.8%) patients. Of these, 120 (45% of the initial

Table 1
Patients' demographic, clinical and hemodynamic characteristics at the time of starting inh-ILO and after 12 and 36 months.

	Month 0 ± 3 (n = 267)		Month 12 ± 3 (n = 157)			Month 36 ± 6 (n = 97)		
Variable	N	Value	N	Value	*P*-value Δ	N	Value	*P*-value Δ
Age, years, median (Q1;Q3)	267	54 (43;67)	157	53 (40;63)	–	97	52 (40;62)	–
Sex, men, n (%)	267	77 (29)	157	45 (29)	–	97	24 (25)	–
WHO FC, n (%)	267		110			82		
I-II		67 (25)		69 (63)	<**0.001**		50 (61)	<**0.001**
III		162 (61)		39 (36)	<**0.001**		28 (34)	<**0.001**
IV		38 (14)		2 (2)	**0.034**		4 (5)	**0.004**
6MWT, m, median (Q1;Q3)	222	329 (184;435)	78	417 (310;488)	0.204	67	411 (310;478)	**0.006**
Treatment strategy with inh-ILO, n (%)	267		–	–	–	–	–	
First-line:								
Monotherapy		60 (23)						
Dual upfront combination (+ PDE5i or ERA)		25 (9)						
Triple upfront combination (+ PDE5i and ERA)		2 (1)						
Sequential:								
Monotherapy[a]		7 (3)						
Dual (after PDE5i or ERA)		81 (30)						
Triple (after PDE5i and ERA)		92 (34)						
Supportive treatment, n (%)	267		–	–	–	–	–	–
Diuretics		147 (55)						
Oxygen		100 (38)						
Changes in the treatment with inh-ILO, n (%)[b]			157		–	97		
Still on inh-ILO		–		120 (45)			65 (24)	
No changes		–		109 (41)			42 (16)	
Oral treatment (PDE5i or ERA) is added		–		11 (4)			23 (9)	
Switch to other prostanoid (i.v. or s.c.)		–		12 (5)			14 (5)	
Other change				25 (9)			18 (7)	

ERA, endothelin receptor antagonist; i.v., intravenous; mPAP, mean pulmonary arterial pressure; PDE5i, phosphodiesterase 5 inhibitors; PVR, pulmonary vascular resistance; Q1;Q3, quartiles 1 and 3; RAP, right atrial pressure; s.c., subcutaneous; WHO FC, World Health Organization functional class; 6MWT, 6-minute walking test. Significant differences are indicated in bold.
[a] Seven patients switched to iloprost and were not being administered PDE5i or ERA.
[b] Percentages are given for the initial population (n = 267).

population) patients continued the initial therapy with inh-ILO. Significant improvements were observed in WHO FC, but not in physical performance (Table 1).

At 36 months, 99 (30%) patients died and 10 (4%) patients underwent pulmonary transplantation. WHO FC and 6MWT follow-up assessment was missing in 57 (21%) patients. Data was thus available

Table 2
Patient demographic, clinical and hemodynamic characteristics at the time of starting inh-ILO according to its place in the treatment sequence.

		First-line		Sequential (n = 180)	P-value		
Variable	n	Monotherapy (n = 60)	Upfront (n = 27)		M vs. U vs. S	M vs. U	M vs. S
Age, years, median (Q1;Q3)	267	52 (44;62)	46 (34;59)	56 (43;69)	**0.020**	0.289	**0.056**
Sex, men, n (%)	267	20 (33)	9 (33)	48 (27)	0.530	1.000	0.326
WHO FC, n (%)							
I-II	267	15 (25)	6 (22)	46 (26)	0.933	1.000	1.000
III	267	39 (65)	12 (44)	111 (62)	0.172	0.100	0.758
IV	267	6 (10)	9 (33)	22 (12)	**0.010**	**0.013**	0.654
6MWT, m, median (Q1;Q3)	222	386 (218;457)	350 (260;403)	320 (160;426)	0.416	0.525	0.207
Hemodynamics, median (Q1;Q3)							
Cardiac output, L/min	141	4.4 (3.3;5.7)	3.3 (2.6;4.4)	4.0 (3.3;5.2)	**0.013**	**0.006**	0.382
PVR, Wood units	115	9.5 (6.2;12.9)	14.4 (11.5;18.4)	11.6 (7.5;14.7)	**0.002**	<**0.001**	0.052
mPAP, mmHg	141	50 (45;57)	60 (47;73)	57 (48;65)	**0.034**	**0.029**	**0.033**
RAP, mmHg	137	10 (6;14)	125 (8;16)	9 (6;16)	0.267	0.112	0.286
PCP	134	9 (7;14)	12 (7;13)	10 (9;14)	0.518	0.760	0.223
Time between diagnosis and starting iloprost, months, median (Q1;Q3)	267	0.4 (0.0;2.2)	0.0 (0.0;0.7)	17,5 (4,7;43,6)	<**0.001**	0.112	<**0.001**
Treatment strategy with inh-ILO, n (%)	267				–	–	–
First-line:							
Monotherapy		60 (100)	–	7 (4)[a]			
Dual upfront combination (+ PDE5i or ERA)		–	25 (93)	–			
Triple upfront combination (+ PDE5i and ERA)		–	2 (7)	–			
Sequential:							
Dual (after PDE5i or ERA)		–	–	81 (45)			
Triple (after PDE5i and ERA)		–	–	92 (51)			
Supportive treatment, n (%)	267						
Diuretics		33 (55)	10 (37)	104 (58)	0.130	0.165	0.764
Oxygen		17 (28)	11 (41)	72 (40)	0.252	0.322	0.124

ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PCP, pulmonary capillary pressure; PDE5i, phosphodiesterase 5 inhibitors; PVR, pulmonary vascular resistance; Q1;Q3, quartiles 1 and 3; RAP, right atrial pressure; WHO FC, World Health Organization functional class; 6MWT, 6-minute walking test. Significant differences are indicated in bold.
[a] Seven patients switched to iloprost and were not being administered PDE5i or ERA.

for 97 patients. Of these, 65 (24% of the initial population) patients continued the initial therapy with inh-ILO. Significant improvements were observed in both, WHO FC and physical performance (Table 1).

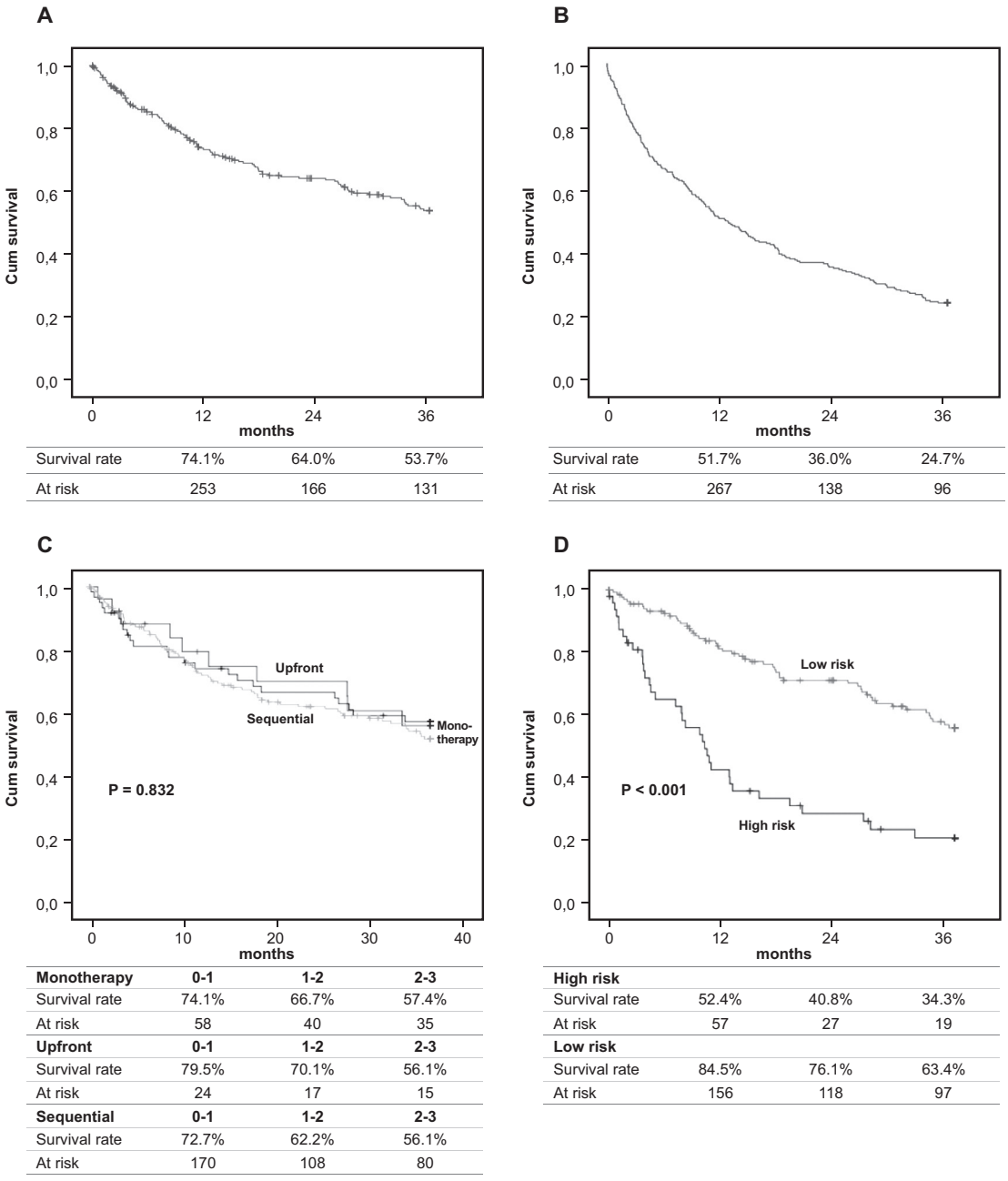
One- and 3-year cumulative transplant-free survival rates from the beginning of treatment with inh-ILO in the ITT population were 74% and 54%, respectively (Fig. 1A). One- and 3-year after stopping inh-ILO-related survival rates were 52% and 25%, respectively (Fig. 1B).

3.3. Transplant-free survival according to place in the treatment sequence

Median (Q1;Q3) time to start inh-ILO as monotherapy was 0.4 (0.0;2.2) months, 0.0 (0.0;0.7) months as upfront combination therapy and 17.5 (4.7;43.6) months as sequential strategy ($P = 0.112$ for monotherapy vs. upfront and $P < 0.001$ for monotherapy vs. sequential). Compared to patients receiving monotherapy as first-line treatment, those receiving upfront combination had a worse physical performance and hemodynamic status: lower cardiac output (median [Q1;Q3] of 3.3 [2.6;4.4] vs. 4.4 [3.3;5.7] L/min, $P = 0.006$) and higher PVR and mPAP (14.4 [11.5;18.4] vs. 9.5 [6.2;12.0] Wood units, $P < 0.001$ and 60 [47;73] vs. 50.0 [45;57] mmHg, $P = 0.034$, respectively), with no differences in clinical status. Compared to patients receiving monotherapy as first-line treatment, those receiving sequential combination therapy were older and had higher mPAP. No differences with respect to physical performance or clinical status were observed (Table 2). No differences were observed in 1- and 3-year transplant-free survival rates: 74% and 57% for monotherapy, 80% and 56% for upfront combination therapy and 73% and 56% for sequential combination therapy; $P = 0.832$ (Fig. 1C).

3.4. Transplant-free survival according to risk of clinical worsening or death

Patients with a higher risk (WHO FC IV or 6MWT <165 m, n = 59, 27%) were older than those with a lower risk (WHO FC ≤ III and 6MWT



A			
Survival rate	74.1%	64.0%	53.7%
At risk	253	166	131

B			
Survival rate	51.7%	36.0%	24.7%
At risk	267	138	96

C			
Monotherapy	**0-1**	**1-2**	**2-3**
Survival rate	74.1%	66.7%	57.4%
At risk	58	40	35
Upfront	**0-1**	**1-2**	**2-3**
Survival rate	79.5%	70.1%	56.1%
At risk	24	17	15
Sequential	**0-1**	**1-2**	**2-3**
Survival rate	72.7%	62.2%	56.1%
At risk	170	108	80

D			
High risk			
Survival rate	52.4%	40.8%	34.3%
At risk	57	27	19
Low risk			
Survival rate	84.5%	76.1%	63.4%
At risk	156	118	97

Fig. 1. Kaplan-Meier estimates of cumulative survival from the start of treatment with inh-ILO: A. In the overall population (censoring date: death or transplantation); B. In the overall population (censoring date: withdrawal of iloprost for any reason); C. According to the place of inh-ILO in the treatment sequence; D) According to patient risk.

>165 m, n = 163, 73%): median (Q1;Q3) was 61 (52;70) vs. 50 (41;62) years, $P < 0.001$. They also received supportive therapy with oxygen more frequently (58% vs. 29%, $P < 0.001$) and took shorter to receive inh-ILO (median [Q1;Q3] 2.3 [0.1;16.5] vs. 9.1 [0.5;39.6] months, $P = 0.010$). No differences were observed with regard to treatment strategy (Table 3). One- and 3-year transplant-free survival rates were also poorer (52% vs. 85% at 1 year and 34% vs. 63% at 3 years, $P < 0.001$) (Fig. 1D).

3.5. Evolution of treatment strategy

Monotherapy was the only strategy up to 2002, when combination therapy (upfront or sequential strategy) was introduced, accounting for 57% of treatments. Since then, sequential strategy increased up to 88% in 2011–2013 and 84 in 2014–2018 (see Fig. 2 at the Supplemental Materials section, available at the online version).

4. Discussion

Our analysis of incident PAH patients enrolled in the REHAP registry shows that inh-ILO is the prostanoid most widely used in Spain (58.4%) and the overall effectiveness of this treatment in patients receiving it as first-line therapy (treatment-naïve patients) –either as monotherapy or as upfront combination with a PDE-5i or ERA-, or sequentially on top of these treatments, is reduced, with a cumulative transplant-free survival rate of 53% at 3 years after starting treatment despite significant improvements in physical (6MWT) and functional (WHO FC) performance.

The effectiveness of inh-ILO observed in our study has to be interpreted after taking several factors into consideration. Firstly, the REHAP registry collects real-life clinical practice in a representative Spanish centers, these including PH specialist centres and small hospitals, reflecting thus the diversity of real-world treatment strategies among physicians treating PH patients or even among centres. The period analyzed (up to 2016) reflects both past and current patient characteristics and practices in the management of the disease as a result of a greater awareness of PH and the emergence of new therapeutic approaches. As such, sequential combination therapy was the most frequently used strategy with inh-ILO (67%) during the period analyzed, followed by monotherapy (22%) and upfront combination therapy (12%). However, we have also observed that during this time period treatment strategies have evolved dramatically, with monotherapy being the only initial treatment in the early years (1998–2002), when no other PAH treatments were available. The use of monotherapy decreased over time as the value of combination therapy was evidenced [5–8], accounting for scarcely 4% in the later period (2014–2016). Sequential strategy – appearing in the 2002–2004 period and rapidly increasing in the next years- was the strategy used in >85% of patients receiving inh-ILO in the last 6 years analyzed. The widespread use of sequential combination therapy is consistent with current clinical practice worldwide [14], as promoted by the international guidelines for PAH treatment issued in 2009 [15]. Upfront combination therapy has also been used since 2002–2004 in our setting, although at a lower rate and with no clear evolution over time. This may result from the use of upfront combination therapy in patients for whom systemic prostanoids would be indicated, given the complications associated to their use.

Evidence of the long-term benefits of inh-ILO is scarce, especially in unselected real-world populations and under circumstances in the current treatment era, which precludes comparison of our results. In the two studies assessing the long-term efficacy of inh-ILO, it was administered as monotherapy and the results were inconsistent [10,11]; while Opitz et al. [10] reported that only a minority of the 76 patients included in the study were able to be stabilized with inh-ILO monotherapy during a follow-up period of up to 5 years, Olschewski et al. [11] suggested a long-term benefit of inh-ILO monotherapy during the 2-year follow-up. Gall et al. [16] have recently reported their experience with inh-ILO from 1993 to 2013 in 148 patients with PH (idiopathic PAH and PAH associated with other conditions being the most frequent aetiologies) included in the single-centre Giessen Pulmonary Hypertension Registry (Germany). In this study, the cumulative transplant-free survival rate at 3 years was higher in patients on sequential therapy starting with inh-ILO followed by sidenafil (n = 61) vs. patients starting with sildenafil followed by inh-ILO (n = 63): 81.8% vs. 68.1%; $P = 0.035$. It was lowest in patients receiving upfront combination therapy (n = 24): 58%. Transplant-free survival at 3 years was lower in our study (54%) with no differences when inh-ILO was used in treatment-naïve patients –either as monotherapy (57%) or as upfront combination therapy (56%)- or as an add-on in a sequential strategy (56%). Besides the fact that our results are based on reports from a number of centers, the lower survival rate observed in our study may also be explained because transplant-free survival was assessed from the start of treatment with inh-ILO, which in our sequential group (the most common one) differed from that of diagnosis and took place after a median of 17.5 months. We did not analyze survival of patients starting on inh-ILO with an ERA or PDE5i sequentially added. Similarly to the Giessen study, patients receiving upfront combination therapy had a worse hemodynamic status compared to those receiving monotherapy and probably also compared to patients receiving sequential therapy. However, the significance of this latter difference was not analyzed.

Only 24% of patients were still receiving inh-ILO after 3 years of starting treatment (those with no change in treatment [15.7%] or with an ERA or PDE5i added-on [9%], Table 1). As expected, stop inh-ILO-related survival was even poorer than transplant-free survival (25% vs. 54% at 3 years), which reflects the deleterious effect of treatment discontinuation. The reasons for withdrawal were not gathered in the REHAP registry, but it can be assumed that besides adverse events or lack of efficacy concerns, changes in therapeutic strategy during the

Table 3
Patient demographic, clinical and hemodynamic characteristics at the time of starting inh-ILO according to the severity (functional class/physical performance) of the patient.

Variable	Risk			
	n	Low risk (n = 163)	High risk (n = 59)	P-value
Age, years, median (Q1;Q3)	222	50 (41;62)	61 (52;70)	<**0.001**
Sex, men, n (%)	222	48 (29)	13 (22)	0.311
NYHA FC, n (%)	222			
I-II		51 (31)	6 (10)	**0.002**
III		112 (69)	26 (44)	**0.001**
IV		0 (0)	27 (46)	<**0.001**
6MWT, m, median (Q1;Q3)	222	390 (300;473)	50 (50;144)	<**0.001**
Hemodynamics, median (Q1;Q3)				
Cardiac output, L/min	120	4.0 (3.3;5.1)	3.8 (3.0;4.8)	0.535
PVR, Wood units	117	12.2 (7.8;16.3)	11.4 (8.6;14.8)	0.793
mPAP, mmHg	120	56.0 (48;64)	55 (45;67)	0.765
RAP, mmHg	118	10 (6;14)	12 (7;18)	0.078
PCP	115	10 (7;14)	11 (9;14)	0.254
Time between diagnosis and starting inh-ILO, months, median (Q1;Q3)	222	9.1 (0.5;39.6)	2.3 (0.1;16.5)	**0.010**
Treatment strategy with inh-ILO, n (%)	222			
First-line:				
Monotherapy		44 (27)	11 (19)	0.223
Dual upfront combination (+ PDE5i or ERA)		11 (7)	8 (14)	0.171
Triple upfront combination (+ PDE5i and ERA)		2 (1)	0 (0)	1.000
Sequential:				
Dual (after PDE5i or ERA)		44 (27)	23 (39)	0.099
Triple (after PDE5i and ERA)		62 (38)	17 (29)	0.267
Supportive treatment, n (%)	222			
Diuretics		88 (54)	36 (61)	0.364
Oxygen		47 (29)	34 (58)	<**0.001**

ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PDE5i, phosphodiesterase 5 inhibitors; PCP, pulmonary capillary pressure; PVR, pulmonary vascular resistance; Q1;Q3, quartiles 1 and 3; RAP, right atrial pressure; WHO FC, World Health Organization functional class; 6MWT, 6-minute walking test. Significant differences are indicated in bold.

study period as a result of the availability of new therapies and prescribing preferences may also have had an influence. The high rate of discontinuation of inh-ILO as monotherapy has been evidenced in the two long-term studies previously commented: after 2 years of starting inh-ILO, only 18% of patients were still on monotherapy in the study by Opitz et al. [10], while this percentage was 25% in the study by Olschewski et al. [11]. In this latter study, lack of efficacy was the most frequent reason for discontinuation (46%) [11]. There has been hardly any analysis of the reasons for discontinuation of inh-ILO in the current treatment era. A preliminary study conducted in our setting in 18 patients receiving inh-ILO in combination with a PDE5i and/or ERA has revealed that only 53% of patients were compliant with the treatment and that 30% of patients were partially non-compliant (<80% doses or inhalations), either due to forgetting a dose (intention) or to not completing the inhalation (error) [17]. A recently published study aimed at investigating the medication adherence of patients on pulmonary hypertension (PH)-targeted therapies has revealed that factors like "higher administration frequency" –as is the case with inh-ILO- or "taking a combination of PH medicines" –which is the case of most patients taking inh-ILO in the REHAP registry- compared to taking monotherapy seems to have a detrimental association with adherence [18]. The recent launch of the selective prostacyclin I2 receptor agonist selexipag, licensed for the treatment of patients with PAH in WHO classes II-III [19], which besides being an easier and more effective way of delivery compared to inh-ILO also reduces the frequency of administration to twice-daily, is likely to benefit adherence.

It is also worth noting that 14.2% of patients who were treated with inh-ILO (monotherapy or combination therapy) were classified as WHO FC IV which, according to current international guidelines, should be treated with epoprostenol, the only treatment recommended (IA) for patients with severe PAH [1]. Cumulative transplant-free survival of patients classified as "high risk" for clinical worsening or death in our study (26.6%) was poorer (34% vs. 63% in patients with a low risk at 3 years, $P < 0.001$), which supports that these patients should have received more effective treatment (i.e. epoprostenol i.v. and treprostinil s.c.) from the beginning [20,21]. Ten percent of patients in our study in whom three-year follow-up data was available had switched to an i.v. or s.c. prostanoid. Several studies have also highlighted the benefits on right hemodynamics, FC and exercise capacity and survival associated to early upfront treatment with prostanoids, including epoprostenol, in severe PAH patients [22–24]. Despite the benefit on adherence commented above, selexipag would not have been an option in these severe cases [25]. Surprisingly, we did not observe significant differences in the treatment strategies with inh-ILO between both severity groups, which may be a consequence of the long period analyzed and the successive changes in treatment strategies with this drug as shown in Fig. 2 at the Supplemental Materials. The reduced size of the treatment groups may also have affected the statistical power. It is also worth noting that up to 25% of patients receiving inh-ILO were WHO FC II, when these patients might have benefitted from monotherapy with a PDE5i or ERA [1].

Most limitations of this study are inherent to voluntary registries, which may affect the collection of information. However, the variables included in our analysis were subjected to quality assessment to ensure that they applied to at least 85% of patients. Nearly 30% of patients receiving inh-ILO (n = 109) were excluded from the analysis because of missing data regarding hemodynamics and FC, which represents an important bias. These patients were younger (median [95%CI] 48 [38;62] vs. 54 [43;67] years in those included in the analysis). No other sociodemographic or treatment strategies were observed (data not shown). Censoring date was 6 months after the upper limit of the date for inclusion of patients and therefore some patients did not achieve three years of follow-up. This is likely to have affected ~10% patients analyzed.

Other subanalyses may have provided more evidence of factors affecting the effectiveness of inh-ILO, especially with regard to adherence, as recently published by Gravy et al. [18]. However, this was not the objective of the study and some of the findings in this study (number of comorbidities or concomitant treatments) may be considered to be age-related.

5. Conclusions

Our results show that inh-ILO –the most frequently used prostanoid in Spain-, has low effectiveness in patients receiving it as first-line therapy –either as monotherapy or as upfront combination therapy with a PDE5i or ERA-, or as an add-on in a sequential strategy with a 3-year survival rate of 53% despite significant physical and functional performance. The treatment of patients with severe PAH (for whom the use of inh-ILO is not licensed) is likely to contribute to the low effectiveness observed. Abandon rate is high, with 25% patients still on inh-ILO after 3 years of starting treatment. Adequate use of the different prostanoids according to severity of patients may help to overcome the underuse of prostanoids in our setting [2,26].

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Appendix A

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