Preliminary Data Analysis

Treatment patterns in pulmonary arterial hypertension

Administrative details of the data analysis	
Substance(s)	Macitentan/Tadalafil
Condition/ADR(s)	Pulmonary arterial hypertension
Short title of topic	Treatment patterns in patients with pulmonary arterial hypertension
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1. Problem statement

1.1. Rationale and Background

Pulmonary arterial hypertension is a rare type of pulmonary hypertension characterized by increased mean pulmonary arterial pressure and can be idiopathic, heritable, drug-induced, or secondary to other chronic diseases as HIV infection, congenital heart diseases, portal hypertension [1]. The median survival is about 7 years from the time of diagnostic catheterization.

The therapeutic management differs based on type and severity and usually involves a mono or combination therapy from the following agents: endothelin receptor antagonist (ERA) plus phosphodiesterase-5 inhibitor (PDE5i) and calcium channel blockers (CCB).

To evaluate the feasibility of an RCT in PAH patients it was suggested to conduct an analysis of RWD to describe the actual treatment patterns for patients with PAH in Germany and UK.

1.2. Research question

The following research questions were investigated:

- What is the first line treatment for patients diagnosed with PAH focusing on ERA and PDE5i classes (monotherapy or combined)?
- After how long patients initiating single therapy receive a second drug (combination therapy)?

2. Aim and methods

A cohort of patients with a history of PAH (both idiopathic, secondary) was created, with follow-up starting at date of diagnosis.

Study period was between January 2006 and June 2021 in IQVIA™ Disease Analyser Germany and between 1998 and 2021 in IQVIA™ Medical Research Data (IMRD) UK.

Patients with a history of PAH were followed since their first incident prescription of either ERA and PDE5i (incident use) and treatment patterns were reported. Other therapies were not captured.

A patient was considered to have started directly on combination therapy if a substance from both classes was initiated within 30 days (sensitivity analysis: 60 days).

Since PDE5I's are also indicated for treatment of erectile dysfunction, the analysis in IQVIA™ Disease Analyser Germany was restricted to the EphMRA ATC code for treatment of PAH (as inclusion of the EphMRA ATC code for treatment of erectile dysfunction resulted in a markedly higher proportion of male patients). For IMRD (UK) prescriptions for sildenafil were excluded if the quantity prescribed was 2, 4, 8, or 16 (pack sizes used almost exclusively for erectile dysfunction). Prescriptions for tadalafil were excluded if the quantity supplied was 4 or 8, or if the tablet strength was 2.5mg or 5mg (both used exclusively for erectile dysfunction).

The following variables were calculated and reported:

- Number of PAH patients
- Number of PAH patients that initiated incident treatment with ERA or PDE5i

- Treatment initiation patterns over time in PAH patients (overall and specifically for macitentan, tadalafil)
- Number of patients initially treated with monotherapy which progressed to combination therapy, (assuming that they stayed on the initial therapy), within 1 year and respectively 2 years since start of treatment

3. Preliminary results

3.1. Total drug exposure counts

Table 1 Exposure to ERA and PDE5i, irrespective of indication

Database name/country	Drug	N prescriptions	N patients	Date of first use in database	Date of last use in database
IQVIA™ Disease Analyser Germany	Endothelin antagonists	4,478	379	02/12/2002	29/06/2021
IQVIA™ Disease Analyser Germany	PDE5i	11,503	1,526	23/01/2006	30/06/2021
IMRD (UK)	Endothelin antagonists	110	69	13/02/2009	28/05/2021
IMRD (UK)	PDE5i	1,221,719*	68,348*	28/09/1998	03/07/2021

For IQVIA™ Disease Analyser Germany, Endothelin receptor antagonists were identified using EphMRA ATC code C06B1 (endothelin receptor antagonists for treatment of pulmonary hypertension). They included ambrisentan, bosentan, macitentan and sitaxentan. PDE5 inhibitors were identified using the EphMRA ATC code C06B2 (PDE5 inhibitors for treatment of pulmonary hypertension). It included sildenafil and tadalafil.
For IMRD (UK) PDE5 inhibitors were any use of sildenafil and tadalafil (the only PDE5 inhibitors licensed for treatment of pulmonary hypertension in the UK).
For IMRD (UK) the exclusion of prescriptions for sildenafil and tadalafil that are related to erectile dysfunction is not applied in this table

3.2. Crude counts of exposed patients in the PAH diagnosed population

In IQVIA™ Disease Analyser Germany, 66,614 patients had a diagnosis of PAH[1] out of a total of more than 30 million patients captured in the database. The gender distribution for all PAH patients was 43.5% males and 56.5% females. For all patients treated with ERAs the gender distribution was 33.8% males and 66.2%% females, and for all patients treated with PDE5-I's the gender distribution was 54.0% males and 46.0% females.

Since ERAs were marketed prior to PDE5i inhibitors in IMS Germany, the study period was restricted to 2006 or later (this excluded 3 patients with PAH that initiated incident ERA treatment before 2006).

[1] PAH was identified using ICD 10 codes: I27.0 (Primary pulmonary hypertension), I27.1 (Kyphoscoliotic heart disease), I27.2 (Other secondary pulmonary hypertension), I27.8 (Other specified pulmonary heart diseases), and (I27.9 Pulmonary heart disease, unspecified).

A total of 555 patients with PAH were identified that initiated first ever treatment with either a PDE5i and/or ERA in 2006 or later. Of these patients 513 had initiated a PDE5i[2], out of which 65 used tadalafil, while 100 patients had initiated an ERA, out of which 39 had initiated macitentan (see Table 2). These numbers are not mutually exclusive as the same patient could initiate both treatments at the same time, or one of the treatments could be initiated first, later followed by the other treatment, or the patient could remain on single treatment throughout the study period.

In IMRD UK there were 1,364 patients with a diagnosis of PAH[3], 46.2% male and 53.8% female. Equivalent figure to those presented for IMS Germany are given for IMRD UK in Table 2.

Table 2 Patients with pulmonary hypertension that initiated incident treatment with endothelin receptor antagonist or PDE5 inhibitor

Database	Total no. of patients	Endothelin receptor antagonist	Out of which, started with macitentan	PDE5 inhibitor	Out of which, started with tadalafil
IQVIA™ Disease Analyser Germany	555	99	39	513	65
IMRD UK	79	35	9	75	9

In IQVIA™ Disease Analyser Germany, out of 555 patients that initiated either ERA or PDE5i, the majority started on PDE5i monotherapy (85.6%), followed by ERA monotherapy (10.5%) and only 4.0% started on combination of both. If we extend the window for considering initiating combination therapy, the percentage of combinations only slightly increases to 5.0% (see Table3). The gender distribution in the 555 patients is 47.83% males and 52.17% females (35.5% males among patients treated with endothelin antagonists and 48.63% males among patients treated with PDE5-I's).

In IMRD UK, PDE5i monotherapy is also the starting treatment for most of the patient (64.2%); while the percentage of patients starting with a combination is higher (18.9%) (see Table 3). See Annex 2 for a sensitivity analysis that includes only patients with a minimum follow up time.

Table 3 Treatment initiation patterns in PAH patients

Time period after first incident prescription	Incident treatment with ERA alone	Incident treatment with PDE5i alone	Combined treatment
IQVIA™ Disease Analyser Germany			
0-1 days	58 (10.5%)	475 (85.6%)	22 (4.0%)
0-30 days	55 (9.9%)	475 (85.6%)	25 (4.5%)
0-60 days	54 (9.7%)	473 (85.2%)	28 (5.0%)
IMRD UK			
0-1 days	13 (16.5%)	51 (64.6%)	15 (19.0%)

[2] This does not consider other treatments for PAH, only ERA and PDE5i were investigated.
[3] Read codes (G410 Pulmonary arterial hypertension; 7Q010 Primary pulmonary hypertension drugs Band 1; 7Q011 Primary pulmonary hypertension drugs Band 2; 7Q014 Pulmonary arterial hypertension drugs Band 1; 7Q015 Pulmonary arterial hypertension drugs Band 2; 7Q016 Pulmonary arterial hypertension drugs Band 3)

0-30 days	13 (16.5%)	51 (64.6%)	15 (19.0%)
0-60 days	11 (13.9%)	51 (64.6%)	17 (21.5%)

Table 4 shows whether the starting therapy has changed over time and it can be noted how in both databases the combined treatment became more frequent with time.

Table 4 Treatment initiation patterns over time in PAH patients

Year of treatment initiation	Time period after first incident prescription	Incident treatment with ERA alone	Incident treatment with PDE5i alone	Combined treatment
IQVIA™ Disease Analyser Germany				
2006-2010	0-1 days	10 (9.9%)	91 (90.1%)	0 (0.0%)
	0-30 days	10 (9.9%)	91 (90.1%)	0 (0.0%)
	0-60 days	<10 (8.9%)	90 (89.1%)	<10(2.0%)
2011-2015	0-1 days	15 (10.1%)	129 (86.6%)	<10 (3.4%)
	0-30 days	14 (9.4%)	129 (86.6%)	<10 (4.0%)
	0-60 days	14 (9.4%)	129 (86.6%)	<10 (4.0%)
2016-2021	0-1 days	33 (10.8%)	255 (83.6%)	17 (5.6%)
	0-30 days	31 (10.2%)	255 (83.6%)	19 (6.2%)
	0-60 days	31 (10.2%)	254 (83.3%)	20 (6.6%)
IMRD UK				
1998- 2015	0-1 days	<6 (13.3%)	13 (86.7%)	0 (0.0%)
	0-30 days	<6 (13.3%)	13 (86.7%)	0 (0.0%)
	0-60 days	<6 (13.3%)	13 (86.7%)	0 (0.0%)
2016-2021	0-1 days	11 (17.2%)	38 (59.4%)	15 (23.4%)
	0-30 days	11 (17.2%)	38 (59.4%)	15 (23.4%)
	0-60 days	9 (14.1%)	38 (59.4%)	17 (26.6%)

Table 5 replicates the analysis focusing on the macitentan or tadalafil substances; the percentage of patients that start with a combination of the two substances is still the minority.

Table 5 Treatment initiation patterns for patients initiating macitentan or tadalafil in PAH patients

Time period after first incident prescription	Incident treatment with macitentan alone	Incident treatment with tadalafil alone	Combined treatment
IQVIA™ Disease Analyser Germany			
0-1 days	59 (62.1%)	32 (33.7%)	<10 (4.2%)
0-30 days	58 (61.1%)	32 (33.7%)	<10 (5.3%)
0-60 days	58 (61.1%)	32 (33.7%)	<10 (5.3%)

3.3. Number of patients that start on monotherapy and then are upgraded to combination therapy

The number of patients that have initiated monotherapy[1] with either ERA or PDE5i that have later started the other treatment within one or two years are presented in tables 6 and 7. Table 6 offers a stratification by the initial treatment and refers only to IQVIA™ Disease Analyser Germany, while Table 7 pools all the initiators together.

Table 6 Percent of patients that have initiated monotherapy[1] with either ERA or PDE5i and later were upgraded to combination treatment [2] in the IQVIA™ Disease Analyser Germany

Follow-up [3]	Time period	Start ERA	Add on (%)	Start PDE5i	Add on (%)
365 days	All	35	<10 (8,57%)	295	<10 (2,03%)
	2006-2010	<10	<10 (12,50%)	62	<10 (3,23%)
	2011-2015	11	<10 (9,09%)	91	0 (0,00%)
	2016-2021	16	<10 (6,25%)	142	<10 (2,82%)
730 days	All	27	<10 (14,81%)	201	<10 (1,99%)
	2006-2010	<10	0 (0,00%)	51	<10 (3,92%)
	2011-2015	<10	<10 (22,22%)	69	0 (0,00%)
	2016-2021	11	<10 (18,18%)	81	<10 (2,47%)

[1] Single-arm treatment is defined as initiation of treatment with either ERA or PDE5i but not both within a time period of 60 days.
[2] Start of a PDE5i in a patient treated with ERA or vice versa.
[3] Patients included in the analysis have a minimum follow-up after initiation of treatment of 365 days or 730 days. Patients lost to follow up are not counted.

Table 7 Percent of patients that have initiated single-arm treatment with either ERA or PDE5i (not stratified by substance) and later were upgraded to combination treatment

Follow-up [3]	Time period	IMS-Germany		IMRD (UK)	
		Start single therapy[1]	Add on (%)[2]	Start single therapy[1]	Add on (%)[2]
365 days	All	330	<10 (2.7)	46	<10 (8.7)
	2006-2010	70	<10 (4.3)	-	-
	2011-2015	102	<10 (1.0)	12	0 (0)
	2016-2021	158	<10 (3.2)	34	<104 (11.8)
730 days	All	228	<10 (3.5)	33	<10 (18.2)
	2006-2010	58	<10 (3.4)	-	-
	2011-2015	78	<10 (2.6)	11	<10 (9.1)
	2016-2021	92	<10 (4.3)	22	<10 (22.7)

[1] Single-arm treatment is defined as initiation of treatment with either ERA or PDE5i but not both within a time period of 60 days.
[2] Start of a PDE5i in a patient treated with ERA or vice versa.
[3] Patients included in the analysis have a minimum follow-up after initiation of treatment of 365 days or 730 days. Patients lost to follow up are not counted

3.4. Summary of preliminary results

The results for IQVIA™ Disease Analyser Germany and IMRD UK seem to suggest that treatment with PDE5i alone was the most prescribed first treatment in patients with PAH that initiated treatment with either a PDE5i or an ERA, with around 85% (IQVIA™ Disease Analyser Germany) and 64% (IMRD UK) of patients receiving only a PDE5i during the first 60 days. Prescribing of ERA alone as first treatment during the first 60 days included only around 10% of the patients (15% in IMRD UK), and only around 4-5% of the patients initiated both treatments during the first 60 days (higher in the UK at around 20%). However, the proportion of patients with combined treatment has slightly increased over time and was around 6% between the years 2016 to 2021 (higher in IMRD at 20-25%). The proportion of patients treated with ERA alone was relatively stable over time whereas the proportion of patients treated with PDE5i alone decreased with time.

Among patients initiating monotherapy (i.e. patients not initiating both an ERA and a PDE5i within 60 days of each other), a limited proportion of patients, between 2.7% and 22.7% of all patients, later initiated the other treatment

3.5. Limitations

- In IQVIA™ Disease Analyser Germany there is a risk that patients might visit another practice to receive prescriptions for PAH. However, it would seem unlikely that such behaviour would depend on the treatment prescribed
- We have not distinguished between switching to the other treatment and actual combined treatment. However, most patients with 'combined' treatment during the first 60 days (after initiating treatment with either therapy) initiated both treatments on the same day, which indicates that they were intended to be taken together
- Some of the treatment with PDE5-I's may relate to treatment of erectile dysfunction, although we tried to minimise this bias by including only PDE5-I's that were indicated for treatment of pulmonary hypertension. For both data sources used, a more sensitive approach to identifying PDE5-Is used for erectile dysfunction could have been developed if more time was available.

4. References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913. doi: 10.1183/13993003.01913-2018. PMID: 30545968; PMCID: PMC6351336.

Annex 1 – Information on Databases and Healthcare systems included

IMRD-UK

In the United Kingdom, GPs play a gatekeeper role in the healthcare system, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests. IMRD-UK contains longitudinal electronic patient records extracted from the VISION practice management software, which has been contributed to by > 790 general practices across the United Kingdom covering up to 6% of the UK population. Data are largely representative of the UK population in terms of age, sex, deprivation status, and geographic distribution. It contains GP prescriptions with medicinal products identified through a bespoke system of drug codes linked to generic drug names (substance names) or a substitute thereof in a drug and device dictionary.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects anonymized electronic health records (EHRs) through a representative panel of GPs, some specialists in internal medicine, and other specialist physicians (~ 3% of all GPs in Germany), stratified for specialist group, region, community size, and age of physician. In Germany, patients can visit a physician of choice, including specialist physicians in gynaecology, dermatology and paediatric, whenever a medical need emerges.

Annex 2 –Sensitivity analysis with minimum follow up time

Table 3A summarises the same analysis when we add the condition of a minimum follow up of 30 and 60 days respectively.

Time period after first incident prescription	Minimum follow-up time after first incident prescription	All PAH patients with incident treatment	Incident treatment with endothelin receptor antagonist alone	Incident treatment with PDE5 inhibitor alone	Combined treatment (cumulative)
0-1 days	≥0 days	555	58 (10.5%)	475 (85.6%)	22 (4.0%)
0-30 days	≥30 days	506	53 (10.5%)	429 (84.8%)	24 (4.7%)
0-60 days	≥60 days	487	50 (10.3%)	413 (84.8%)	24 (4.9%)