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Experience with Selexipag to Treat Pulmonary Arterial Hypertension

Aim	To present an own experience in using a medication selexipag in patients with pulmonary arterial hypertension (PAH) included into the V. A. Almazov National Medical Research Center registry and participating in the GRIPHON and GRIPHON OL clinical studies.
Material and methods	26 patients with PAH were included into this study since 2010: 20 patients with idiopathic PAH, 4 patients with PAH associated with systemic scleroderma, and 2 patients with corrected congenital heart defects. At the time of randomization, 19 patients had been receiving therapy with phosphodiesterase type 5 inhibitors for at least one month. Among the patients treated with selexipag (n=14), 4 patients reached a high individual maintenance dose (1200–1600 μg b.i.d.), 4 patients reached a medium dose (600–1000 μg b.i.d.), and 6 patients reached a low dose (200–400 μg b.i.d.).
Results	The selexipag therapy exerted a positive effect on secondary endpoints, specifically, on changes in the functional class of pulmonary hypertension, serum concentration of NT-proBNP, and physical working capacity of patients. Adverse events associated with the selexipag treatment, which resulted in termination of study participation, were observed in one patient.
Conclusion	To achieve the main goal of drug therapy, low risk of death with selexipag it is critical to observe the titration schedule and to aim at reaching the highest individual maintenance dose.

Keywords	Pulmonary arterial hypertension; selexipag; GRIPHON; combination therapy
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Modern tactics of combination therapy have proven successful for the treatment of a wide range of cardiovascular diseases. In recent years, evidence of the efficacy of starting and sequential combination therapy has been noted for patients with pulmonary arterial hypertension (PAH). This was reflected in the 2015 ESC/ERS Guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [1]. This conclusion was based on the findings of three long-term clinical trials, one of which evaluated the efficacy of a new, selective prostacyclin receptor blocker as well as the standard combination of phosphodiesterase type 5 (PDE5) inhibitors and endothelin receptor antagonists (ERAs) [2–4].

Disturbance of endogenous prostacyclin synthesis is considered a key mechanism for the development of PAH [5]. Therefore, the efficacy of synthetic prostacyclin analogs (prostanoids) for the treatment of diseases of this group has been confirmed [6]. However, the use of these drugs is limited by a short half-life, less than 5 min for intravenous epoprostenol, 20–30 min for inhalation iloprost, and 180–270 min for subcutaneous treprostinil. Their use is also limited by possible complications related to the active agent delivery system. Moreover, prostanoids with a high affinity for prostacyclin receptors (IR) have a stimulating effect on the prostanoid receptors of the gastrointestinal tract, central nervous system, and peripheral arteries of the systemic circulation. In addition, prostanoids cause dyspeptic disorders, jaw and limb pains, systemic hypotension, and headache. In the Russian Federation, only inhalation iloprost is approved. It improved exercise tolerance and downgraded the PAH functional class in a short-term randomized clinical trial (RCT). However, long-term monotherapy with iloprost was not accompanied by increased survival of PAH patients or a lower rate of PAH-associated complications. Thus, iloprost is now used only in combination with PAH-specific oral drugs in patients with functional class (FC) III PAH (WHO).

The search for a chemically stable oral drug that selectively affects IP receptors has been a key area of research. These studies resulted in the first and so far the only non-prostanoid selective IP receptor agonist: oral selexipag (Apbravi®), approved in the Russian Federation on June 7, 2019.

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The objective of this study was to present our experience using selexipag for patients with PAH. These patients were included in the Almazov National Medical Research Center Register and were subjects in the clinical studies GRIPHON (multicenter, double-blind, placebo-controlled, phase III study to demonstrate efficacy and safety of AST-293987 in patients with PAH) and GRIPHON OL (long-term, open-label, single-arm study to evaluate safety and tolerance of selexipag (ACT-293987)) in patients with PAH.

Material and Methods

The analysis included prospective follow-up data of 26 patients with PAH, randomized to the GRIPHON clinical trial carried out at the Almazov National Medical Research Center since 2010. The study was approved by the Central Ethics Committee of the Russian Federation Ministry of Health and the Local Ethics Committee of the Almazov National Medical Research Center. All patients included in the study signed an informed consent form. The clinical characteristics of patients are presented in Table 1.

Echocardiography was performed with the VIVID 7 Dimension imaging system. The right cardiac chambers were assessed under 2015 echocardiography guidance [7]. These chambers were catheterized using a Swan-Ganz 7F thermodilution balloon catheter to evaluate hemodynamics by measuring mean right atrial pressure, systolic, diastolic, and mean pulmonary pressures, pulmonary wedge pressure, and cardiac output. Pulmonary vascular resistance, systolic output, and cardiac index were calculated using standard formulas. All patients underwent a complex pulmonary function test performed on a VIASYS Healthcare system, that included spirometry and body plethysmography with standard and dynamic measurements and static lung volumes. Diffusion lung capacity for carbon monoxide (DLCO) was evaluated using a single-breath technique involving breath-hold and hemoglobin correction. DLCO was expressed as a percentage of the reference value. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined in the central laboratory.

Study findings were analyzed with Statistica v10.0 for Windows. Results with approximately normal distribution are presented as arithmetic means (M) and standard deviations (σ), otherwise as medians and percentiles. The significance level was set at $p<0.05$. Parameters with normal distributions were analyzed with one factor analyses of variance (ANOVA), otherwise with non-parametric Mann–Whitney U-tests. Patient survival rate was calculated using the Kaplan–Mayer method.

Table 1. Clinical characteristics of patients with PAH included in the GRIPHON study at Almazov National Medical Research Center

Parameter	Value
Age, years	48±15
Female	72% (n=22)
PAH FC III-IV	81% (n=21)
PAH etiology, %	
IPAH	77
SSD	15
cCPB	8
6MWD, m	363±72
Echocardiographic measurements	
RA area, cm^2	26.3±9.2
Parasternal RV dimension, mm	38±7
RV:LV	1.19±0.34
PA diameter, mm	34±7
FAC, %	30±9
TAPSE, mm	18±4
TAS'V, m/s	9±2
PA systolic pressure, mmHg	88±24
Pericardial Effusion, %	15% (n=4)
Hemodynamics	
Mean PA pressure, mmHg	59±19
PCWP, mmHg	8±4
CVP, mmHg	6.5 (3.0; 10.0)
Cardiac index, $l/min/m^2$	2.3±0.6
PVR, $dyn{\cdot}s/cm^{-5}$	855 (531; 1440)
SvO_2, %	66±15
Additional tests	
NT-proBNP, pg/mL	517 (175; 2271)
FEV1, %	88±24
TLC, %	97±12
DLco, %	57±15

IPH, idiopathic PAH; SSD, systemic scleroderma; cCPB, corrected congenital heart defect; FC, functional class; 6MWT, 6-min walking test; RA, right atrium; RV, right ventricle; RV/LV, ratio of the basal dimensions of the right and left ventricles; TAPSE, tricuspid annular plane systolic excursion; TAS'V, pulsed Doppler peak at the annulus; FAC, fractional area change; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation, NT-proBNP; N-terminal pro-brain natriuretic peptide; FEV1, forced exhalation volume in 1 sec; TLC, total lung capacity; Dlco, lung diffusing capacity. Data are expressed as the mean (M)±standard deviation (σ) or as the median (25^{th} percentile; 75^{th} percentile) of the distribution.

Results

According to the clinical trial design, 20 patients with idiopathic PAH, 4 patients with systemic scleroderma, and 2 patients with corrected congenital heart defects

were selected from the Center's register. Of the 26 patients in the study, 5 patients had FC II PAH, 19 patients had FC III PAH, and 2 patients had FC IV PAH. At the time of randomization, 19 patients had been treated with the PDE5 inhibitors, sildenafil (n=12) and tadalafil (n=7) for at least one month. After screening, patients were randomized 1:1 to either the selexipag or the placebo group. Subsequently, the dose of selexipag was titrated during 12 weeks, starting from 200 μg twice a day and increasing the dose by 200 μg a week until the maximum tolerated dose was reached. Among all patients, the maximum tolerated dose of selexipag was 1600 μg twice a day. Of the patients treated with the study drug (n=14), only 4 patients reached a high individual maintenance dose (1200–1600 μg twice a day), 4 patients reached a moderate maintenance dose (600–1000 μg twice a day), and 6 patients reached a low maintenance dose (200–400 μg twice a day). Thus, the median individual maintenance dose of selexipag in our Center did not exceed 700 μg (200; 1400) twice a day, which was fundamentally different from the structure of the maintenance dose in the study as a whole (total n=1156, 574 in the selexipag group) where 42.9%, 31.2%, and 23.2% received high, medium, and low doses, respectively.

The double-blind period of the GRIPHON study was finished when 331 outcomes were reached. Time to the first PAH-associated complication or patient's death was chosen as the combined primary endpoint. Changes in 6-min walk distance (6MWD), PAH FC (WHO), levels of serum NT-proBNP, and hospitalizations due to the aggravation of PAH, and patient's death of PAH or any other cause before the end of the study were used as the secondary endpoints. The findings of the GRIPHON clinical trial [4] demonstrate that the use of selexipag increased time to the first outcome by 40% (odds ratio [OR] 0.60, 99% confidence interval [CI] 0.46–0.78; $p < 0.001$). It should be noted that the efficacy of selexipag was independent of whether the drug was used as a monotherapy (OR 0.57; 99% CI 0.32–1.03) or in combination with other PAH specific drugs, e.g., PDE5 inhibitors (OR 0.66; 99% CI 0.32–1.35) or ERAs (OR 0.66; 99% CI 0.32–1.35). The efficacy of the drug did not depend on the patient's age or the origin of the disease [8, 9].

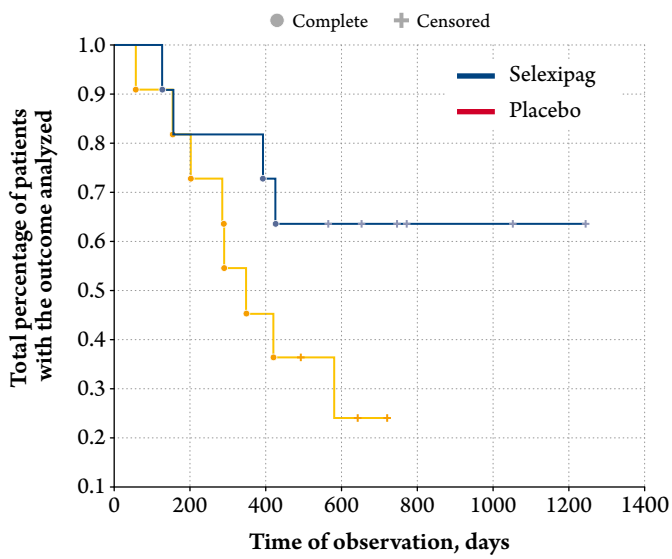
Similar trends were observed for the primary endpoint analysis at our Center (p=0.098; Figure 1). The lack of significant differences can be attributed to the small size of the sample and the lower percentage of patients receiving high maintenance doses. Moreover, a positive effect of selexipag on secondary endpoints was noted, including the effect on PAH FC over time, the levels of serum NT-proBNP (Figure 2), and the patients' physical performance (Figure 3).

Selexipag-related adverse events were responsible for discontinuation of the GRIPHON study in 14.3% of cases vs. 7.1% ($p < 0.001$) in the placebo group. At our Center, one patient (3.8%) withdrew from the study due to the development of side effects. The most frequent adverse events associated with the use of selexipag were headache, diarrhea, jaw pain, and redness of the face (Table 2). It should be noted that side effects were more often reported during the drug titration process, which significantly limited reaching the maximum maintenance dose. Hyperthyroidism associated with increased hormone synthesis in follicular thyroid cells due to hyperproduction of cyclic adenosine monophosphate, as occurs when levels of prostacyclin increase [10], is extremely rare for selexipag (1.4%), but this caused discontinuation of the drug at our Center. These findings emphasize the importance of careful titration of the drug to minimize side effects and to reach the maximum tolerated dose of the drug.

Discussion

Selexipag is a prodrug hydrolyzed in the liver to form an active metabolite, MRE-269, with the properties of a highly selective IP receptor agonist. When studied on an animal model of monocrotaline PAH, the drug improved the functional state of pulmonary vascular endothelium, controlled hypertrophy/hyperplasia of smooth muscle cells of the media, and hypertrophy of the right ventricle, and resulted improved survival [11]. Due to its high functional selectivity, selexipag and its metabolite did not stimulate gastric smooth muscle, which minimized prostanoid-specific side effects, such as nausea and

Figure 1. Time to the outcome analyzed in the selexipag and placebo groups



Log-rank test 2.83; p=0.098.

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Первый и единственный пероральный селективный агонист IP-рецепторов простациклина[1]

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На **40%** снижает риск прогрессирования заболевания/смерти у всех пациентов с ЛАГ независимо от линии терапии[2]

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Регистрационный номер: ЛП-005577. **Торговое наименование:** Апбрави. **Международное непатентованное наименование:** селексипаг. **Лекарственная форма:** таблетки, покрытые плёночной оболочкой. **Показания:** Апбрави показан для длительного лечения лёгочной артериальной гипертензии у взрослых пациентов (ЛАГ, группа I по классификации ВОЗ) II-IV ФК по классификации ВОЗ, с целью предотвращения прогрессирования заболевания. Апбрави эффективен в комбинации с АРЭ и/или иФДЭ-5, или в составе тройной терапии с АРЭ и иФДЭ-5, или в монотерапии. Эффективность Апбрави доказана в отношении идиопатической и наследственной ЛАГ, ЛАГ, ассоциированной с заболеваниями соединительной ткани, ЛАГ, ассоциированной с компенсированным простым врождённым пороком сердца. **Противопоказания:** повышенная чувствительность к действующему и вспомогательным веществам; тяжёлая ишемическая болезнь сердца или нестабильная стенокардия; инфаркт миокарда, перенесённый в течение предшествующих 6 месяцев; декомпенсированная сердечная недостаточность при отсутствии пристального наблюдения врача; тяжёлые нарушения сердечного ритма; цереброваскулярные заболевания (например, преходящее нарушение мозгового кровообращения, инсульт), перенесённые в течение предшествующих 3 месяцев; врождённые или приобретённые пороки сердца с клинически значимыми нарушениями функции миокарда, не связанными с ЛАГ; совместное применение с мощными ингибиторами CYP2C8 (например, гемфиброзилом); беременность и период грудного вскармливания; детский возраст до 18 лет (эффективность и безопасность не изучены). **С осторожностью:** у пациентов с артериальной гипотензией, у пациентов с вено-окклюзионной болезнью лёгких, при совместном применении с умеренными ингибиторами изофермента CYP2C8 (например, клопидогрелем, деферазироксом, терифлуномидом), у пациентов старше 75 лет (ограниченный опыт применения), у пациентов с нарушением функции печени тяжёлой степени (класс С по классификации Чайлд-Пью), у пациентов с нарушением функции почек тяжёлой степени (рСКФ < 30 мл/мин/1,73 м2), у пациентов с гипертиреозом и у женщин детородного возраста. **Способ применения и дозы:** Апбрави применяют внутрь 2 раза в сутки (утром и вечером), запивая необходимым количеством воды. *Титрование дозы*. Для каждого пациента с помощью титрования дозы должна быть подобрана индивидуальная максимальная переносимая доза, в диапазоне от 200 мкг 2 раза в день до 1600 мкг 2 раза в день (индивидуальная поддерживающая доза). Рекомендуемая начальная доза – 200 мкг 2 раза в день с интервалом примерно 12 ч между приёмами. Дозу увеличивают с шагом 200 мкг 2 раза в день, обычно с периодичностью 1 раз в неделю. В начале терапии и в начале каждого этапа повышения дозы рекомендуется принимать первую дозу вечером. **Побочное действие:** наиболее часто отмечавшимися нежелательными реакциями являются головная боль, диарея, тошнота, рвота, боль в челюсти, боль в конечностях, артралгия, приливы крови к лицу и верхней половине тела. Данные реакции наиболее часто наблюдаются во время титрования дозы.

ПОЖАЛУЙСТА, ОЗНАКОМЬТЕСЬ С ПОЛНОЙ ИНСТРУКЦИЕЙ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ПЕРЕД НАЗНАЧЕНИЕМ ПРЕПАРАТА.

Сокращения: АРЭ – антагонисты рецепторов эндотелина, ВОЗ – Всемирная организация здравоохранения, иФДЭ-5 – ингибиторы фосфодиэстеразы 5-го типа, ЛАГ – лёгочная артериальная гипертензия, ФК – функциональный класс.

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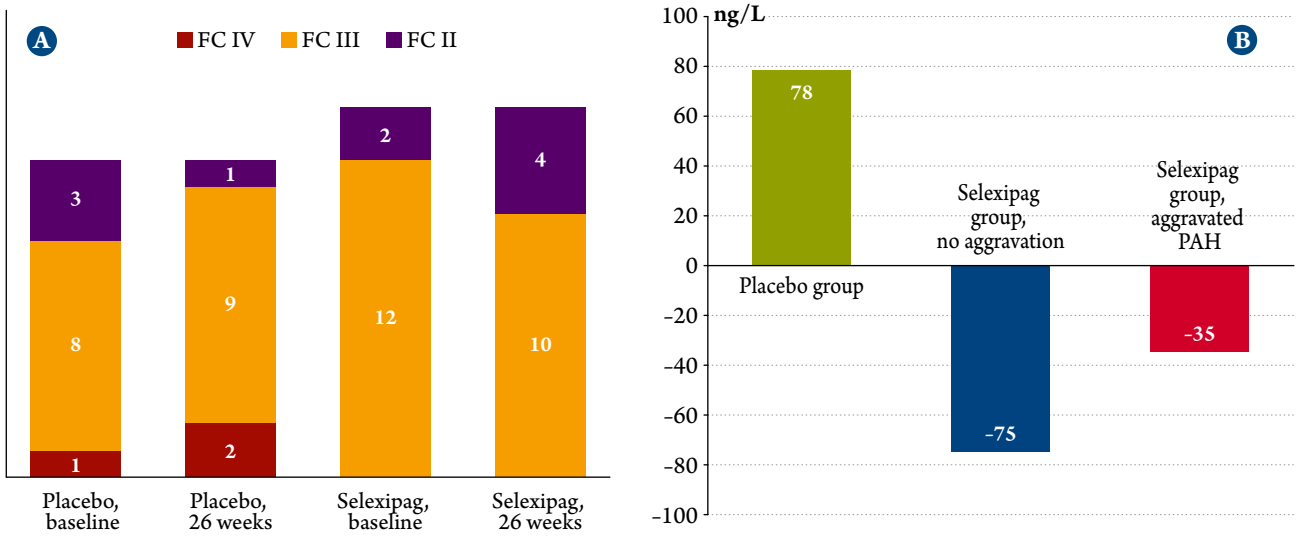
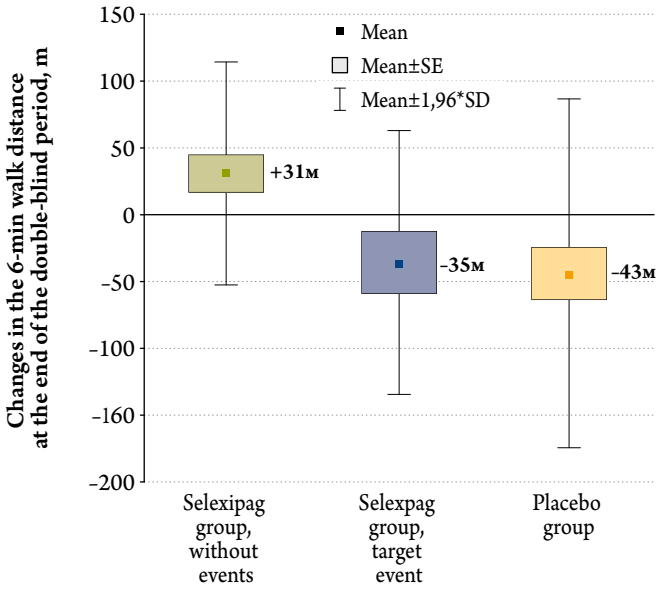
Figure 2. Changes in PAH (A) and levels of serum NT-proBNP (B) over time in patients with PAH at the end of the double-blind period (p > 0.05)



FC, functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension.

Figure 3. Changes in the 6-min walk distance in the placebo and selexipag groups (the Mann–Whitney U-test; p=0.029)



6MWD, 6 min walk distance; PAH, pulmonary arterial hypertension.

Table 2. Selexipag-associated adverse events (AE) reported at the site

Parameter	Placebo (n=12)	Selexipag (n=14)	p
≥1 AE associated with the study drug	6 (50)	12 (85.7)	0.046
AE, abs. (%)			
Headache	3 (25)	10 (71.4)	0.016
Diarrhea	1 (8.3)	7 (50)	0.016
Jaw pain	2 (16.7)	6 (42.9)	0.14
Facial redness	0	3 (21.4)	0.044
Myalgias	0	2 (9.4)	0.11
Muscle weakness	2 (16)	0	0.070
Dizziness	0	1 (10.4)	0.26
Thyrotoxicosis	0	1 (10.4)	0.26

vomiting. The pharmacokinetics of selexipag and its active metabolite are proportional to the dose. Their maximum concentrations are reached in 2.5 and 4 hr, respectively, and a stable concentration is achieved in 3 days. This fact emphasizes the importance of slow titration of the drug, which reduces the risk of side effects. Selexipag is safe in combination with inhibitors of organic anion transport polypeptides, p-glycoprotei,ns, and CYP3A4. This broadens the possibility for its administration in patients with drug-induced PAH or PAH associated with other diseases. During Phase 2 of a RCT (n=43), the use of selexipag was not only associated with a 30.3% decrease in pulmonary vascular resistance, but it also had a positive effect on the patients' physical performance (6MWD+24.2 m, 95% CI 23.7–72.2 m) and on the main hemodynamic parameters that determine an adverse prognosis: cardiac index +0.5 (0.13–0.83) l/min/m^2 (p=0.01) and right atrial pressure –3.2 (0.8–5.7) mmHg (p=0.02) [12].

Due to several limitations associated with the use of the 6MWD test as the primary measure of the results of previous RCTs, in the mid-2000s it was suggested to use combined endpoints presenting the time before the onset of clinical deterioration in newly authorized studies to evaluate the efficacy of PAH-specific therapy [13]. A similar approach was applied in the GRIPHON RCT, which not only confirmed the efficacy

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of selexipag in controlling the disease progression, but also demonstrated for the first time the benefits of three-component combination therapy with selexipag versus the previous two-component therapy with PDE5 inhibitors and ERAs, 37% reduction of risk (OR 0.63, 95% CI 0.44–0.90). The efficacy of three-component oral combination therapy in patients with FC PAH II was higher (64% (OR 0.36, 95% CI 0.14–0.91)) than in patients with FC PAH III (26% (OR 0.74, 95% CI 0.50–1.10)) [14]. Given that the annual mortality of patients with FC PAH II and III when stratified initially as intermediate risk is 17%, the transition to a low-risk zone during treatment lessens the differences in survival between these patients and those stratified initially at a low risk of death [15].

In recent years, the replacement of a drug of one group with a drug of another group has been discussed as an alternative to escalating PAH-specific therapy by adding a second and a third drug. In this regard, single observations of a successful transfer of stable patients from prostanoid therapy to oral selexipag [16] are promising and merit further evaluation.

Management of patients with PAH aims now to achieve a low risk of death, which implies low FC PAH (I– II), good tolerance of physical exercise (6MWD>440 m), favorable hemodynamics according to the catheterization of the right cardiac chambers (right atrial pressure <8 mmHg, cardiac index ≥ 2.5 l/min/m^2), low levels of NT-pro (<330 ng/L), and no evidence of right ventricular dysfunction. According to the theory of PAH development, a simultaneous effect on different pathogenetic pathways may prevent disease progression and will more effectively influence the outcome. The effectiveness of such tactics is supported by the results of a meta-analysis of 15 RCTs (n=3,906), which showed for combination therapy versus monotherapy, a 38% decrease in the risk of progression of PAH (OR 0.62, 95% CI 0.50–0.77) and an improvement of hemodynamic parameters and physical performance (6MWD+23 m, 95% CI 15.9–30.1 m) [17]. Based on RCT findings, it was concluded that early combined PAH-specific therapy was reasonable even in patients with FC PAH II who can be ascribed to both low and intermediate risks of death. The Cologne Consensus Conference 2018 and the 6th World Symposium on PAH proposed a new approach to starting combination therapy: Starting combination therapy is indicated even for patients at low risk of death in order to achieve a stable low-risk stratum [18, 19]. However, most patients with PAH continue to receive monotherapy, which continues to determine a low three-year survival rate in patients with PAH, ranging from 67 to 74% [15, 20].

Conclusion

The significance of the GRIPHON study for clinical practice should be highlighted. The current findings clearly demonstrated the efficacy of selexipag, not only for improving the physical performance of patients but primarily for preventing the progression of PAH, when used as monotherapy or in two- and three-component combination therapies, regardless of the patient's age, PAH origin and functional class. It is necessary to observe the titration regimen and seek to reach the highest individual maintenance dose of selexipag to achieve the primary goal of drug therapy, i.e., a low risk of mortality.

No conflict of interest is reported.

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