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THE ROLE OF RIOCIGUAT IN THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

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SUMMARY

Soluble guanylate cyclase (sGC) is a key signal-transduction enzyme activated by nitric oxide (NO). Binding NO with sGC - enzyme catalyzes the synthesis of a signal molecule of cyclic guanosine monophosphate (cGMP), which plays an important role in the regulation of processes that affect vascular tone, proliferation, fibrosis and inflammation. Impaired bioavailability and/or responsiveness to endogenous NO has been implicated in the pathogenesis of cardiovascular and other diseases. Pulmonary arterial hypertension (PAH) is a well-known complication of systemic connective tissue diseases (CTD) and ranks second among the most common types of PAH after idiopathic PAH (IPAH). The usage of organic nitrates and other NO donors has limitations, including non-specific interactions of NO with various biomolecules, lack of response and the development of tolerance following prolonged administration. Compounds that activate sGC in NO-independent manner might therefore provide considerable therapeutic advantages. The purpose of this article is to provide contemporary data on the management and treatment of patients, as well as the role of specific therapy and the place of riociguat in the treatment of patients with CTD associated PAH.

Keywords: *pulmonary hypertension (PH), pulmonary arterial hypertension (PAH), pulmonary arterial hypertension associated with systemic connective tissue diseases (PAH CTD), PAH-specific therapy, riociguat*

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INTRODUCTION

The term PAH describes a group of conditions associated with PH, that have similar hemodynamic characteristics: precapillary PH with increased mean pulmonary arterial pressure (mean PAP) ≥ 25 mm Hg at rest (as assessed by right heart catheterization (RHC)), as well as a number of other parameters, such as pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg and pulmonary vascular resistance (PVR) of > 3 Wood units [2,3].

PAH is a well-known complication of systemic connective tissue diseases (CTDs), especially systemic scleroderma, systemic lupus erythematosus, mixed connective tissue diseases (MCTD) and, to a lesser extent, rheumatoid arthritis, dermatomyositis and Sjogren's syndrome. PAH CTD is one of the most common types of PAH in the western countries. Systemic scleroderma is a CTD associated with PAH, which is most prevalent in Europe and the United States, while systemic lupus erythematosus is more common in Asia. In these patients, PAH can develop due to interstitial lung damage, sarcoidosis, myositis, or as a result of isolated damage to the pulmonary vessels with the involvement of postcapillary venules [2,4]. This article provides a summary of the prevalence, current approaches to the diagnosis and treatment of patients with PAH CTD.

EPIDEMIOLOGY

Data on the prevalence of PAH are well known and, according to various estimates, vary from 2.4 to 15 cases per million adults, reaching about 15–60 patients per million population in Europe [2,3]. PAH CTDs, mainly systemic scleroderma, are the leading cause [2] of PAH in the subgroup of PAH-associated forms. There is another point of view, about 90% of cases of PAH CTDs are associated with systemic sclerosis (74%), mixed connective tissue disease (8%) or systemic lupus erythematosus (8%) [5]. However, there is currently no accurate epidemiological data on the prevalence of both systemic diseases and PAH CTDs [1].

SYSTEMIC SCLERODERMA

The data on the prevalence of PH in scleroderma depend on the used diagnostic method (RHC, Echocardiography), diagnostic approach and its accuracy (but often the method is based on the assessment of clinical symptoms or other "active screening" methods), and also SSc duration.

Despite of the fact that RHC was carried out in many recently published researchers, it should be noted that the pre-test likelihood of PH and the results of diagnostic tests were significantly different. In addition, there is lack of corresponding data on the relevant diagnostic measures and the screening protocols in most publications. Some changes in definition of PH proposed by the World Symposium on Pulmonary Hypertension (WSPH) may affect the prevalence of PAH SSc [2,4]. More recent studies showed the prevalence of PAH SSc as more than 10% in the population with at least 10 years disease duration. The incidence of PH in the patient population with SSc was estimated as 1–2% per year. According to some authors, there is a steady increase in the number of patients with PAH SSc [4].

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

There is still a significant uncertainty in prevalence of SLE, presumably of 0.5 to 17.5%. These data are based on small studies using echocardiography as the only assessment method. For example, the PAH SLE prevalence as 0.1% was calculated based on 28 patients with PAH SLE who were included in the register in the UK, between 2001 and 2006. Similar conclusions on the low prevalence of PAH SLE were obtained in several other countries, France and the United States [4].

MIXED CONNECTIVE TISSUE DISEASES (MCTD)

The prevalence of other MCTDs associated with PH is rather difficult to estimate due to the high prevalence of SSc, the absence of clear criteria for differential diagnosis between MCTD subtypes, and misdiagnosis of some scleroderma forms as other MCTD subtypes [4].

PATIENTS AND CLINICAL PICTURE

As in case with IPAH, impaired synthesis of vasoactive mediators, such as NO and prostacyclin, and increased levels of vasoconstrictors and proliferative mediators (endothelin-1) play a key role in the regulation of vascular tone and contribute to their remodeling in PAH CTD [5]. It should be noted that many modern theories of the PH pathogenesis focus on damage to the endothelium and the imbalance between vasoconstriction and vasodilation mediators [3]. Pulmonary vascular endothelial dysfunction is considered to be an integral pathophysiological factor that triggers the development and progression of PH [3,6]. Another interesting moment in the pathogenesis of PAH is the releasing of chemotactic factors responsible for the smooth muscle cell migration into the vascular intima due to the damage of endothelial cells [8]. Permanent damage of the endothelium causes an increase in vascular obstruction and obliteration, and contributes to progressive remodeling of the pulmonary vessels [3].

There is growing evidence that inflammation and an autoimmune response could contribute to the onset and progression of PAH CTD, especially in patients with SLE and mixed CTD who require early usage of corticosteroids and immunosuppressants to avoid irreversible abnormal changes in the pulmonary vessels, and vice versa, immunosuppressant drugs are ineffective in PAH SSc, which requires aggressive PAH-specific therapy [5].

J.P. Nunes et al. reviewed PAH CTD reports from two main scientific databases. The strong relationship between autoimmune mechanisms and pulmonary hypertension in patients with SSc was analyzed and demonstrated in one of their studies [10].

Patients with PAH CTD are mostly females (female to male ratio of 4:1), mainly older (mean age at the time of diagnosis is more than 60 years old), who may have comorbidities and lower survival rate. The unadjusted risk of death for PAH SSc compared with IPAH is 2.9 years, which is generally similar to that for IPAH [2].

The symptoms and clinical manifestations of PAH CTD and IPAH are very similar, with only screening immunological tests allowing to correctly diagnose PAH CTD. Patients with SSc without PH symptoms are recommended to annually undergo echocardiography as a screening investigation, determine the diffusing capacity of the lung (DL) and biomarker levels [2].

Clinical symptoms of PAH are primarily caused by signs of right heart failure and include dyspnea, fatigue and weakness, chest pain, syncope, irregular heart rate, cough and hemoptysis, and lower extremities edema [2,3].

Inspiratory dyspnea with a tendency to progression is one of the first symptoms of the disease and is often accompanied by fatigue, chest pain, dizziness and syncope [3,7].

Chest pain in IPAH patients has different features. Dizziness and syncope as a result of decreased cardiac output (CO) are also not uncommon manifestations of PAH and are observed in more than half of patients with PH [7].

In 60–65% of patients, palpitations and irregular heart rate often occur during intensive physical activity, while "malignant arrhythmias" are not recorded on the ECG even in the terminal stage of the disease [3].

Nonproductive cough occurs in one third of patients with IPAH and associated with a number of factors (pulmonary congestion, inflammatory changes in the bronchi, lungs, irritation of the recurrent laryngeal nerve (with dilated pulmonary artery)). Rare manifestations of PAH include hoarseness due to compression of the recurrent laryngeal nerve by the dilated PA [7].

Edema of the lower extremities, ascites, significant weakness are rather symptoms of disease progression and indicate right ventricular dysfunction and increasing severity of tricuspid regurgitation [2,3].

Hemoptysis is less common than most other symptoms (about 9%) and can be most often caused by ruptures of small bronchial arteries in the bronchial mucosa due to high PAP and by thromboembolism into small branches of the pulmonary artery (associated with coagulation disorders) [3,8].

An examination of patients with IPAH reveals about 70% of patients with cyanosis and acrocyanosis of different severity [3]. Intense "black" cyanosis, deformation of the fingers also known as "clubbed fingers", and "watch-glass nails" are a rather rare signs of the disease and mainly in the terminal stage [9]. Patients with severe RV hypertrophy and dilatation may have epigastric pulsation over PA in the 2nd and 3rd left intercostal space. In severe RA hypertrophy, the pulsation moves to the apical region (RV becomes the heart apex as a result of rotation). Signs of decompensation in IPAH patients in the systemic circulation are swelling of the legs and feet, hepatomegaly, the "caput medusae" sign (dilated cutaneous veins around the umbilicus) [7].

Auscultation remains an important tool in the clinician's practice. It allows to identify typical auscultatory murmurs: second heart sound over PA, which is detected in the overwhelming majority of IPAH patients, as well as the systolic murmur of tricuspid regurgitation over the xiphoid process, radiating to the right side of the sternum and to the apex of the heart. The murmur may shift to the left in RV hypertrophy [7].

DIAGNOSIS AND TREATMENT

The role of a rheumatologist is not only making a diagnosis; in some conditions, such as SLE, optimal immunosuppressive therapy is the key to successful treatment of PH, and, unlike IPAH, PAH CTD can often be accompanied by complications of CTD, as well as symptoms

of PH progression or development of adverse events due to taken specific therapy [4].

There are no PAH-specific symptoms; early diagnosis is difficult, for this reason, the time from manifestation to the final diagnosis takes about 1.5 to 2 years. Early diagnosis remains a priority for current medicine throughout the world and is the key to early treatment, since pathogenetic treatment is started under conditions of intact right ventricular (RV) function [2,3,7]. It is necessary to rule out primarily the left heart disease as the most common cause of PH (about 75%), as well as lung disease, CTEPH, and other rare conditions leading to increased PAP in all patients [2].

Current diagnostic methods for PAH and PAH CTD during an examination of patients are well known and will not differ significantly from each other. Echocardiography is a non-invasive screening method for examination patients with PH. It not only allows to measure several parameters (PAP, TAPSE, CO, dimensions of the cardiac chambers and PA), so necessary to determine the echocardiographic probability of PH, but also to rule out PH due to a left heart disease (congenital heart defects (CHD), mitral and aortic valve diseases) [3].

The "gold standard" in the diagnosis of PH is RHC — an invasive method that allows to determine the PH hemodynamic type and determine a diagnosis. An integral component in RHC for IPAH patients is an assessment of vasoreactivity or the so-called acute vasodilator testing (AVT). Its purpose is to identify those few responders with IPAH (about 10–25%) to possible therapy with calcium channel blockers (CCBs). The situation with PAH CTD patients is different. Less than 1% of patients experience a long-term response to CCB therapy, which is one of the reasons for not performing AVT in PAH CTD patients in routine practice [2,3].

Indeed, laboratory tests are less useful than others in detecting PH, but they are necessary for verification of some PH variants. Serological tests play a key role in ruling out CTDs, as well as other possible causes of associated forms of PAH (HIV infection, viral hepatitis) [2]. Interestingly, about 40% of PAH patients have increased titers of antinuclear antibodies, but usually low (1:80). Close attention should be paid to ruling out systemic diseases, in particular SSc because of its high prevalence among PAH patients [2].

In limited SSc, antinuclear antibodies are usually detected, including anti-centromere, anti-dsDNA, anti-Ro, anti-U3-RNP, anti-B23, anti-Th/To and anti-U1-RNP antibodies. Diffuse scleroderma is usually associated with positive anti-U3-RNP antibodies. Patients with SLE, for example, may have anticardiolipin antibodies [2].

THE ROLES OF CONSERVATIVE TREATMENT AND RIOCIGUAT FOR THE TREATMENT OF PAH CTD

An imbalance between endogenous mediators is the cause and consequence of pathological processes in PH; drug effects on certain molecular pathways are the basis of current PAH-specific therapy with prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5 inhibitors) and soluble guanylate cyclase (sGC) stimulators [2,3]. The theoretical evidence for PAH-specific therapy usage in PAH CTD is based on physiological, pathomorphological, and functional similarities of these PH forms [3,14].

The absolute goal of therapy for PAH is to achieve a low-risk status, which is usually associated with good exercise tolerance, good quality of life, good RV function, and low risk of mortality [2].

In general, the management of patients with PAH CTD and patients with IPAH should be similar. This recommendation comes from the fact that many patients with CTDs were included in the majority of randomized clinical trials (RCTs) conducted to receive approvals for a range of PAH-specific drugs, including combination therapy trials. A subgroup analysis of patients with CTDs in most RCTs showed the beneficial efficacy of specific therapy. In some RCTs, the response to treatment in the PAH CTD group was more modest compared to the IPAH group [2]. One of these major studies is a phase III RCT, PATENT-1 (NCT00810693), the objective of which was to investigate the efficacy and safety of riociguat for the treatment of PAH. The study included 443 PAH patients, with a quarter of them (about 25%) having PAH CTD. All randomized patients were both: naive and pretreated with PAH-specific therapy (except for PDE5 inhibitors).

The patients were assessed during the titration period and after 12 weeks of therapy (the end of the maintenance phase of the study). Riociguat significantly improved exercise capacity and some other parameters in PAH patients (mean 6MWD increased to 30 m in patients treated with the maximum single dose of riociguat (2.5 mg) and decreased to 6 m in the placebo group at study week 12 (the mean difference calculated by the least squares method is 36 m; 95% CI: 20–52; p <0.001). Significant improvements were also noted in PVR (p <0.001), NT-proBNP (p <0.001), and WHO FC (p = 0.003) [19].

Long-term treatment of PAH was studied in the PATENT-2 RCT (NCT00863681) and included 363 patients (including those with PAH CTD) who completed the PATENT-1 study. The mean treatment duration of it was 438 days. An assessment of the safety and tolerability of long-term treatment with riociguat was selected as the primary endpoint. The PATENT-2 study showed further improvements in 6MWD and WHO FC. The survival rate for PAH patients at 1 year was 97% (95% CI 94–98%) [20]. The two-year survival rate for PAH patients in the PATENT-2 study was 93% (90–95) [21].

Humbert M. et al. separately studied the efficacy and safety of riociguat for the treatment of PAH CTD patients based on results of both trials: the PATENT-1 and PATENT-2 studies [23]. This research is a prospectively planned analysis of the safety and efficacy of riociguat in a cohort of patients with PAH CTD. Patients with CTD in PATENT-1 (111 patients) in a prospectively defined PAH CTD cohort were stratified into three subgroups:

- PAH SSc (66 patients);
- PAH associated with other specific CTDs (39 patients). Of these: PAH associated with SLE (18 patients), rheumatoid arthritis (11 patients) and other mixed CTDs (10 patients);
- PAH associated with an unspecified CTD (6 patients).

86 patients out of 111, received riociguat (about 77%) (of which 71 patients received a maximum single dose of 2.5 mg, and 15 patients - a maximum single dose of 1.5 mg), the other 25 patients received placebo (23%). Notably, 79 patients from the riociguat group and 19 patients from the placebo group completed the PATENT-1 study. 94 (85%) patients with PAH CTD completed the PATENT-1 study and participated in the PATENT-2 study. The treatment duration (mean (SD)) in the PAH CTD patient population in the PATENT-2 study was 31 ± 14 months.

By the end of week 12, therapy with the maximum daily dose of riociguat, 2.5 mg, allowed to increase 6MWD in the PAH CTD patient population (mean (SD)) by +18 ± 51 m compared with a decrease in that in the placebo group of -8±110 m. Patients with PAH SSc treated with riociguat experienced a smaller increase in 6MWD (+4±43 m), but there was a significant decrease in 6MWD in the placebo group (-37 ± 120 m) by the end of week 12. Similar improvements were observed in the riociguat and placebo groups by the end of week 12 in the subgroup of patients with PAH associated with other specific CTDs.

Similar changes (compared to the baseline) in 6MWD (mean (SD)) by the end of Week 12 (21 ± 53, 17 ± 50, 14 ± 63, respectively) were demonstrated in naive patients, patients previously treated with PAH-specific therapy, and patients treated with concomitant immunosuppressive therapy.

In the PATENT-2 study, improvements in 6MWD were significantly maintained for 2 years in patients with PAH CTD; groups of PAH SSc and PAH associated with other specific CTDs. The WHO FC improved or remained unchanged (compared to 75% in the placebo group) in 97% of patients with PAH CTD during the treatment with riociguat by the end of week 12. The results were similar in the PAH SSc and PAH associated with other specific CTDs subgroups.

The authors concluded that riociguat improved a number of efficacy endpoints in patients with PAH CTD, including 6MWD, WHO FC, PVR and cardiac index, although the improvements were less pronounced

than in the whole PATENT-1 patient population.

Over 2 years of riociguat therapy in the PATENT-2 study, the survival rate of patients with PAH CTD was similar to that observed in patients with idiopathic/heritable PAH in the PATENT-2 study (93%). This is an important observation, as it was previously reported that mortality from PAH CTD is higher than that in IPAH, despite current therapy.

Improvements in 6MWD in patients previously treated with ERA (53% of the PAH CTD population) suggest that riociguat may have an additional therapeutic effect (benefit) for ERA-treated patients with PAH CTD. This fact supports the potential use of combination therapy in this patient subgroup.

The same evidence can be found in the updated recommendations from the Cologne Consensus Conference 2018, according to which, the initial combination therapy (dual oral combination therapy with ERA and sGC stimulators or ERA and PDE5 inhibitors) is recommended as the standard approach for patients newly diagnosed with classic forms of PAH, i.e. younger patients without significant (serious) cardiopulmonary comorbidities. The use of monotherapies was no longer considered appropriate in such patients.

In high-risk patients with "classic" PAH, triple combination therapy including prostacyclin analogues should be considered.

For patients who suffer from PAH and significant cardiopulmonary comorbidities, initial monotherapy is recommended. The use of combination therapies for such patients should be considered individually.

These recommendations also support the switch therapy from PDE5 inhibitors to sGC stimulators on an individual basis, which, in some cases, may be the best approach in comparison with escalation of therapy [22]. This approach is not unreasonable, since most patients with PAH (according to some reports, up to 60%) do not respond properly to PDE5 inhibitors [24].

The reasons for this may lie in the reduced concentration of endogenous NO in the pulmonary vascular walls of patients with PAH, as well as in the breakdown of cGMP by PDE isoenzymes, in relation to which sildenafil has low or no activity [25]. In this regard, sGC stimulators were suggested to be a good alternative for PAH patients not responding to PDE5 inhibitors [26].

Riociguat has a dual mechanism of action: first, it helps increase the synthesis of cGMP through direct stimulation of sGC, similar to NO and independently of it; second, it sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. By restoring the natural metabolic NO-sGC-cGMP pathway, it causes an increase of cGMP production. The ability of riociguat to stimulate the synthesis of cGMP under NO deficiency, often observed in PAH, represents a potential advantage over PDE5 inhibitors [16, 24, 26].

The presence of generalized microangiopathy and other vascular damage such as digital ulcers should be taken into consideration when it comes to the choice of PAH-specific therapy for the treatment of PAH patients with systemic diseases, particularly with SSc. The treatment for patients with PAH CTDs is more complex than the treatment for IPAH patients. Immunosuppressive therapy, combination glucocorticoid therapy, and cyclophosphamide can improve the clinical condition of patients with PAH SLE or mixed CTDs [2].

The possibilities of using combination therapy in PAH CTD were studied in a systematic review and meta-analysis by Pan J. et al. The search was conducted among randomized controlled trials in the Cochrane Library, MEDLINE, PubMed and EMBASE databases, which directly compared the efficacy of PAH-specific combination therapy and monotherapy in patients with PAH CTD. This meta-analysis was one of the largest ones and included 6 RCTs involving 963 patients. The authors concluded that combination PAH-specific therapy can provide preferable therapeutic efficacy compared with monotherapy in patients with PAH CTD, through significant reduction of the risk of clinical deterioration and exercise capacity improvement [11].

There have also been few reports of combination therapy for patients with PAH SSc and SLE (overlap syndrome). The combination therapy included a sGC stimulator, riociguat, and immunosuppressive therapy. Due to this approach, there was a decrease in systolic PAP and less severe symptoms of CDT [12].

A series of clinical cases described patients with PAH CDT who were switched from a PDE5 inhibitor to riociguat because of an inadequate therapeutic response. Switching to riociguat improved respiratory and hemodynamic parameters and demonstrated a favorable safety profile [13].

Nowadays, riociguat is the only sGC stimulator approved in Russia for the following indications: some forms of PAH (IPAH, inherited PAH, PAH CTD) and CTEPH in monotherapy or as part of combination therapy with ERA or prostanoids [16]. Due to the dual mechanism of action, it affects the increase of cGMP level, stimulates vasorelaxation, and suppresses proliferation, which were demonstrated in experimental PH models [15,18]. Such groups of drugs as prostanoids, PDE5 inhibitors and ERAs contribute to the improvement of hemodynamics and (or) WHO FC, however, morphological changes in PH probably limit the efficacy of this therapy [8]. The clinical advantage of riociguat is its efficacy in PAH CTDs, while potentially beneficial features of its mechanism of action are independence from endogenous nitric oxide levels in cGMP synthesis and independence from other (apart from PDE5 inhibitors) phosphodiesterase enzymes [15,17].

DISCUSSION

PAH CTDs is a group of complex and diverse conditions, in which establishing a correct diagnosis both in relation to CTD and the PH form is the first and very important step to optimal treatment. Diagnosis, treatment and monitoring of such patients require attention not only to PH, but also to the underlying systemic disease, since the disease progression and worsening of the condition can be caused by both the underlying disease and its complication (PH) in the form of heart failure and exercise capacity [4].

It is recommended to use the same therapy for patients with PAH CTD as well as for IPAH, which has a high class of recommendations and level of evidence (IC) [2].

Patients with PAH CTD have a poorer prognosis than patients with IPAH; the survival rate of patients with PAH SSc is worse than that in patients with PAH CTD not associated with scleroderma. The response to PAH-specific therapy in patients with PAH CTD (in particular PAH SSc) is often lower than in IPAH patients [23].

Current PAH-specific therapy can improve the functional status, hemodynamic and laboratory parameters in some forms of PAH, including PAH CTD. The use of targeted therapy is associated with relatively high survival rates for patients, which is confirmed by a number of clinical studies and registers [27].

In addition to vasodilation activity, riociguat also has antifibrotic, antiproliferative and anti-inflammatory effects. Riociguat may have an additional therapeutic effect (benefit) for ERA-treated patients with PAH CTD. This fact, in turn, supports the potential use of combination therapy in this patient subgroup [23].

Potential benefits of the combination therapy were reflected in the updated recommendations from the Cologne Consensus Conference. Initial combination therapy for treatment-naive patients and withholding it for elderly patients with severe comorbidities, as well as switching from PDE5 inhibitors to sGC stimulators on an individual basis, is considered the most optimal treatment approach for PAH patients [22]. The safety and efficacy of switching from PDE5 inhibitors to riociguat has been demonstrated in a number of studies [24].

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