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Soluble Guanylate Cyclase Modulators in Heart Failure

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Abstract This review summarizes the role of soluble guanylate cyclase (sGC)-cyclic guanosine 3′, 5′-monophosphate pathways in heart failure and several new drugs that modify guanylate cyclase. The sGC activators and stimulators as modulators of sGC are promising drugs in the therapy for decompensated heart failure and pulmonary hypertension. Cinaciguat is a nitric oxide (NO)–independent direct activator of sGC, which also may be effective under oxidative stress conditions resulting in oxidized or heme-free sGC refractory to organic nitrates. Riociguat is an NO-independent direct stimulator of sGC with beneficial effects in patients with decompensated heart failure and pulmonary hypertension. The sGC modulators play an important role in patients with heart failure and pulmonary hypertension.

Keywords Heart failure · Guanylate cyclase · Cyclic guanosine monophosphate · sCG stimulator Cinaciguat · sGC activator Riociguat

Introduction

Despite significant advances in the modern diagnosis and pharmacologic and nonpharmacologic therapy for heart failure, with a reduction of mortality of more than 50%, long-term prognosis of the disease still is poor and, often, with uncertain outcome [1, 2].

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The great expectations set in vasopeptidase inhibitors, tumor necrosis factor–α antagonists, metalloproteinase inhibitors, endothelin antagonists, and adenosine A1-receptor antagonists could not be verified by findings as has been shown in large-scale clinical trials. The calcium sensitizer levosimendan, the vasopressin V2-receptor antagonist tolvaptan, and the natriuretic peptide (NP) nesiritide only partially fulfilled the expectations. There remains an urgent unmet need for new therapies with new drugs and new modes of action.

Drugs that modulate soluble guanylate cyclase (sGC) and cyclic guanosine 3′, 5′-monophosphate (cGMP) levels are emerging as promising therapies for heart failure. The sGC activator cinaciguat and sGC stimulators riociguat and BAY 60-4552 as modulators of sGC are promising drugs with favorable effects such as vasodilatation; inodilation; and antiproliferative, antiapoptotic, and antiremodeling effects through protein kinase G-type and phosphodiesterases as well as calcium ion channels [3].

Cinaciguat (BAY 58-2667) is a novel molecule that activates regulatory sites on both the α and β subunits of sGC, a key signal transduction enzyme that synthesizes cGMP in response to binding of nitric oxide. Cinaciguat has a unique feature, to activate sGC independently of NO and of the prosthetic heme group. Cinaciguat is even more potent if the heme group is oxidized and insensitive to NO.

Riociguat (BAY 63-2521) is a direct stimulator of sGC in vitro and in vivo that is independent from NO, the endogenous activator of the enzyme. Moreover, in the presence of NO, it enhances the effect of NO [4, 5••]. In previous clinical studies, riociguat revealed beneficial effects and good tolerability in patients with pulmonary hypertension [6] and patients with severe heart failure [7].

This article summarizes the pathophysiologic relevance and therapeutic potential of the sGC–cGMP signalling system in acute and chronic heart failure.

Guanylate Cyclase Pathway

Cyclic guanosine 3′, 5′-monophosphate is a second messenger that plays a role in various crucial physiologic pathways, including cardiovascular homeostasis, cellular growth and contractility, inflammation, sensory transduction, and neuronal plasticity and learning [8]. Guanylate cyclases (GC) are enzymes that catalyze the conversion of guanosine-5'-triphosphate to cGMP. The GC family includes both membrane-bound and soluble isoforms that are expressed in nearly all cell types. Membrane-bound particulate guanylate cyclase (pGC) serves as a receptor for NPs, whereas plasmatic sGC acts as a receptor for biological messenger NO. Subsequently, cGMP effectors include cGMP-dependent protein kinases, cGMP-regulated phosphodiesterases, and cyclic nucleotide-gated ion channels (Fig. 1) [9].

Both the NO–sGC–cGMP pathway and the NP–pGC–cGMP pathway are disordered in a range of cardiovascular conditions, including acute decompensated heart failure (ADHF) [10••].

The NP–pGC signalling pathway has been shown to play an important role as a compensatory mechanism that reduces neurohumoral activation in heart failure. pGC contains an extracellular ligand-binding domain and an intracellular catalytic domain connected by a single transmembrane domain [11]. At least seven pGC family members have been identified and sequenced (GC-A to GC-G).

In humans, NPs constitute a family of at least four identified members: atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), of myocardial origin; C-type natriuretic peptide (CNP), derived from the endothelial cells; and urodilatin, produced in the kidneys [12, 13]. The GC-A

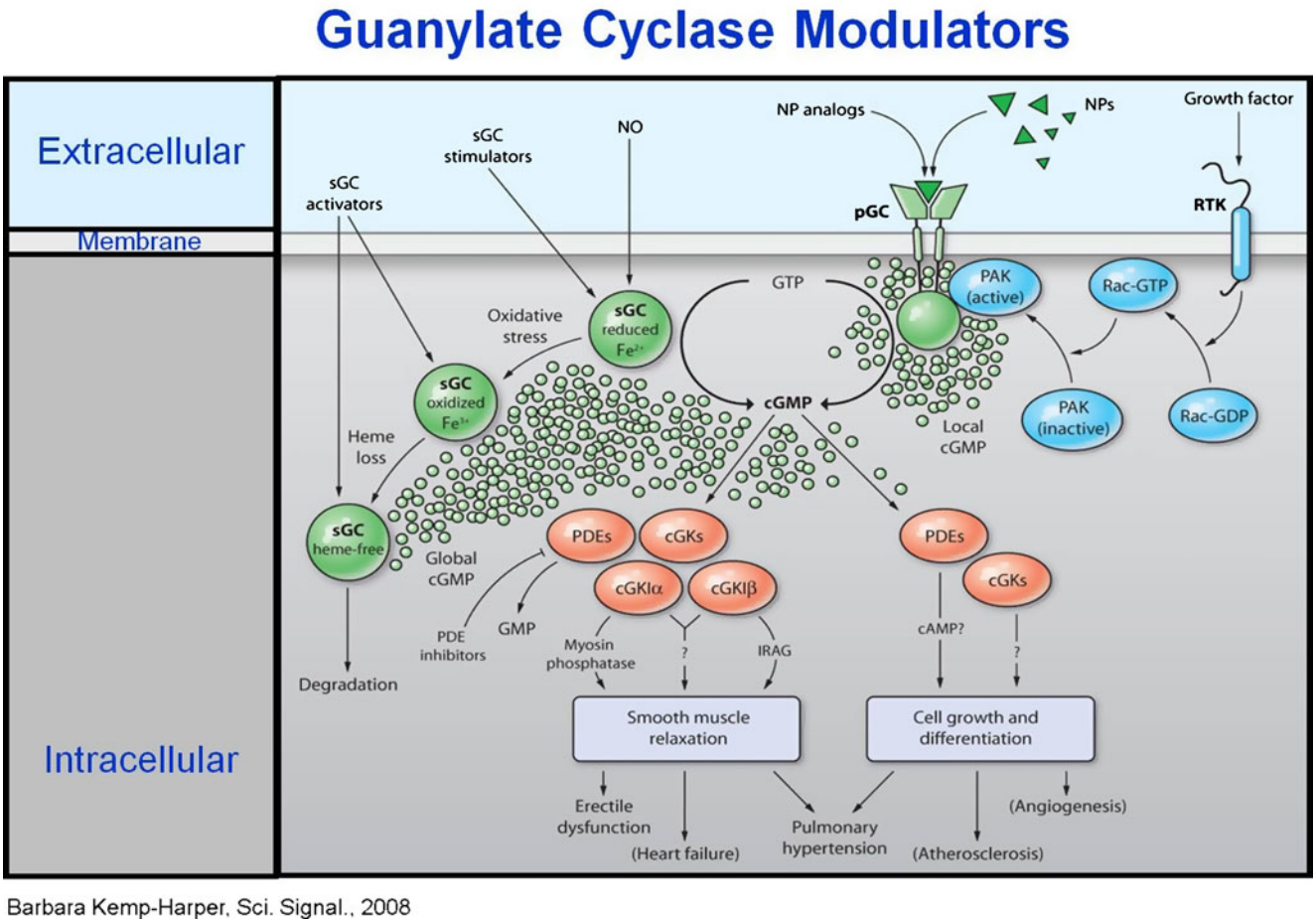

Fig. 1 sGC– and pGC–cGMP signalling pathways. cGMP acts through cGMP effectors including cGMP-dependent protein kinases, cGMP-modulated cation channels, and cGMP-regulated phosphodiesterases that hydrolyze cyclic nucleotides. NO—nitric oxide; NP—natriuretic peptide; RTK—receptor tyrosine kinase; pGC—particulate guanylate cyclase; sGC—soluble guanylate cyclase; cGMP—cyclic guanosine 3', 5'-monophosphate; PDEs—phosphodiesterases; cGKs—cGMP-dependent protein kinases; GTP—guanosine-5'-triphosphate; PAK—p21 activated kinase; GDP—guanosine diphosphate; IRAG—inositol 1,4,5-trisphosphate receptor I–associated protein; cAMP—cyclic adenosine monophosphate. (*From* Kemp-Harper and Feil [36], with permission from AAAS)

binding ligands ANP and BNP are produced predominantly in the cardiac atria and ventricles and released in the circulation in response to hypervolemia, as seen, for example, in congestive heart failure. An activation of a GC-A binding domain by ANP and BNP results in cGMP increase mediating hypotensive and cardioprotective actions through increased natriuresis, inhibition of the renin-aldosterone pathway, as well as vasorelaxant, antifibrotic, antihypertrophic, and lusitropic effects [10••, 13].

In patients with heart failure, the described compensatory response to NPs is disturbed due to markedly altered distribution and degradation of the NPs [14]. It has been demonstrated that there is an inadequate neurohumoral response to volume/sodium overload not only in advanced stages of heart failure, but also in patients with only very mild symptoms of the disease [15].

As for the NO–sGC–cGMP pathway, in conditions of oxidative stress that typically occur with cardiovascular diseases, the NO production is reduced. On the other hand, the NO degradation and neutralization by oxidants such as superoxide is excessively increased, contributing to an overall NO deficiency [3, 16•]. Additionally, the oxidation of the heme group on sGC impairs the enzyme bioavailability and responsiveness to endogenous NO and exogenous nitrovasodilators reducing the activation of this signalling pathway even further [3].

The described disruption of physiologic signalling response in patients with heart failure builds the rationale for new therapeutic agents that target these GC pathways.

Several novel drugs that induce the pGC–cGMP pathway include NP analogues nesiritide and ularitide. Both compounds show natriuretic, diuretic, and vasodilating effects [17, 18]. While there is good evidence of positive short-term hemodynamic effects of nesiritide in ADHF [19], there still is controversy that needs to be addressed in future trials regarding its safety risks, including renal dysfunction and long-term mortality [20]. Ularitide currently is being evaluated and is showing promising effects on preserving renal function in patients with ADHF. These results also need to be further investigated in larger trials [21, 22].

Although the activation of sGC and pGC cascades produce the same second messenger, it has been demonstrated that the effects of cGMP differ in dependence of the origin of production. The probable explanation for this effect are different locations of GCs within the cardiac myocytes with sGC being mainly located in the cytosol and pGC being mainly found in subsarcolemmal areas [23]. This concept of compartmentalization of cGMP is particularly interesting for predicting effects of novel therapies modulating either one or the other signalling pathway. Thus, the effects of synthetic NP analogues like nesiritide or ularitide as ligands of pGC differ slightly from therapeutic agents that target sGC like cinaciguat.

In the following section, we focus on the sGC–cGMP pathway and its activation through a novel NO-independent activator cinaciguat (BAY 58-2667).

Soluble Guanylate Cyclase Signalling Pathway

NO is a key signalling molecule in a variety of physiologic processes in mammals. NO is produced endogenously from the amino acid L-arginine by the enzyme NOS. There are different NOS isoforms that were isolated from the brain, vascular endothelium, and macrophages [24]. Endothelial NOS (eNOS) is a Ca^{2+}- and calmodulin-dependent NO-synthase that originally was identified as constitutive in vascular endothelial cells. Activation of eNOS is induced by two basic pathways: sheering forces produced by blood flow and endothelial receptors for a variety of ligands like bradykinin, acetylcholine, adenosine, and other vasoactive substances. Both pathways cause a release of calcium with subsequent eNOS activation. eNOS produces NO and activates sGC located in the adjacent vascular smooth muscle cells, thereby increasing levels of cGMP and inducing vasorelaxation. This mechanism is thought to play a major role in the regulation of vascular tone and blood pressure [24].

Reduced bioavailability and/or responsiveness to endogenous NO contribute to the development of cardiovascular diseases [3, 10••]. Organic nitrates, such as nitroglycerin, and other NO-donor drugs, known as vasodilators, showed beneficial effects on a variety of cardiovascular diseases including coronary artery disease and congestive heart failure. During short-term therapy, nitrates rapidly improve hemodynamics by increasing levels of cGMP in the vascular smooth muscle cell with resultant peripheral arteriolar and venous vasodilatation providing a decrease in filling pressures and systemic vascular resistance, and thereby lowering myocardial oxygen consumption [25]. However, one of the major limitations of nitrates is the development of dose-related tolerance in long-term treatment, as well as nonspecific interactions of NO with other biological molecules [3, 26]. Furthermore, despite potent short-term symptoms relief, there is no clear evidence of long-term mortality reduction in patients with cardiovascular disease [3].

To understand the difference between the mechanisms of actions of traditional therapeutics like nitrates and new compound like cinaciguat, it is important to outline the structure of their receptor sGC. sGC is a heterodimer consisting of an α- and a heme-containing β-subunit. NO only can induce sGC upon binding to its reduced Fe^{2+} heme moiety. It its oxidized state, sGC heme strongly reduces its affinity for the sGC heme binding site, often resulting in a subsequent loss of the prosthetic heme group.

Its loss renders the enzyme insensitive to endogenous and exogenous NO [3, 27, 28].

Cardiovascular diseases like atherosclerosis, diabetes, and hypertension are associated with a high degree of oxidative stress. During oxidative stress, reactive oxygen species (ROS) interfere with NO–sGC signalling pathway by reducing NO bioavailability and by oxidizing the sGC heme moiety, thereby leading to sGC degradation.

Unlike conventional nitrovasodilators, two novel therapeutic groups can induce sGC in its NO-insensitive state, so-called sGC-activators and sGC-stimulators. sGC-activators like cinaciguat induce sGC in its NO-insensitive, oxidized ferric (Fe^{3+}) heme-free state. On the other hand, sCG-stimulators like YC-1, BAY 41-2272, CFM-1571, A-350619, and riociguat enhance the affinity of sGC to already very low levels of NO, thereby producing synergistic effects with NO (Fig. 2).

Cinaciguat: Clinical Benefits in Decompensated Heart Failure

Cinaciguat, the first of a new class of sGC activator, is in early clinical development for the treatment of ADHF. The few preclinical and clinical data show that it has great potential as an effective substance for treatment of ADHF. In animal experimental studies, the cardiorenal effects of intravenous cinaciguat, 0.1 or 0.3 μg/kg/min, were evalu-

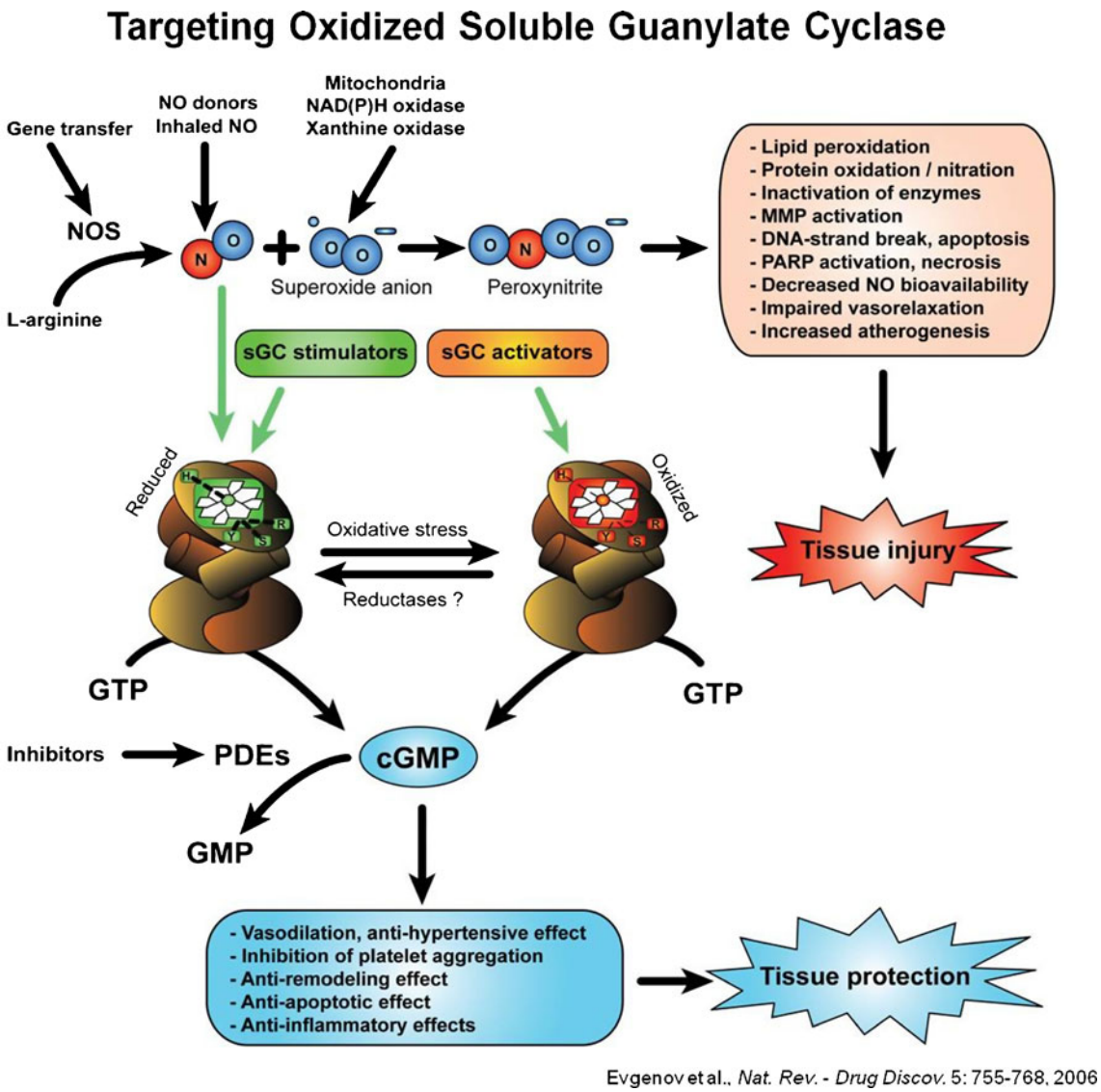

Fig. 2 NO–sGC–cGMP signalling pathway. Mechanism of action of sGC stimulators and sGC activators. See text for explanation. NO—nitric oxide; GTP—guanosine-5'-triphosphate; sGC—soluble guanylate cyclase; PDEs—phosphodiesterases; GMP—guanosine monophosphate; MMP—matrix metalloproteinase; PARP—poly (ADP-ribose) polymerase; NOS—nitric oxide synthase. (*Adapted by permission from* Macmillan Publishers Ltd: Nature Reviews Drug Discovery [3], 2006)

ated [29•, 30]. Cinaciguat potently unloads the heart by reducing arterial pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP), thereby increasing the cardiac output (CO), renal blood flow, and glomerular filtration rate.

Initial studies in healthy volunteers have demonstrated the clinical utility of cinaciguat. A favorable safety profile and efficacy were documented in lower doses of 50 to 250 μg/h for up to 4 h [31••].

After initial dose finding, cinaciguat was evaluated in a nonrandomized, uncontrolled, proof-of-concept study that included 33 patients with ADHF of functional New York Heart Association (NYHA) classes III and IV and PCWP of 18 mm Hg or greater using a starting dose of 100 μg/h, which could be uptitrated to final doses of 50 to 400 μg/h depending on hemodynamic response.

Patients were categorized as responders to the new substance if the PCWP decreased by 4 mm Hg or more compared with baseline. The responder rate was 53% after 2 h, 83% after 4 h, and 90% after 6 h. The proportion of patients reporting improvements in dyspnea scores increased during and after 6 h of cinaciguat intravenous infusion [32, 34••].

Initial results showed promising evidence of the therapeutic potential and safety of cinaciguat: continuous intravenous administration was well tolerated and increased the potent venous and arterial dilation, which led to significant cardiac preload and afterload reduction and increased cardiac index. Compared with baseline, a 6-hour infusion of cinaciguat led to significant reductions in mean pulmonary artery pressure (–6.5 mm Hg), PCWP (7–8 mm Hg), mean right arterial pressure (–2.9 mm Hg), pulmonary vascular resistance (PVR; –43.4 dynes/s/cm^{-5}), and systemic vascular resistance (SVR; –597 dynes/s/cm^{-5}), while increasing heart rate by 4.4 bpm and CO by 1.68 L/min [33, 34••].

Of 60 patients, 13 reported 14 drug-related treatment-emergent adverse events of mild to moderate intensity, most commonly hypotension.

In a placebo-controlled, randomized, double-blind, multicenter, international phase 2b study, the safety and efficacy of intravenous cinaciguat as an add-on to standard therapy was investigated in 159 patients with ADHF. Hemodynamic effects were monitored via Swan-Ganz thermodilution catheter (Edwards Lifesciences, Irvine, CA) in patients with NYHA functional class III and IV heart failure and PCWP of 18 mm Hg or greater [35].

Cinaciguat dose was titrated from 100 μg/h to a maximum of 600 μg/h for the first 8 h and was then maintained for up to 40 h. Primary end point was a change in PCWP after 8 h compared with placebo; secondary end points included hemodynamic and safety parameters, organ protection, and 30-day mortality.

In this study, 159 patients on stable standard therapy were enrolled within 48 h after hospital admission to receive placebo or cinaciguat. The new substance caused a rapid and sustained decrease in the primary end point PCWP, increased CO, and decreased PVR without changing heart rate. No adverse effects on cardiac or renal function or 30-day mortality were observed despite increased occurrence of several cases of oligosymptomatic hypotension at high doses of cinaciguat, which led to prematurely termination of the study [35].

Under low dosage of intravenous Cinaciguat, a phase 2b study (COMPOSE EARLY) currently is recruiting participants to investigate the efficacy and tolerability of Cinaciguat (150 μg/h, 100 μg/h, 50 μg/h) [35]. The results are expected within the next 2 years.

Riociguat: Clinical Utility in Heart Failure and Pulmonary Hypertension

Riociguat has shown its unique mechanism of action through simultaneous lowering SVR and PVR in a phase 2 trial in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) [6].

The trials confirmed the expected pharmacologic mode of action, which is consistent with the properties of a sGC stimulator, and showed significant effects on pulmonary hemodynamics (decrease of PVR, increase of CO), echocardiographic parameters, N-terminal proBNP levels, and functional capacity (improvement in 6-minute walking distance) without major safety concerns. Improvements also were observed in NYHA functional class and Borg dyspnea score. Riociguat was well tolerated and had a favorable safety profile [6, 31••].

Based on these data, two randomized, placebo-controlled, phase 3 studies have begun: the CHEST-1 study (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With CTEPH) in patients with CTEPH and the PATENT-1 trial (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With Pulmonary Arterial Hypertension) for patients with PAH. Both studies will be followed by open long-term studies (CHEST-2 and PATENT-2). Recruitment for CHEST-1 and PATENT-1 is ongoing. Results from the study program are expected in 2011.

Similar reduction of SVR and PVR was seen in a single-dose study in 42 patients with biventricular heart failure (LVEF≤45%, pulmonary artery pressure [PAP] mean≥25 mm Hg, and PCWP≥18 mm Hg) to evaluate the acute hemodynamic response to BAY 60-4552, a main metabolite of riociguat. Oral administration of doses from 1 to 10 mg was well tolerated and mediated a potent vasodilation. Biventricular preload and afterload were improved, subsequently resulting in a significant increase of cardiac index. Riociguat shows great promise

for treatment in pulmonary hypertension associated with left ventricular systolic dysfunction on top of standard congestive heart failure therapy.

Currently, riociguat is being investigated in a multicenter study in patients with congestive heart failure and pulmonary hypertension (LEPHT study [A Study to Test the Effects of Riociguat in Patients With Pulmonary Hypertension Associated With Left Ventricular Systolic Dysfunction]).

Conclusions

Cyclic guanosine-3', 5' monophosphate is a second messenger that plays a role in various physiologic signalling pathways. It is produced either by membrane-bound pGC or sGC. pGC is induced by NPs; sGC by NO. In cardiovascular diseases like ADHF, the physiological NO–sGC and NP–pGC signalling pathways are disrupted.

Cinaciguat, a novel NO-independent sGC activator, offers many advantages over traditional organic nitrates and other NO-donor drugs, whose use often is limited due to tolerance development, limited biometabolism, nonspecific interactions, lack of sGC activation in the absence of the sGC heme moiety, and lack of benefit in long-term mortality.

Cinaciguat is a novel sGC activator that binds to the NO-sensitive oxidized ferric (Fe^{3+}) or heme-free sGC, thus stimulating cGMP synthesis. In this way, the substance is effective under oxidative stress, which is present in many cardiovascular diseases.

Despite limited clinical data for cinaciguat, preliminary studies in patients with ADHF demonstrate a significant hemodynamic benefit and reduction of symptoms. Further studies are required to evaluate cinaciguat, in particular, because of its novel and promising mode of action. There is a need for studies that address long-term symptoms and mortality in a larger number of patients with ADHF.

Riociguat (BAY 63-2521) has been investigated in 14 clinical pharmacological studies confirming the mechanism of action of the compound as an sGC stimulator.

A proof-of-concept study in patients with pulmonary hypertension showed that sGC stimulation exerted by a single dose of riociguat had the expected favorable hemodynamic effects on subjects with pulmonary hypertension.

In a phase 2 study, riociguat, at doses between 1 mg three times daily and 2.5 mg three times daily, was administered for 12 weeks to 72 subjects with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension [6].

Riociguat was generally safe and well tolerated and exerted significant and favorable effects on pulmonary hemodynamics and functional capacity. This was supported by evidence from echocardiography biomarker and functional class assessment.

Disclosures No potential conflicts of interest relevant to this article were reported.

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