Vericiguat in Heart Failure

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Despite advances in heart failure (HF) management, the risk of death and hospitalizations remains high in the long term. HF is characterized by endothelial dysfunction, inflammation and increased oxidative stress, due to a reduction in the activity of the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway. All these factors contribute to direct damage at the myocardial, vascular and renal level. Vericiguat restores the deficiency in this signaling pathway, through stimulation and activation of sGC, aiming to increase cGMP levels, with a reduction in HF-related oxidative stress and endothelial dysfunction.

Keywords: heart failure ; treatment ; vericiguat

1. Mechanism of Drug Action

Vericiguat is a drug that stimulates the cyclic guanosine monophosphate (cGMP) pathway through direct and indirect stimulation of soluble guanylate cyclase (sGC) [1]. The downstream effects of this stimulation pathway are smooth muscle cell relaxation, reduction in hypertrophy, inflammation and fibrosis [2].

The nitric oxide (NO)-sGC-cGMP pathway begins with NO production by vascular endothelial cells. NO is synthesized from L-arginine by three nitric oxide synthases, among which endothelial nitric oxide synthase (eNOS) plays a major role. NO diffuses rapidly into vessel smooth muscle cells, binds to the heme subunit of sGC and catalyzes the conversion of guanosine triphosphate (GTP) into the second intracellular messenger, cGMP [3]. CGMP interacts with three types of intracellular proteins: cGMP-dependent protein kinases, cGMP-regulated ion channels and phosphodiesterases (PDEs) [4]. Subsequently, these transduction cascades mediate various physiological and tissue-protective effects, including smooth muscle relaxation, inhibition of smooth muscle proliferation, leukocyte recruitment and platelet function [2][5].

In HFrEF, tissue hypoperfusion caused by a reduction in cardiac output induces inflammation and oxidative stress, leading to a decrease in NO bioavailability and decreased activity of cGMP [6]. Reduced sGC activity is associated with coronary microvascular dysfunction, cardiomyocyte stiffness and interstitial fibrosis, fundamental elements that lead to the progression of myocardial dysfunction [2]. Therefore, sGC stimulators, such as vericiguat, may be particularly effective in this condition, counteracting endothelial dysfunction and increased oxidative stress through cGMP elevation by a double pathway for enzyme activation [2].

CGMP is also enhanced by others signaling pathways. The natriuretic peptides (NPs, atrial natriuretic peptide and the B-type natriuretic peptide) increase cGMP through activation of membrane-bound guanylate cyclase (particularly guanylate cyclase, pGC) [7][8]. Some therapeutic strategies, which act in the NP-pGC-cGMP pathway, have been evaluated, such as synthetic NPs and NP analogs (nesiritide, ularitide) and ARNI (sacubitril/valsartan), that increase NPs through inhibition of neprilysin. In clinical trials, the use of sacubritil/valsartan has been shown to significantly improve outcomes in HF [9][10].

Degradation of cGMP in GMP is catalyzed by seven, differentially expressed PDE families [4]. PDE inhibitors, such as milrinone and enoximone (PDE-3 inhibitors) and sildenafil (PDE-5 inhibitors), have also been evaluated as therapeutic strategies in the context of HF [8]. PDE-5 inhibitors improve contractile function in systolic HF and reduce remodeling of the left ventricle [6]. However, to date, no randomized clinical trial has demonstrated an improved outcome in HF with the use of PDE inhibitors [2][8].

2. Pharmacological Proprieties of Vericiguat

Vericiguat is a weakly basic drug with a low water solubility and high intestinal permeability (class II according to the Biopharmaceutics Classification System) [11].

In six phase I studies, analysis on healthy volunteers [12], carried out with the aim of evaluating the safety, tolerability, pharmacodynamic and pharmacokinetic of vericiguat demonstrated that its chemical structure exhibits an excellent oral bioavailability (93%) with a long half-life (18–22 h) that allows oral administration once daily. It also has a high pharmacokinetic stability and a lower variability after administration with food [6][12]. Vericiguat is a low-clearance drug (1.6 L/h in healthy volunteers and 1.3 L/h in patients with HFrEF) with a plasma protein binding of approximately 98%, serum albumin being the main binding component without alterations in the case of renal or hepatic impairment [13].

In healthy subjects, after an oral administration of vericiguat, about 53% of the dose is excreted in the urine and 45% is excreted in the feces. For this reason, as demonstrated in phase I clinical trials during the titration regimen (from 0.5 mg to 15 mg daily), the drug can be administered without dose adjustments in patients with renal impairment up to an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m^2 or with moderate liver disease [12].

Vericiguat is mainly metabolized by glucuronidation through uridine diphosphate-glucuronosyltransferase (UGT 1A9 and UGT 1A1) to N-glucuronide M-1, which is pharmacologically inactive against sGC. A small part of the drug (<5%) is metabolized by the CYP clearance pathway [11][13]. In vitro studies in phase I drug–drug interaction studies revealed that vericiguat shows a low potential for pharmacological interactions: the main molecule and its N-glucuronide metabolite do not act as inhibitors of major CYP isoforms, UGT isoforms, major transport proteins or as inductors of cytochrome P450 [11][13].

3. Main HF Clinical Trials

3.1. Vericiguat in HFrEF

Two main clinical trials provided the initial evidence for the use of vericiguat in the context of HFrEF: the phase II study SOCRATES–REDUCED [14] and the phase III study VICTORIA [15].

The SOCRATES-REDUCED trial was designed to evaluate the tolerability and the optimal dose of vericiguat in patients with chronic HF and reduced left ventricular ejection fraction (LVEF), in addiction to standard therapy. Thus, 456 patients with chronic HFrEF (LVEF < 45%) were enrolled (NYHA functional classes II–IV) with an episode of worsening HF within 4 weeks of randomization, defined by symptoms or signs of congestion that required hospitalization or outpatient administration of intravenous (IV) diuretics together with an elevated level of B-natriuretic peptide (BNP) ≥ 300 pg/mL or N-terminal pro-B natriuretic peptide (NT-proBNP ≥ 1000 pg/mL if in sinus rhythm; BNP ≥ 500 pg/mL or NT-proBNP ≥ 1600 pg/mL if in atrial fibrillation) [14]. The mean LVEF of the patients enrolled was 29.6% and all of them were already on treatment with HF guideline-directed medical therapy for at least 1 month before HF hospitalization (HFH) or outpatient IV diuretics administration. None of the patients received ARNI or SGLT2i therapies. They were randomized to placebo or to vericiguat on one of the four target doses (1.25 mg, 2.5 mg, 5 mg or 10 mg once daily). Planned total treatment duration was 12 weeks, followed by a safety follow-up at 16 weeks after randomization [14][16].

The study found that over a 12-week period, the change in log-transformed NT-proBNP levels (primary endpoint) was not considerably different in the pooled vericiguat group compared with the placebo group ($p = 0.15$). However, a secondary exploratory analysis of the primary endpoint showed that higher doses of vericiguat were associated with a greater reduction in NT-proBNP values ($p < 0.02$). Additional echocardiographic analyses showed that patients in the vericiguat 10 mg group had an increase in LVEF at 12 weeks compared with placebo (+3.7% vs. +1.5%; $p = 0.02$), but no significant differences were found in the change in left ventricular end-diastolic volume (LVEDV) or left ventricular end-systolic volume (LVESV) in the two groups. HFH were accounted among the secondary endpoints along with blood pressure, heart rate and changes in the levels of multiple biomarkers [14]. Despite no differences encountered for the secondary endpoints, patients receiving the two highest doses of vericiguat experienced a reduced rate of HFH (9.9% vericiguat vs. 17.4% placebo), suggesting a dose–response relationship with higher doses of vericiguat. No significant changes in mean blood pressure (systolic and diastolic) and mean heart rate from baseline to 12 weeks were found between the clusters (all $p \geq 0.57$) [14].

The recent phase III randomized, multicenter VICTORIA trial, where high-risk HF patients were treated with vericiguat, showed a considerable reduction in the composite primary endpoint of death from cardiovascular causes or first HFH [3]. The secondary outcomes were the components of the primary outcome, first and subsequent HFH, a composite of death from any cause or first HFH and death from any cause [17].

The VICTORIA trial enrolled 5050 subjects (≥18 aa) with chronic HFrEF (NYHA functional classes II–IV) with reduced LVEF (defined as LVEF < 45% within 12 months before randomization) and a recent episode of worsening HF defined by symptoms of HF or signs of congestion that required hospitalization or outpatient administration of IV diuretics and an

elevated natriuretic peptide level within 30 days before randomization (BNP ≥ 300 pg/mL or NT-proBNP ≥ 1000 pg/mL if in sinus rhythm; BNP ≥ 500 pg/mL or NT-proBNP ≥ 1600 pg/mL if in atrial fibrillation). They were categorized into three groups based on the timing of deterioration: those hospitalized within 3 months before randomization, those hospitalized 3 to 6 months before randomization and those receiving outpatient IV diuretic therapy within 3 months before randomization. The estimated eGFR of the patients enrolled was up to 15 mL/min/1.73 m^2 within 30 days before randomization, the mean LVEF was 29% and all of them were already on treatment with HF guideline-directed OMT [17][18].

Patients were randomized to placebo or vericiguat 2.5 mg once daily, up-titrated to 5 mg and then to 10 mg at 2-week intervals. This titration criterion is based on evaluation of mean systolic blood pressure and clinical symptoms at 2-week intervals. In 89.2% of cases, the target dose of vericiguat was reached [15].

The study showed that in patients treated with vericiguat, the incidence of primary outcomes was lower than in patients treated with placebo. Specifically, the incidence of first HFH or death from cardiovascular causes occurred in 897 patients (35.5%) in the vericiguat group and in 972 patients (38.5%) in the placebo group (HR 0.90; CI 0.82–0.98; $p = 0.02$). There were 1223 total HFH, including first and recurrent events (38.3 events per 100 patient-years) in the vericiguat group compared with 1336 total HFH recorded (42.4 events per 100 patient-years) in the placebo group ($p = 0.02$). Death from any cause or first HFH (a composite secondary outcome) occurred in 957 patients (37.9%) in the vericiguat group and in 1032 patients (40.9%) in the placebo group (HR 0.90; CI 0.83–0.98; $p = 0.02$) [15][18].

During follow-up (median duration of 10.8 months), treatment with vericiguat was significantly associated with a 10% reduction in the primary outcome. This finding translates into an absolute event rate reduction of 4.2 events per 100 patient-years; in other words, it is possible to assert that it is necessary to treat 24 patients with vericiguat for 1 year to prevent a primary event. This important result was obtained in patients who were already undergoing guideline-based OMT. Ultimately, the incidence of death from any cause showed no difference between the two groups [15].

Some significant differences emerge comparing the characteristics of these patients with those of previous clinical trials, specifically regarding the basal risk profile and the severity of HF at randomization. Patients included in the VICTORIA trial were older, less stable and with worse clinical conditions compared with the PARADIGM-HF [10] and DAPA-HF [19] study populations. All patients included in the VICTORIA trial had a recent episode of HFH, while the PARADIGM-HF and DAPA-HF trials only had rates of HFH of 62.5% and 47.5%, respectively. Furthermore, patients included in the VICTORIA study exhibited higher values of NT-proBNP (2816 pg/mL) compared to the PARADIGM-HF and DAPA-HF trials (1608 and 1437 pg/mL respectively) and a greater number of patients (41%) were in NYHA class III- IV compared to the 25% and 32% of the patients in the PARADIGM-HF and DAPA-HF trials, respectively [10][19][20][21].

A comparative analysis of the absolute risk reduction between these studies suggested that the absolute risk reduction was similar between vericiguat and SGLT2i, whereas the risk reduction was greater for vericiguat compared to sacubitril/valsartan [20][22].

The results regarding the primary outcome were consistent in the different subgroups of patients analyzed.

Subgroup analysis showed that patients randomized for a longer time since last HFH had a greater benefit. Therefore, the benefit of vericiguat was independent from the baseline patient's treatment of HF, either when analyzed alone or in combination. Moreover, the combination of vericiguat with the concomitant use of sacubritil/valsartan did not demonstrate an additional benefit (use of sacubritil/valsartan: HR 0.88 vs. no use of sacubritil/valsartan: HR 0.90). Finally, the efficacy of vericiguat on LVEF value demonstrated a greater benefit in patients with a moderate reduction in ejection fraction (LVEF < 40%) [15].

Voors AA et al. [23] evaluated the relationship between vericiguat efficacy and changes in renal function, showing a beneficial effect of this drug, regardless of the patient's renal function. This analysis verified that the beneficial effects of vericiguat on the primary endpoint of cardiovascular death or HFH were maintained across all the eGFR spectrum at baseline and that they were comparable in both patients who developed a reduction in renal function and those who maintained the initial values.

Analyses of the drug according to the NT-proBNP levels at randomization found that major benefits were more evident in patients with NT-proBNP levels < 8000 pg/mL. This was further amplified in patients with <4000 pg/mL levels [24].

All these findings may suggest some favorable effect on the outcome in some specific subgroups of patients with advanced HF and prone to recurrent HFH.

3.2. Vericiguat in HFpEF

Due to its pharmacodynamic features, vericiguat has been tested in HF with preserved ejection fraction (HFpEF). Two main clinical trials have been published in this field: the phase II study SOCRATES–PRESERVE [25] and the phase III study VITALITY (Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Daily Living Activities of Patients With Heart Failure and Preserved Ejection Fraction) [26].

The phase II SOCRATES-PRESERVED was a randomized, double-blind, placebo-controlled, dose-finding clinical trial in 477 patients with symptomatic chronic HF (NYHA functional classes II–IV) with preserved LVEF (defined as LVEF ≥ 45%) and a recent episode of worsening HF within 4 weeks, which required hospitalization or IV outpatient's diuretic treatment, together with an elevation in natriuretic peptide levels at randomization (BNP ≥ 100 pg/mL or NT-proBNP levels ≥ 300 pg/mL if in sinus rhythm; BNP ≥ 200 pg/mL or NTproBNP ≥ 600 pg/mL if in atrial fibrillation) [21][25].

This was designed to analyze safety, tolerability and pharmacological proprieties of four different doses of vericiguat for 12 weeks. The primary outcome of the SOCRATES-PRESERVED included the change in log-transformed NT-proBNP levels (one-sided $p = 0.90$, two-sided $p = 0.20$) and left atrial volume over 12 weeks of treatment (one-sided $p = 0.81$, two-sided $p = 0.37$). It was not significantly different in the pooled vericiguat treatment group compared to the placebo group. Despite the absence of effect on these markers, an improvement in quality of life and health status, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), was observed in patients treated with the two highest doses of vericiguat (mean difference 19.8 points from baseline) compared to placebo (mean difference 9.2 points from baseline) [25][27].

The VITALITY study analyzed the efficacy and safety of vericiguat on quality of life and exercise tolerance in patients with HFpEF assessed by KCCQ scores and the six-minute walk test (6MWT), respectively.

The study included 789 patients with chronic HFpEF (NYHA functional class II--III) and a preserved LVEF (defined as LVEF ≥ 45%) with an episode of decompensation in the previous 6 months that required hospitalization or outpatient administration of IV diuretics and elevated natriuretic peptides. In randomized study, there were three arms, two in which vericiguat was tried up to 15 mg or 10 mg and one who received placebo. After 24 weeks of treatment, there were no significant differences between the two groups concerning KCCQ scores or the six-minute walk test [21][26].

The cGMP pathway plays a role in HFpEF pathophysiology. Improved characterization of cGMP signaling and its relation to cardiac function revealed multiple options for targeted therapy [28][29]. To date, no large phase III HFpEF trial has definitively tested the effects of a pharmacologically mediated increase in cGMP activity. This needs to be further investigated [28].

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