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Original Research Article

Review on the Role of Vericiguat in Heart Failure

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Abstract:

Vericiguat is approved for the treatment of adults with symptomatic, chronic heart failure with reduced ejection fraction (HFrEF) and is the first oral soluble guanylate cyclase (sGC) stimulator. Due to oxidative stress and endothelial dysfunction, the activity of sGC and NO bioavailability were decreased, which resulted in myocardial and vascular dysfunction. Vericiguat function, through increasing NO availability and reducing the oxidized forms of sGC, results in smooth muscle relaxation and vasodilatation. The objective of the Phase-II SOCRATES-REDUCED study was to determine the optimal dose and tolerability in patients with worsening chronic heart failure and reduced left ventricular ejection fraction (LVEF), whereas the Phase III VICTORIA trial was associated with significantly reducing the cardiovascular death and first hospitalization from heart failure. Vericiguat therapy can successfully lower the risk of mortality rate and first hospitalization from heart failure but the only adverse events were symptomatic hypotension and syncope. Thus, vericiguat was proved to be an effective treatment well tolerated with opinion in patients with symptomatic chronic heart failure with a recent worsening effect. This review consists of introduction, mechanism of action of vericiguat, dose and pharmacokinetics, efficacy, safety, precautions, regulatory status and future perspective and conclusion.

Keywords: Vericiguat, Endothelial Dysfunction, Vasodilation, Tolerability, Hospitalization.

Introduction

Heart failure (HF) is one of the most prevalent diseases worldwide, with an estimated 64.34 million cases in 2017 (8.52 per 1,000 inhabitants, 51% severe, 29% mild, and 19% moderate). As of 2019, the mortality rate of cardiovascular diseases was estimated to be 17.9 million, representing 32% of all global deaths. Among these, 85% of deaths were due to stroke and MI [1]. Risk factors associated with HF include age, gender, diabetes mellitus, hypertension, obesity, family history, smoking, diet, sedentary lifestyle, and lack of exercise.

In addition, coronary artery disease (CAD) patients are reported to have a higher risk of HF [2]. A recent study observed that elderly males had an increased risk of HF compared to females [3]. The standard method of treatment for HF is a combination of angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptors (ARBs), and beta-blockers [4]. In the U.S., approximately 6.2 million adults (20 years of age and older) have heart failure, and approximately 50% of patients have HFrEF. An observational cohort analysis of PINNACLE registry data showed that approximately half of the patients with worsening chronic HFrEF are rehospitalized within 30 days of a worsening event, and an estimated one in five patients with worsening chronic HFrEF will die within two years. HF affects the quality of life of the patients and the cost associated with hospitalization, thereby making medical management expensive. Therefore, newer treatment strategies and medications are required to eliminate the burden of HF. Future cardiovascular events in patients with HF can be minimized via early treatment with drugs demonstrated to improve the prognosis.

The European HF guidelines state that treatment with vericiguat should be provided to symptomatic patients with worsening HF despite the fact that the first-line treatment reduces the risk of cardiovascular death and hospitalization due to HF [5]. Bayer and Merck produced a novel agent called vericiguat, which functions as a soluble guanylyl cyclase activator. It is used to treat HF with reduced ejection fraction (HFrEF) [6]. Vericiguat was first approved by Food and Drug Administration (FDA) in January 2021, for patients with HFrEF [7]. This article attempts to review the mechanism of action, safety, efficacy, pharmacokinetics, current

regulatory status, and future prospects of vericiguat in heart failure.

Mechanism of action

Vericiguat is composed of pyrazolopyridine, comprising nitrogen-containing fused heterocycles. These classes of drugs possess anti-inflammatory, antibacterial, and antitumor properties. It is a 5-fluoro-1H-pyrazolo [3, 4-b] pyridine in which a 2-fluorobenzyl group replaces the amino hydrogen at 1st position, and the hydrogen at the position 3 is substituted by a 4,6-diamino-5-[(methoxycarbonyl) amino] pyrimidine-2-yl group. This drug is a guanylate cyclase stimulator, that is used to treat chronic HF. HF is generally associated with nitric oxide (NO) bioavailability, cyclic guanosine monophosphate (cGMP) synthesis, and decreased (sGC) activity, causing vasoconstriction and smooth muscle contraction, eventually leading to myocardial and vascular dysfunction. The mechanism of action of vericiguat is vasodilation and smooth muscle relaxation by producing elevated levels of cGMP via directly stimulating sGC independently and synergistically with NO (as shown in Figure 1). Vericiguat mitigates the need for a functional NO-sGC-cGMP axis and helps to prevent the vascular and myocardial dysfunction associated with decreased sGC activity in HF [8].

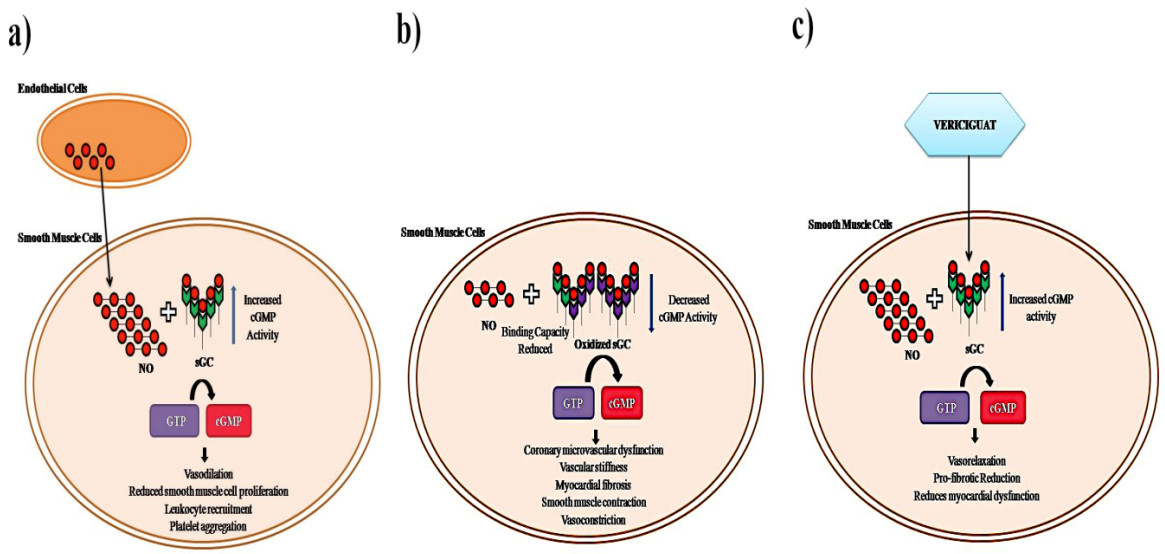

Figure 1: Mechanism of action of vericiguat (a) NO-sGC-cGMP pathway in physiological state; (b) NO-sGC-cGMP pathway in HF; (c) Vericiguat action in NO-sGC-cGMP pathway.

cGMP – cyclic guanosine monophosphate; GTP – guanosine triphosphate; HF – heart failure; NO – nitric oxide; sGC – soluble guanylate cyclase

NO-sGC-cGMP pathway increases the therapeutic target for HF. NO is released into smooth muscle cells from the endothelial cells, where it binds to sGC and triggers the synthesis of the second messenger, cGMP by converting GTP to cGMP. The activation of the NO-sGC-cGMP pathway contributes to vasodilation, reduced smooth muscle cell proliferation, leukocyte recruitment, and platelet aggregation [9]. cGMP is essential for the normal functioning of the cardiovascular system, and dysfunction in cGMP may result in coronary microvascular dysfunction, vascular stiffness, and myocardial fibrosis.

HF is also associated with increased levels of oxidized sGC, which makes NO insensitive to binding with sGC, thereby limiting the conversion of GTP to cGMP. In HF patients, reduced cGMP activity is the primary factor contributing to vasoconstriction or vascular stiffness, and smooth muscle contraction. Vericiguat functions by increasing cGMP activity, thereby reducing the progression of ventricular hypertrophy, and fibrosis [10]. It primarily functions as a dual character (increasing NO availability and reducing the oxidized forms of sGC) to restore the NO-sGC-cGMP pathway [11].

Dosage and pharmacokinetics

Vericiguat is a biopharmaceutics classification system class II drug possessing low solubility, high permeability, and weakly basic properties. It also exhibits linear pharmacokinetics, wherein the drug's higher bioavailability and lower variability were observed after food consumption compared to without food consumption. When administered with food, it stimulates the secretion of bile salts, and the drug solubilizes better with food. The absolute bioavailability of vericiguat was 93% after food consumption [12]. The drug has been reported to have low hepatic clearance (1.6 L/h in healthy

volunteers and 1.3 L/h in patients with HFrEF). The starting dose of the drug is 2.5 mg, administered orally post-meal, once daily. It has been reported that vericiguat has no effect on the pharmacokinetics of other drugs, such as digoxin 0.375 mg and warfarin 25mg, prescribed for cardiovascular diseases. Similarly, aspirin (500mg single dose) and sacubitril/valsartan (97/103 mg twice daily) also did not report any effects, which supports concomitant medications commonly used by HF patients. However, it is not recommended to use vericiguat with phosphodiesterase 5 (PDE5) inhibitor concomitant medications since it have not been studied in patients with HF and also due to the likely risk of hypotension [13].

Steady-state mean Cmax and AUC values of 350µg/L and 6680 µg h/L (after six days) were observed in HF patients six days after administration of vericiguat. After consuming 10 mg vericiguat with a rich-fat, high-calorie meal compared to 1 hour without food, the plasma concentration-time was found to be 4 hours, associated with increased vericiguat AUC and Cmax of 44 and 41%, respectively, and reduced pharmacokinetic variability. The half-life of the drug was 30 hours in patients with HF. A study on volunteers reported that drug excretion was 45% in faeces and 53% in urine. The clinically relevant difference in the pharmacokinetics of vericiguat based on ethnicity, age, gender, body weight, and baseline log transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels was not observed [14].

Efficacy

The phase II dose-finding study (SOCRATES) was performed on patients with worsening chronic HF and HFrEF to determine the optimal dose of vericiguat and the tolerability of the drug in HF patients. 456 patients were randomized into placebo (N=92) and vericiguat (N=364) groups [15]. Vericiguat was administered to 364 patients in doses of 1.25 mg, 2.5mg, 5mg, and 10 mg, each group comprising 91 patients, and was followed up for 12 weeks. The primary endpoint was a reduction or change in the log-transformed NT-proBNP values from baseline to 12 weeks of treatment [16]. The findings of this phase II trial revealed that as the dose of the drug increased, the log-transferred levels of NT-proBNP decreased. Therefore, 10 mg of vericiguat was found to be the ideal dose for reducing the levels of NT-proBNP in HF patients [17].

Phase III VICTORIA study was an event-driven study of vericiguat that investigated the time to the first occurrence of the composite of CV death or HF hospitalization in patients with HFrEF. The primary outcome of the trial was a composite of CV death for HF or first hospitalization. About 5050 participants were randomized into vericiguat (target dose 10 mg, N=2526) and placebo groups (N=2534) [18]. Guideline-based concomitant medication (such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or sacubitril-valsartan) was well maintained among the groups. During the trial, 610 patients and 565 patients from the vericiguat and placebo groups, respectively, were discontinued from the trial.897 patients in the vericiguat group achieved the primary outcome compared to 972 patients in the placebo group [19]. The study revealed that 1223 patients in the vericiguat group and 1336 patients in the placebo group (hazard ratio, 0.91; 95% CI, 0.84 to 0.99; p=0.02) were hospitalized (42.4 events per 100 patients-years). 957 patients (37.9%) in the vericiguat group and 1032 patients (40.9%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.83 to 0.98; P=0.02) died from any cause or first hospitalization for heart failure.512 patients (20.3%) in the vericiguat group and 534 patients (21.2%) in the placebo group (Hazard ratio, 0.95; 95% CI, 0.84 TO 1.07; P=0.38) were reported for death from any cause. Excluding subgroups such as age and NT-proBNP levels, the effect of vericiguat on the primary outcome was consistent across most prespecified subgroups (including patients receiving sacubitril-valsartan) [6].

Safety

The rate of occurrence of adverse events was similar among those taking placebo (77.2%) and 2.5 mg vericiguat (78.9%). Serious adverse events (SAEs) were reported in 39.1% of individuals in the placebo group, as compared to 34.1% in the1.25 mg vericiguat group, 38.9% in 2.5 mg vericiguat group, 26.4% in patients taking 2.5 to 5 mg vericiguat and 31.9% in patients taking 2.5 to 10 mg vericiguat [21]. Drug discontinuation due to SAEs was found in 2.2%-7.7% of patients taking vericiguat and 5.4% in the placebo group.

Drug-related syncope was most frequently observed in the 10 mg vericiguat group (4.4%), among which 3/4th had an occurrence of events during the first two weeks post-randomization. Hypotension was highest (15.4%) in patients consuming 10 mg vericiguat, followed by the 2.5 mg vericiguat group (6 patients, 6.7%). Eight patients in the 10mg vericiguat group had hypotension between weeks 0 and 2 when the highest dose/study titration schedule was 2.5 mg once daily. Between weeks 2 and 4, two patients experienced hypotension when the highest dose was scheduled as 5 mg once daily. Two patients, one in each placebo group and 5mg vericiguat, were discontinued from the trial due to hypotension [21]. Further studies should be implemented for longer follow-up, prognostic outcomes, and higher drug doses to produce a clinically significant outcome in HFrEF.

The phase III clinical trial reported that 32.8 % and 34.8% of patients among the vericiguat and placebo groups had serious adverse events. Adverse events were observed in 80.5% of patients in the vericiguat group compared to 81.0% in the placebo group. 9.1% and 7.9% of patients among vericiguat and placebo groups reported symptomatic hypotension. Similarly, syncope was reported in 4.0% of patients receiving vericiguat and 3.5% receiving placebo. There was no difference in the baseline systolic blood pressure between the vericiguat (121.2 mm Hg) and placebo groups (121.5 mm Hg) [22].

Moreover, the systolic blood pressure slightly decreased during the first 16 weeks, which then returned to baseline thereafter. Around 7.6% and 5.7% of patients receiving vericiguat and placebo, respectively, were found to have anaemia, and of these patients, 1.6% in the vericiguat group reported SAEs than 0.9% in the placebo group (Paul W. Armstrong et al., 2020). Since the hemodynamic functions of the patients were not affected following vericiguat treatment, and the SAEs reported were lower than those in the placebo group, vericiguat was considered safe. The tolerability of the drug was confirmed by the high rate of target dose achievement [23]. Hence, the findings of the VICTORIA study revealed that the incidence of death from CV causes or hospitalization for HF was lower among those who received vericiguat than those who received placebo, especially among patients with high-risk heart failure.

Precautions

Vericiguat, when administered to pregnant women, was found to harm the fetus; hence, the risk involved for the fetus should be communicated to all female patients prior to receiving the drug. In addition, all females should be tested for pregnancy before initiation of the treatment and put under effective contraception during and continued until at least one month after the final dose of vericiguat to prevent conceiving [24]. Preclinical studies have reported that vericiguat is present in the milk of lactating rats, suggesting that vericiguat and its metabolites can also be found in the milk of human lactating mothers. Hence, breastfeeding is not recommended during vericiguat treatment since safety and efficacy data for pediatric patients are not yet established. A vericiguat overdose may cause hypotension. This drug is not recommended for renal or hepatic impaired patients due to the lack of data on the safety and efficacy of vericiguat in such patients [25].

Regulatory status and future perspective

Vericiguat was approved initially by the FDA in 2021 under the brand name VERQUO. It is indicated to reduce the risk of cardiovascular death and hospitalization for HF or the need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%. The European Medicine Agency has also approved vericiguat in 2021. One clinical trial is on-going to evaluate the efficacy and safety of the sGC stimulator vericiguat/MK-1242 in adults with chronic heart failure with reduced ejection fraction. This is a phase 3 clinical trial consisting of 6000 participants, which was initiated on November 2, 2021, and is expected to be completed on June 15, 2025. The participants will be given a dose of 2.5 mg of vericiguat orally once daily, which will be titrated to 5mg and 10mg [25]. Similarly, a dose-matching placebo also, will be included. The findings of this clinical trial are expected.

The predominant adverse event was symptomatic hypotension; hence, further clinical trials involving HFrEF patients with hypotension may be essential.

Authorship statement

All authors have significantly contributed to this manuscript. Dr. Melvin George and Nichila Mary Philip conceptualized this article. Literature review, data collection and manuscript writing done by Nichila Mary Philip. Dr. priyanka Venugopal, Dr. Melvin George and Damal Kandadai Sriram, reviewed the final draft and approved the manuscript. All authors read and gave final approval for manuscript submission and comply with the journal's Authorship policy.

Reference

1. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME medical journal. 2020 Jun 25; 5.
2. Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. Cardiovascular research. 2019 Apr 15; 115(5):844-53.
3. Cediel G, Codina P, Spitaleri G, Domingo M, Santiago-Vacas E, Lupón J, Bayes-Genis A. Gender-related differences in heart failure biomarkers. Frontiers in Cardiovascular Medicine. 2021 Jan 5; 7:617705.
4. Machaj F, Dembowska E, Rosik J, Szostak B, Mazurek-Mochol M, Pawlik A. New therapies for the treatment of heart failure: a summary of recent accomplishments. Therapeutics and clinical risk management. 2019 Jan 22:147-55.
5. González-Juanatey JR, Anguita-Sánchez M, Bayes-Genís A, Comín-Colet J, García-Quintana A, Recio-Mayoral A, Zamorano-Gómez JL, Cepeda-Rodrigo JM, Manzano L. Vericiguat in heart failure: from scientific evidence to clinical practice. Revista Clínica Española (English Edition). 2022 Jun 1; 222(6):359-69.
6. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CS, Ponikowski P, Voors AA, Jia G, McNulty SE. Vericiguat in patients with heart failure and reduced ejection fraction. New England Journal of Medicine. 2020 May 14; 382(20):1883-93.

7. Vyas A, Onteddu N. Vericiguat., National library of medicine. Statperl publishing book, 2022.
8. Reyes VM, Martínez O, Hernández GF. National center for biotechnology information. Plant Breeding. Universidad Autónoma Agraria Antonio Narro, Calzada Antonio Narro. 1923.
9. Evora RB, M Evora P, C Celotto A, J Rodrigues A, E Joviliano E. Cardiovascular therapeutics targets on the NO–sGC–cGMP signaling pathway: a critical overview. Current drug targets. 2012 Aug 1; 13(9):1207-14.
10. Xia J, Hui N, Tian L, Liang C, Zhang J, Liu J, Wang J, Ren X, Xie X, Wang K. Development of vericiguat: The first soluble guanylate cyclase (sGC) stimulator launched for heart failure with reduced ejection fraction (HFrEF). Biomedicine & Pharmacotherapy. 2022 May 1; 149:112894.
11. Hulot JS, Trochu JN, Donal E, Galinier M, Logeart D, De Groote P, Juilliere Y. Vericiguat for the treatment of heart failure: mechanism of action and pharmacological properties compared with other emerging therapeutic options. Expert Opinion on Pharmacotherapy. 2021 Sep 22; 22(14):1847-55.
12. Aimo A, Castiglione V, Vergaro G, Panichella G, Senni M, Lombardi CM, Emdin M. The place of vericiguat in the landscape of treatment for heart failure with reduced ejection fraction. Heart Failure Reviews. 2022 Jul 1:1-7.
13. Boettcher M, Loewen S, Gerrits M, Becker C. Pharmacodynamic and pharmacokinetic interaction profile of vericiguat: results from three randomized phase I studies in healthy volunteers. Clinical Pharmacokinetics. 2021 Mar; 60:337-51.
14. Markham A, Duggan S. Vericiguat: first approval. Drugs. 2021 Apr; 81:721-6.
15. Cleland JG, Mueller C. What can we learn from SOCRATES: more questions than answers?. European heart journal. 2017 Apr 14; 38(15):1128-31.
16. Ruehs H, Klein D, Frei M, Grevel J, Austin R, Becker C, Roessig L, Pieske B, Garmann D, Meyer M. Population pharmacokinetics and pharmacodynamics of vericiguat in patients with heart failure and reduced ejection fraction. Clinical Pharmacokinetics. 2021 Nov; 60(11):1407-21.
17. Kassis-George H, Verlinden NJ, Fu S, Kanwar M. Vericiguat in heart failure with a reduced ejection fraction: patient selection and special considerations. Therapeutics and clinical risk management. 2022 Mar 30:315-22.
18. Lee, A., Natarajan, P. P., Kar-Hang, R., Shah, K., Chien, C., & Jefferies, J. L. (n.d.). The Role of Vericiguat in the Expanding Realm of Heart Failure Pharmacotherapy: An Overview of the Victoria Trial. 5. 2020. https://www.acc.org/latest-in-cardiology/ articles/2020/07/08/08/49/the-role-of-vericiguat-in-the-expanding-realm-of-hf-pharmacotherapy
19. Alsumali A, Djatche LM, Briggs A, Liu R, Diakite I, Patel D, Wang Y, Lautsch D. Cost effectiveness of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening heart failure event from a US Medicare perspective. Pharmacoeconomics. 2021 Nov; 39:1343-54.
20. Kansakar S, Guragain A, Verma D, Sharma P, Dhungana B, Bhattarai B, Yadav S, Gautam N, Yadav S. Soluble guanylate cyclase stimulators in heart failure. Cureus. 2021 Sep 6; 13(9).
21. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. Jama. 2015 Dec 1; 314(21):2251-62.
22. Emdin M, Aimo A, Castiglione V, Vergaro G, Georgiopoulos G, Saccaro LF, Lombardi CM, Passino C, Cerbai E, Metra M, Senni M. Targeting cyclic guanosine monophosphate to treat heart failure: JACC review topic of the week. Journal of the American College of Cardiology. 2020 Oct 13; 76(15):1795-807.
23. Lombardi CM, Cimino G, Pagnesi M, Dell'Aquila A, Tomasoni D, Ravera A, Inciardi R, Carubelli V, Vizzardi E, Nodari S, Emdin M. Vericiguat for heart failure with reduced ejection fraction. Current Cardiology Reports. 2021 Oct; 23(10):144.
24. Nguyen L, Baker DE. Vericiguat. Hospital Pharmacy. 2023 Oct; 58(5):431-6.
25. Siddiqi AK, Greene SJ, Fudim M, Mentz RJ, Butler J, Khan MS. Vericiguat for the treatment of heart failure with reduced ejection fraction. Expert Review of Cardiovascular Therapy. 2023 Apr 3; 21(4):245-57.