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ABSTRACT

Introduction: Ticagrelor is an antiplatelet agent approved for the treatment of patients with an acute coronary syndrome or a history of myocardial infarction. Considering the evidence demonstrating that ticagrelor-mediated inhibition of platelet activation and aggregation have beneficial effects in the treatment of thrombotic conditions, clinical studies have been conducted to evaluate the use of this drug for the treatment of sickle cell disease (SCD), demonstrating satisfactory tolerability and safety.
Areas covered: Clinical investigation has characterized the pharmacokinetic and pharmacodynamical profile, as well as the efficacy and safety of ticagrelor to prevent painful vaso-occlusive crisis (painful episodes and acute chest syndrome) in SCD patients.
Expert opinion: While phase 1 and 2 clinical trials demonstrated satisfactory tolerability and safety, the conclusion of phase 3 clinical trials is crucial to prove the efficacy of ticagrelor as a therapeutic option for the treatment of SCD. Thus, it is expected that ticagrelor, especially in combination with other drugs, will improve the clinical profile and quality of life of patients with SCD.

1. Introduction

Sickle cell anemia (SCA) is the most common form of a group of inherited diseases, collectively known as sickle cell disease (SCD), characterized by the presence of hemoglobin S (Hb S) that is due to a mutation in the gene encoding the β globin subunit of hemoglobin (*HBB*), where valine replaces glutamic acid in the sixth position of the β-globin chain [1]. SCA is an autosomal recessive disorder, resulting in erythrocyte sickling [2], as the Hb S polymerizes, especially under hypoxic conditions. Hb S polymerization causes changes in these corpuscles, which play an essential role in tissue oxygenation, as they contain hemoglobin, the protein responsible for gas exchange. The presence of Hb S inside erythrocytes directly contributes to hemolysis and the release of intracellular products, which act as damage-associated molecular patterns (DAMPs). In addition, sickled erythrocytes express surface molecules that activate signaling pathways associated with the pathophysiology of SCA [1,3].

SCA represents a public health concern in terms of its incidence, prevalence, morbidity and mortality. While the life expectancy of SCA patients has increased considerably in developed countries, cohort studies in countries such as the United States and the United Kingdom [4,5] have suggested that it still remains significantly lower than that of comparatively healthy populations [1]. However, in low-income countries, such as those on the African continent, it is estimated that infant mortality due to SCA ranges between 50% and 90% [6]. The most recent epidemiological data suggest that approximately 176,000 people die annually worldwide from disease-related complications [3,7]. In Brazil, it is estimated that around 30,000 individuals live with SCA, many of whom reside in the state of Bahia [8].

The pathophysiology of SCA is characterized by a sterile inflammatory response [9] triggered by both the release of intracellular products during hemolysis and the binding of sickled red blood cells to the endothelium [10]. These stimuli can activate signaling pathways in a wide variety of leukocytes and endothelial cells [11], leading to a chronic inflammatory state associated with increased inflammatory mediator production, the expression of adhesion molecules, platelet activation, and the formation of extracellular neutrophil networks (NETs). Moreover, accumulating evidence has demonstrated that hypoxia-reperfusion episodes and oxidative stress lead to reduced nitric oxide concentrations, which contributes to endothelial cell activation and adhesion with leukocytes, erythrocytes, reticulocytes, and platelets, exacerbating the vaso-occlusion events. Under precipitating factors, these events lead to vaso-occlusion resulting in intense painful episodes [12], which are considered to be a major complication and

Article highlights

- Ticagrelor, a reversible P2Y12 receptor antagonist, is an oral antiplatelet drug indicated for the treatment of patients with ACS or a history of MI. Despite the inconclusive results exhibited by other antiplatelet agents in pre-clinical tests, evidence has identified ticagrelor as a drug with unique properties in SCD treatment.
- The pharmacokinetic parameters of ticagrelor (and its major active metabolite AR-C124910XX), including gastrointestinal absorption, bioavailability, distribution, metabolism meet expected drug development requirements, although some of them can be significantly influenced by the clinical condition of the patient.
- Phase I, II, and III clinical trials conducted in SCD patients and healthy volunteers from different countries to investigate the efficacy and safety of ticagrelor as part of the 'the sickle cell program with ticagrelor (HESTIA)'. The first phase (HESTIA 4) of the program evaluated the pharmacokinetics of ticagrelor formulations in SCA pediatric patients and demonstrated that ticagrelor was rapidly absorbed and well tolerable.
  - Phase II studies of ticagrelor were conducted in SCD patients included in the HESTIA 1 and HESTIA 2 programs, both confirming the safety and tolerability and assessing the efficacy of the drug. While HESTIA 1 demonstrated the existence of a relationship between the dose and exposure to ticagrelor and the inhibition of platelet aggregation in children with SCD, HESTIA 2 concluded that no significant effect on self-reported SCD-related pain could be attributed to ticagrelor treatment.
- Phase III studies are currently in progress as part of the HESTIA3 program, an international, multicenter, double-blind, randomized, parallel group, placebo-control study designed to evaluate the efficacy and safety of ticagrelor to prevent VOC. Thus, the conclusion of these trials is crucial to prove the efficacy of ticagrelor as a therapeutic option for the treatment of SCD alone, or as part of a protocol using combined therapy.

primary cause of hospitalization in SCA patients [13–15]. Clinical manifestations of SCD can be divided into acute and chronic. The former is represented by hiperhemolytic crises, splenic sequestration, infections, painful episodes, acute chest syndrome, aplastic crisis, and stroke that are responsible for hospital admissions of the patients. Chronic complications include retinopathy, pulmonary hypertension, skin ulceration, chronic hemolytic anemia, kidney failure, osteonecrosis, and cardiac disease [16,17].

Studies have demonstrated that SCA patients present a hypercoagulative state mediated by the activation of coagulation pathways, which contributes to thrombotic complications, as well as systemic and vascular inflammation [18,19]. Although the mechanisms underlying the activation of excessive coagulation in SCA have yet to be fully characterized, increasing evidence points to some potential causes: high levels of constitutive and inducible tissue factor (TF) expression [16]; exposure of anionic phospholipids, such as phosphatidylserine, on the surface of sickled red blood cells, possibly leading to the activation of clotting cascade components; the release of microparticles by different cell sources, which contributes to coagulation, possibly due to a phosphatidylserine-dependent mechanism linked to the activation of the coagulation pathway [16,20]. Also, there are continuous activation and aggregation of platelets, due to some or potentially each of the following phenomena: 1) presence of metabolically active platelets, 2) increased plasma levels of platelet agonists in the blood of sickle cell patients, 3) increased receptor expression and activation on the surface of platelets in SCA patients [21–24].

Hydroxyurea (HU) is a disease-modifying therapy indicated for patients with SCA in the context of a severe clinical profile. Major beneficial effects obtained with HU treatment include reduced hospitalization rates and improved quality of life [25]. Nonetheless, its use has also been associated with several side effects, including erythema, alopecia, leukocytoclastic vasculitis, leg ulcers, male infertility, and teratogenesis [26,27], and some evidence has suggested that it could be potentially carcinogenic [28,29], although its long-term effects remain to be better understood [30]. Moreover, the lack of adherence by some patients constitutes a limiting factor in HU therapy [31–33]. Despite all these effects, HU is a well-tolerated and safe drug, although periodically laboratory control of patients is required. The continuous search for drugs that could help to improve the treatment of SCA patients providing more therapeutic options is particularly important to all clinicians. Accordingly, consistent evidence suggests that drugs capable of modulating the excessive activation of coagulation process can contribute significantly to the treatment of SCA [34]. The present review analyzes the use of ticagrelor, an antiplatelet agent for the prevention of thrombotic events [24], in the context of SCA.

2. Overview of the market

Despite the fact that SCD was first described over a century ago, its treatment remains challenging [25]. HU, the only treatment option available during the last 20 years, remains the current mainstay of therapy, despite its limitations and significant side effects. Recently, L-glutamine (Endari) was approved in the USA by the Food and Drug Alimentation (FDA) for the treatment of acute SCD complications in patients aged 5 years and older [35]. Nevertheless, like HU, this drug is not free from side effects, which include constipation, nausea, headache, cough, and abdominal pain. In 2019, the FDA approved two other drugs as therapeutic options for SCD (Crizanlizumab-tmca and Voxelotor). Crizanlizumab-tmca (Adakveo), indicated for patients aged 16 years and older, was found to reduce the number of vaso-occlusive crises (VOC), the main complication of SCD [36]. However, its intravenous administration has been associated with side effects, such as nausea, arthralgia, pain, and pyrexia. Voxelotor (Oxbryta), the most recently approved drug for SCD [37], is available as an oral formulation and, like L-glutamine and crizanlizumab-tmca, can be administered as monotherapy or in association with HU. Unfortunately, none of these drugs alone enable the sufficient control of all the manifestations of SCD [38,39].

As the pathophysiology of SCD results from the activation of complex networks of interdependent pathophysiological processes, increasing evidence has suggested that a multi-agent approach could significantly affect SCD therapy. In this context, drug development research has identified key pathways for targeted SCD drug development. Accordingly, novel therapies for SCD should include pharmacological reactivators of fetal hemoglobin (HbF), anti-adhesion and anti-sickling agents, heme clearance and detoxification agents and anti-inflammatory and anti-thrombotic drugs. In addition, modulators of ischemia–reperfusion injury and oxidative stress, as well as gene therapies and stem cell transplantation may represent promising alternatives [39].

Considering the relevance of thrombin generation in SCD pathophysiology, antithrombotic agents have attracted considerable interest as potential therapeutic agents in SCD. Since the long-term use of anticoagulants has shown clinical benefits in attenuating chronic organ injury in mice, oral thrombin (such as dabigatran), and factor Xa inhibitors (such as apixaban and rivaroxaban) are currently undergoing clinical trials [40]. Despite the fact that preclinical studies involving antiplatelet agents, such as clopidogrel (a P2Y12 antagonist), suggested that the inhibition of platelet activation and aggregation should be useful in SCD management, clinical trials investigating another P2Y12 antagonist, prasugrel, did not yield promising results [39]. However, ticagrelor, a reversible P2Y12 receptor antagonist that, unlike prasugrel, does not require metabolic activation, has demonstrated efficacy as an antiplatelet agent with unique properties in SCD treatment [41].

2.1. Drug background

2.1.1. Chemical Properties

An understanding of ticagrelor's chemical properties is crucial for the comprehension of its molecular mechanism of action and active metabolites that function as antiplatelet agents. Ticagrelor, [(1S,2S,3 R,5S)-3-[7-{[(1 R,2S)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5-(propylthio)-3 H- [1–3] triazolo [4,5-d] pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol], is an antiplatelet agent belonging to the class of cyclopentyl-triazolo-pyrimidines [42–44].

As shown in Figure 1, ticagrelor is a polycyclic aromatic compound containing a triazole ring fused to a pyrimidine ring and is therefore an adenosine triphosphate (ATP) analog.
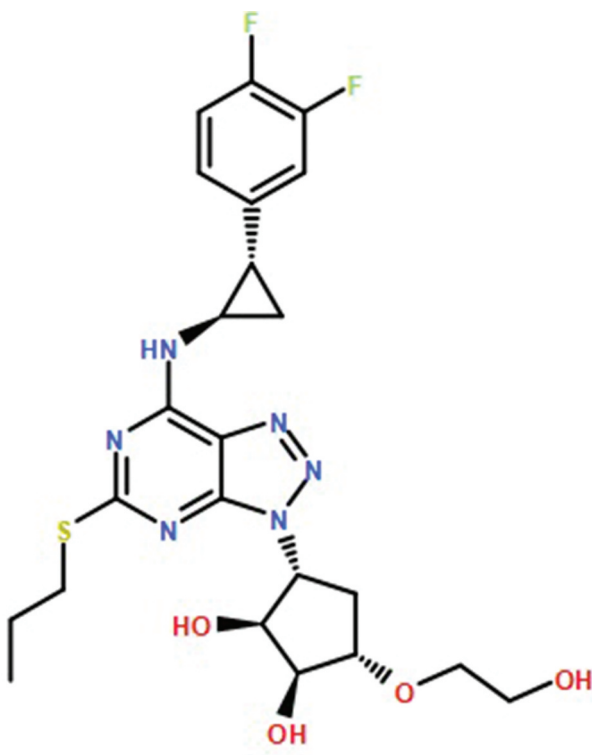

Figure 1. Molecular structure of ticagrelor.

Like ATP, ticagrelor has a ribose-like cyclopentane ring presenting its [1–3] triazole [4,5-d] pyrimidine portion, similar to the structure of adenine [45].

2.1.2. Pharmacodynamics

Ticagrelor is the first of a new class of antiplatelet agents (cyclopentyltriazolopyrimidines) approved by the FDA in 2010 to be used in the treatment of patients with acute coronary syndrome (ACS) or a history of myocardial infarction [46,47]. As platelet activation significantly contributes to thrombosis and inflammation, favoring the progression of atherosclerotic plaque, the use of antiplatelet agents has become a cornerstone therapeutic strategy in these patients [48]. Due to similarity with its naturally occurring agonist, ticagrelor acts as direct P2Y12 receptor antagonist, which reversibly binds to the platelet P2Y12 receptor [45]. Of note, this drug is the first reversible ADP receptor antagonist available for oral use [49].

The P2Y12 receptor is present on the surface of a variety of cell types. Due to elevated expression by platelets, it is considered one of the most important receptors in the orchestration of thrombotic events [45]. Ticagrelor binds reversibly and noncompetitively to the P2Y12 receptor [50], recruiting the αi subunit of the Gi protein that results in the inhibition of adenylyl cyclase, an enzyme that catalyzes the synthesis of cAMP from ATP, leading to the activation of cAMP-dependent kinase (PKA). Since PKA signaling is crucial for ADP-mediated platelet activation, inhibition of the P2Y12 receptor by ticagrelor also results in the inhibition of platelet activation and aggregation [51]. In fact, studies have demonstrated that the significantly higher activation of platelets in SCA patients compared to healthy individuals [17] could justify the hypercoagulation state seen in these patients. Importantly, hypercoagulation has been described to contribute significantly to the development of painful vaso-occlusive events [16]. Together, these findings support the hypothesis that ticagrelor could have beneficial effects in the treatment of thrombotic conditions, such as SCD [51].

In addition to acting as a P2Y12 receptor antagonist, ticagrelor inhibits adenosine uptake by inhibiting equilibrative nucleoside transporter 1 (ENT1) [46,52,53]. Additionally, studies have shown that this drug contributes to vasodilation by increasing the plasma half-life of adenosine [54], which leads to a reduced risk of thrombus formation in SCA patients [55].

2.2. Pharmacokinetics and metabolism

Ticagrelor is rapidly absorbed by the gastrointestinal tract via oral administration [56]. Studies have demonstrated that ticagrelor is a direct-acting drug, i.e. metabolic activation is not required for its action as a P2Y12 receptor antagonist. The metabolism of ticagrelor, which occurs in the liver, is mainly mediated by isoenzymes of the cytochrome P450 3A family (CYP3A) such as CY3A4 and CYP3A5. Among the 10 different ticagrelor's metabolites characterized in plasma, urine, and fecal samples, only the major metabolite AR-C124910XX, detectable at a rate of approximately 30–40% of the administered dose of ticagrelor, exhibits a potent antiplatelet activity [57–60]. Ticagrelor is predominantly eliminated via hepatic

metabolism, while its major metabolite AR-C124910XX is eliminated mainly via biliary excretion [61,62].

Zhu and colleagues observed, in healthy volunteers, peak concentrations (C_{max}) of ticagrelor ranging from 494.3 to 1,929 ng/mL, which was reached between 30 min and 4 h. Contrarily, they observed the slow absorption of AR-C124910XX, with C_{max} ranging from 75.3 to 427 ng/mL, reached between 1 and 6 h [56]. Moreover, they estimated that the mean half-life time ($t_{1/2}$) of ticagrelor and AR-C124910XX were 8.5 and 21.9, respectively, varying significantly among the subjects. However, a recent study estimated that the $t_{1/2}$ of AR-C124910XX was 8.5 h [63].

Evidence has demonstrated that the pharmacokinetic of ticagrelor, including absorption, distribution, metabolism, and excretion, could be significantly influenced by the patient's condition, which may impact not only therapeutic response but also toxicity and drug interactions [57,64]. It has been reported that patients with acute myocardial infarction may present a significant reduction in AR-C124910XX bioavailability, compared to healthy volunteers [57,65]. A study performed by Adamski and colleagues demonstrated that patients with ACS who had ST-elevation myocardial infarction or diabetes mellitus had reduced ticagrelor biotransformation [57]. They also observed that the concomitant administration of morphine during ACS was associated with a reduction in ticagrelor metabolism, while smoking was associated with increased ticagrelor metabolism in patients with ACS. A recent study found that hemodialysis has a minor impact on ticagrelor pharmacokinetic and no influence on its effect, which is consistent with its elimination pathway reported above [62].

2.3. Clinical efficacy

Phase 1, 2, and 3 clinical trials were conducted in SCD patients and healthy volunteers from different countries to investigate the efficacy and safety of ticagrelor (**Table 1**).

2.4. Phase I studies

2.4.1. The Sickle cell program with ticagrelor (HESTIA) 4
The HESTIA 4 program consisted of an interventional, multicenter, phase I, open-label clinical study that started in March 2018 and finished in May 2019. This study evaluated the pharmacokinetics (PK) of ticagrelor in SCD pediatric patients aged from birth to 2 years old. The study was carried out in six different countries (Belgium, Italy, Kenya, Lebanon, Spain, and UK) and involved eight different research centers.

The following inclusion criteria were used in the study: patients diagnosed with SCA (HbSS) or sickle beta-zero-thalassemia (HbS/β⁰) with body weight above 5 Kg and weight-adjusted dose of the anti-sickling agent must be for 3 months. Patients with a history of transient ischemic stroke or cerebrovascular (ischemic or hemorrhagic) accident, severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, proliferative retinopathy, hepatic impairment, renal failure, increased risk of bleeding complications, active untreated malaria or at risk of bradycardic events were excluded. The study also excluded patients with hemoglobin concentration below 6 g/dL and

Table 1. Clinical studies investigating the efficacy safety of ticagrelor in the treatment of patients with SCD, listed by ClinicalTrials.gov reference number.

Reference number	Study locations	Condition	Participants	Age	Phase	Interventions	Status
NCT02482298 (HESTIA2)	USA, Egypt, France, Italy, Kenya, Lebanon, Turkey, UK	SCD	87	18–30y	2¥	Drug: Ticagrelor Drug: Placebo	Completed
NCT03615924 (HESTIA3)	USA, Belgium, Brazil, Egypt, Ghana, Greece, India, Italy, Kenya, Lebanon, South Africa, Spain, Tanzania, Turkey, Uganda, UK	SCD	193	2–17y	3	Drug: Ticagrelor Drug: Placebo	Active, not recruiting
NCT03449291 (HESTIA4)	Belgium, Italy, Kenya, Lebanon, Spain, UK	SCD	21	<24 m	1	Drug: Ticagrelor	Completed
NCT04293172 (HESTIA5)	N/A	SCD	182*	6 m–17y	3	Drug: Brilinta Drug: Placebo	Not yet recruiting
NCT02214121 (HESTIA1)	USA, Canada, Kenya, Lebanon, South Africa, UK	SCD	46	2–17y	2¥	Drug: Ticagrelor Dose 1a + Dose 2a Drug: Ticagrelor Dose 1b + Dose 2b	Completed
NCT03126695	Germany	SCD and healthy volunteers	44	18y–55y	1	Drug: Ticagrelor granule Drug: Ticagrelor pediatric tablets Drug: Ticagrelor pediatric tablets suspended in water Drug: Ticagrelor immediate release (IR) tablets (Commercial tablet)	Completed

SCD: sickle cell disease, USA: United State of America, UK: United Kingdom, N/A: not available, *estimated, m: month, y: year, ¥ results obtained.

platelets counts under 100×10^9/L, in addition to those under continuous treatment with non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, antiplatelet and drugs that interfere with CYP3A4, as well as those patients breastfed by mother under treatment with CYP3A4 inhibitors.

In addition to evaluating the properties of ticagrelor and its active metabolite (AR-C124910XX) after a single oral dose, the HESTIA 4 study aimed to evaluate the acceptability and the palatability of the drug. The peak concentration (Cmax) and systemic exposure were measured at 1, 2, 4, and 6 h after the administration of ticagrelor. The study was concluded with 21 participants. However, no data has been published to the date.

2.4.2. Evaluation of the relative bioavailability of different ticagrelor formulations

A randomized crossover study evaluating the relative bioavailability of different ticagrelor formulations in adult patients was carried out in 2017, using the following inclusion criteria: patients aged between 18 and 55 years old, body weight range: 50 to 100 Kg and a body mass index (BMI) between 18 and 30 Kg/m^2. The following exclusion criteria were used: history or presence of gastrointestinal, hepatic, or renal disease or any clinically relevant illness, surgical procedure, or trauma in the last 4 weeks preceding the study; any clinically significant abnormality on a 12-lead electrocardiogram; significantly altered hematological, biochemical, coagulation, and renal function parameters, as well as patients under the use of drugs such as antacids, analgesics, herbs, high-dose vitamins/minerals, alcohol (excessive consumption), and other toxic substances. The participants were also investigated for pregnancy and the use of concomitant medication to minimize inter-subject variability.

The study was designed as follows: the eligible subjects were admitted to a clinical unit 24 h before the administration of ticagrelor (day 1), where they remained for a minimum period of 3 days. These patients were followed-up daily from days 5 to 10 and the plasma concentrations of both ticagrelor and its major metabolite AR-C124910XX were determined before and after 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h after the administration of ticagrelor in the following formulations: granules, pediatric tablets, water-suspended tablets, and immediate-release (IR) tablets.

The study was conducted at a research center in Germany with 44 healthy volunteers randomly assigned for one of the four treatment formulation (n = 11 subjects per group). The authors concluded that the administration of each of the four formulations resulted in rapid absorption, as well as in comparable bioavailability and plasma concentration profiles of both ticagrelor and AR-C124910XX. In addition, all formulations were well tolerated. Importantly, pediatric tablets and water-suspended tablets were shown to be bioequivalent [66].

2.4.3. Phase II studies

The phase II study of ticagrelor was conducted in SCD patients included in the HESTIA 1 and HESTIA 2 programs. The HESTIA 1 program consisted of a multicenter, randomized, open-label, double-blind, and placebo-controlled study carried out in 18 centers located in countries such as the United States, Canada, Kenya, Lebanon, South Africa, and United Kingdom, from February 2014 to December 2017. The inclusion criteria included HbSS or HbS/β^0 patients aged between 2 and 18 years. The study excluded patients at risk of hemorrhagic or bradycardic events, significant hepatic or renal alterations, as well as patients under intravenous therapy with potent CYP3A4 (cytochrome) inhibitors, CYP3A4 substrates with narrow therapeutic indices, potent CYP3A4 inducers, as well as other drugs with similar adverse reactions.

The study was divided into two parts: A and B. The part A of this clinical trial consisted of a randomized study conducted with 46 patients who received at least one of the following treatment regimens: 1) patients received a single oral administration of ticagrelor (0.125 mg/Kg) followed by administration of a second single dose (0.375 or 0.563 mg/Kg) 7 days later. After receiving the second dose treatment, patients were treated daily with a dose of 0.125 mg/Kg for 7 days; 2) patients were treated with a single dose of 0.75 mg/Kg followed by administration of a second single dose (1.125 or 2.25 mg/Kg) 7 days later. After receiving the second dose treatment, patients were treated daily with a dose of open-label ticagrelor (0.563 or 0.75 mg/Kg) for 1 week. In this phase, pharmacokinetic and pharmacodynamics parameters (such as platelet activation) were monitored daily, for assessment of drug tolerability.

The part B consisted of a double-blind, placebo-controlled randomized study, conducted with 23 patients who completed the treatment in the part A. These patients were treated with ticagrelor (0.125, 0.563, or 0.75 mg/Kg or placebo for 4 weeks). Throughout the study, the children were monitored daily for the occurrence of bleeding events, VOC or pain, and followed for 35 days after the last administration of ticagrelor. Twenty-one (21) patients concluded this phase. None of them showed significant bleeding and only one subject reported an isolated episode of spontaneous epistaxis, 29 days after the end of treatment.

The authors concluded the existence of a relationship between the dose and exposure to ticagrelor and the inhibition of platelet aggregation in children with SCD, which were comparable to those observed in clinical trials performed with adult subjects with ACS/coronary artery disease. However, limitations such as the reduced number of patients and the short period of treatment should be considered [22].

On the other hand, the HESTIA 2 program consisted of randomized and placebo-controlled study was carried out in 26 centers of 08 different countries from 2015 to 2016. This double-blind, double-dummy, and parallel-group study, designed to evaluate the efficacy of ticagrelor in reducing self-reported pain in SCD patients, was conducted with young male and non-pregnant female adults aged 18–30 years with confirmed diagnosis of HbSS or HbS/β^0. The exclusion criteria included patients with stroke, head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, or aneurysm. Patients receiving blood transfusion or under treatment with anticoagulants or antiplatelet drugs, as well as with increased bleeding risk, hepatic impairment, and hemoglobin concentration lower than 40 g/L or platelet counts below 100×10^9/L, were also excluded from the study.

Eighty seven patients were randomly assigned into the following therapeutic protocols over a period of 18 weeks: 1) a 4-week duration single-blind placebo run was conducted for

determination of the baseline pain-associated variables; 2) the second phase consisted of double-blind treatment trial with duration of 12 weeks in which the patients were treated with ticagrelor (10 mg or 45 mg) or placebo; 3) in this last phase, patients were followed up by a period of after treatment by phone call. To evaluate the treatment efficacy, patients were questioned about the pain intensity, as well as analgesic effects. The safety of the treatment was assessed by monitoring the occurrence of bleeding events. Pharmacokinetic analyses of ticagrelor and its active metabolite in the plasma were performed at randomization and during the follow-up period.

The study concluded that no significant effect on self-reported SCD-related pain could be attributed to ticagrelor treatment. However, the drug was well tolerated and no bleeding event was observed [67].

2.4.4. Phase III studies

As phase I and II clinical trials demonstrated that ticagrelor was well tolerated and associated with low bleeding risk, phase III studies are currently in progress as part of the HESTIA3 program, an international, multicenter, double-blind, randomized, parallel group, placebo-control study designed to evaluate the efficacy and safety of ticagrelor to prevent VOC (painful and acute chest syndrome) in pediatric patients (age range: 2–18) with SCD (HbSS and HbS/β^0).

The study will be carried out in 85 centers of 18 different countries, including Brazil. For inclusion in the study, patients should weigh at least 12 Kg and have experienced more than two VOC in the previous year in addition to other criteria. Patients with a history of stroke, proliferative retinopathy, risk or history of hemorrhagic complications, liver and kidney failure, hemoglobin levels below 6 g/dL, platelet counts under 100×10^9/L and transcranial Doppler speed higher than 170 cm/s will also be excluded, as well as those under continuous treatment with non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, antiplatelet, and drugs that interfere with CYP3A4.

A screening period ranging from seven (07) to 28 days will precede the randomization of patients into placebo or ticagrelor treatments for a period of 12–24 months. Ticagrelor will be administered twice a day at doses adjusted according to body weight ranges as follows: 15 mg (12 kg to 24 Kg), 30 mg (25 to 48 kg), and 45 mg (above 48 kg).

Considering the urgent need for effective and well-tolerated therapies to prevent complications of SCD, it is expected that the HESTIA3 program will characterize the clinical profile of ticagrelor administration among these patients. This study, which is in progress with a total number of 193 participants, was initiated in September 2018 and is expected to be concluded by December 2020 [68].

3. Regulatory affairs

Ticagrelor has been approved in over 100 countries [69], such as the United States [70], Canada [71], European Union [72], Australia [73], and Brazil [74]. It is indicated to reduce the rates of cardiovascular diseases, myocardial infarction (MI), and stroke in patients with ACS or a history of MI. The drug was also found to inhibit stent-associated thrombosis in patients who underwent stent implantation for the treatment of ACS [75].

4. Conclusion

Ticagrelor, an antiplatelet agent, is in the latest phase of drug development for SCD. Given the importance of platelet activation and aggregation in the complex and multifactorial pathophysiology of SCD, as well as the evidences raised from phase I and II clinical trials, ticagrelor treatment is expected to be useful in the control of the clinical manifestations of SCD, especially if used as part of a combined therapy protocol. Nevertheless, the conclusion of phase III clinical trials is crucial to prove its efficacy as a therapeutic option for the treatment of SCD.

5. Expert opinion

The treatment of SCD is quite challenging, since it deals with a systemic disease with varied clinical manifestations, distributed heterogeneously among the different age groups. Furthermore, despite the prevalence and high incidence of SCD, there is a deficiency in the options of medication for patients since the biological mechanisms involved are extremely complex. The results of the phase 3 studies including the ticagrelor, as well as many other clinical trials on new drugs that are in progress, may increase the therapeutic options to control SCD's clinical manifestations (e.g. VOC) and further, provide therapeutic alternatives for patients that do not respond to strategies so scarce and available currently.

Associated with these premises of having new therapeutic modalities available, it will also be of equal importance that parallels to studies of new drugs, some studies identify new biomarkers related to the therapeutic response of patients with SCD, as well as to the genetic profile and aspects associated with epigenetics, so that we can establish clearer and more controlled criteria in the follow-up of these patients' group, providing a survival with the minimum possible of serious clinical occurrences. Another aspect that we consider of vital importance is the fact that treatments can be made available to populations with a high number of patients, allowing them to have a dignified and productive life.

Under a pharmacological and therapeutic point of view, the potential use of antiplatelet agents in the treatment of SCD has been supported by evidence, which demonstrates the role of platelet activation and aggregation in the pathophysiology of this condition. However, the characterization of the biochemical, cellular, and molecular mechanisms underlying the clinical manifestations of SCD has revealed that this disease results from a complex inflammatory response triggered both by the release of intracellular products (DAMPs) and by the signaling of altered red cell surface molecules (PAMPs), indicating that platelet activation is part of a complex network of interdependent pathophysiological processes leading clinical manifestations of variable severity and, as such, results in different clinical profiles. Therefore, in our opinion, ticagrelor should be used in combination with other approved drugs, such as HU, as well as with drugs interfering with key inflammatory pathways with a significant impact on the pathophysiology of SCD, which are now under development. Consistent evidence suggests that a combination of therapy associating drugs that have the potential to inhibit the chronic

inflammatory and hypercoagulability state observed in SCD patients could reduce critical clinical events, including VOC and ACS, improving the clinical profile and reducing hospitalization rates of the patients. On the other hand, considering that the metabolism of ticagrelor is performed mainly by enzymes of the CYP 450 system, the use of the drug in combined therapies should be carefully evaluated to avoid drug interactions. Additionally, since the metabolism of this drug can vary significantly according to the patient's condition, the clinical profile of each patient must be considered, and occurrence of toxicity monitored, especially in patients with hepatic and renal impairment, to ensure that the administration of this drug will achieve both effectiveness and safety.

An overall analysis of clinical trials evaluating the use of ticagrelor in patients with SCD reveals promising but inconclusive results concerning its safety and efficacy, respectively. In this context, the phase I studies indicate that the drug can be orally administered in different formulations with no loss for absorption, metabolism, and bioavailability, which could contribute to the therapeutic adhesion. Therefore, the results of the HESTIA 4 study with 21 participants are expected to be conclusive with regard to the pharmacokinetic profile of ticagrelor and its active metabolite. Phase 2 studies brought relevant data concerning both pharmacodynamical and pharmacokinetic profiles of patients of different populations subjected to variable therapeutic protocols. Importantly, these studies revealed that ticagrelor administration is associated with low bleeding risk, which is a positive therapeutic aspect for an antiplatelet agent since this is a significant side effect in this therapeutic class. Nevertheless, these studies have significant limitations, such as the reduced number of patients and a short period of evaluation. In addition, the effectiveness of ticagrelor in improving key clinical manifestations of SCD, such as VOC-associated pain, remains to be demonstrated. Therefore, the conclusion of phase 3 clinical trials is crucial to prove the efficacy of this drug as a therapeutic option treatment of SCD, which precludes its approval by regulatory agencies. Importantly, post-marketing surveillance will confirm the beneficial effects in the management of SCD patient's manifestations, as well as the occurrence of undetected adverse events in the long term.

In summary, the studies with ticagrelor open new perspectives for the investigation of antiplatelet agents in the treatment of SCD. Nevertheless, we encourage the development of both pre-clinical and clinical studies with a multi-targeted approach since combined therapy is likely to be crucial for the management of SCD and other systemic diseases. Thus, it is expected that ticagrelor, especially in combination with other drugs, will improve the clinical profile and quality of life of patients with SCD.

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