Hydrogen sulfide-releasing therapeutics - how far have we come in clinical studies?

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Abstract

Hydrogen sulfide (H_2S) is the youngest member of the gasotransmitters family consisting of nitric oxide (NO) and carbon monoxide (CO). This signalling molecule is implicated in the regulation of a wide range of processes, such as inflammation, pain, and tissue repair, and has an important role in signalling processes affecting cardiovascular health, either as an independent effector or as an enhancer of the NO system.

With the discovery of the H_2S role in the pathogenesis of many diseases, the development of new pharmaceuticals that could be useful in conditions with disturbed levels of endogenous H_2S began. Today, the development of H_2S-releasing drugs has reached the level of clinical studies. Drugs such as SG1002, aimed at the treatment of heart failure, and ATB-346, aimed at the treatment of arthritis, have been tested in Phase I/II clinical studies and have shown significant therapeutic potential. Additionally, it has been shown that some already known drugs, such as zofenopril, produce part of their beneficial effects by releasing H_2S.

Evidence from clinical studies presented in this paper encourages further clinical testing of H_2S-based therapeutics and the possibility of their application in a wide range of diseases, such as hypertension, diabetes and chronic kidney disease.

Key words: hydrogen sulfide, clinical trials, heart failure, NSAID

Introduction

Gaseous mediators or gasotransmitters are endogenously generated gaseous molecules with a proven role in signal transduction, involved in the regulation of both intracellular processes and intercellular interactions. Hydrogen sulfide (H_2S) is the youngest member of this gasotransmitters family consisting of nitric oxide (NO) and carbon monoxide (CO) (1). All three mediators were initially considered to be only toxic and poisonous gases, until it was discovered that mammals, in addition to many other organisms, possess specific enzymes for their synthesis, and that they have specific physiological functions. These gaseous transmitters regulate, often through similar molecular processes, vasodilation, energy metabolism, apoptosis, neural and many other functions, and disturbances in the metabolism and/or levels of these gaseous mediators are associated with several pathophysiological conditions, from cardiovascular and neurodegenerative, to diabetes and cancer (2).

HYDROGEN SULFIDE

The toxic nature of H_2S has been known for more than three centuries. In 1700, an Italian physician Bernardino Ramazzini, in his book *De Morbis Artificum Diatriba* (*Disease of Workers*), described the painful eye irritation and inflammation in sewer workers induced by a "sewer gas", later identified as H_2S. The first evidence that H_2S can be synthesized in mammalian tissue came from the work of biochemist Vincent Du Vigneud, who described in 1942 that liver homogenate synthesized H_2S from sulfur-containing amino acids (3).

During 1989 and 1990, in primarily toxicological studies, the concentrations of H_2S in the brain tissue of animals and humans have been measured after exposure to exogenous H_2S. However, the findings that brain tissue contained a certain amount of this gas, even without exposure to an exogenous source, were more significant. It was then assumed, for the first time, that H_2S may play a role in physiological, as well as pathophysiological processes in the brain (3). Inspired by these discoveries, scientists Abe and Kimura proved for the first time that H_2S could be synthesized in mammalian tissue (in the brain) and that it serves as a biological signalling molecule (4). The work they published in 1996 represents the most cited original work in the field of H_2S biology and it is often considered to be a starting point for all subsequent research of endogenous H_2S significance (3).

Hydrogen sulfide is a colourless, flammable gas. While in small concentrations it has a characteristic smell of rotten eggs, in large concentrations it causes paralysis of the olfactory nerve (5). It is a weak acid and in an aqueous solution exists in equilibrium with hydrogen sulfide (HS^-) and sulfide (S^{2-}) anions. The chemical nature of the molecules responsible for the biological activity of H_2S still remains partly unclear: it has been shown that H_2S itself, HS^- anion, polysulfides, but also S/N hybrid species, affect different signalling pathways causing biological responses (6). It is believed that the primary mechanism by which H_2S affects the activity of signalling proteins is persulfidation or sulfhydration, post-translational modification of cysteine residues (RSH) and persulfide

formation (RSSH), analogous to S-nitrosylation under the influence of NO (7). Depending on the target protein, the effect of H_2S could be manifested within seconds (e.g. persulfidation of K_{ATP} channels leading to hyperpolarization and relaxation of smooth muscle cells), but could also require several hours or days (e.g. persulfidation of Keap-1 protein leading to increased antioxidant genes expression) (6).

Synthesis of H_2S

In mammalian cells, endogenous H_2S is generated in enzyme-catalysed reactions, as well as in non-enzymatic pathways. Enzymatic synthesis includes action of 4 enzymes in 3 enzymatic pathways: cystathionine γ-lyase (CSE, E.C. 4.4.1.1), cystathionine β-synthase (CBS, E.C. 4.2.1.22) and the combined action of 3-mercaptopyruvate sulfurtransferase (3-MST, E.C. 2.8.1.2) and L-cysteine:2-oxoglutarate aminotransferase (CAT, E.C. 4.4.1.13) (8). Additionally, H_2S could be produced by the reduction of thiosulfates and sulfites, as well as from inorganic polysulfides and protein persulfides. So far, the exact contribution of enzymatic and non-enzymatic sources has not been determined in biological systems (9).

Examination of the distribution of enzymes involved in the H_2S synthesis showed that CSE is the main source of H_2S in peripheral tissues, with minimal contribution to the synthesis in the central nervous system, where CBS is dominantly present. CSE has been detected in the cardiovascular and respiratory systems, liver, kidney, and other peripheral organs (9). In addition to the nervous system, the CBS enzyme is also found in the liver, kidneys, pancreas, and recently it was also proven in blood vessels (2, 10). The 3-MST expression has been demonstrated in all mammalian tissues, but its levels can vary significantly (9).

PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL ROLES OF H_2S

Hydrogen sulfide was first identified as an endogenous neuromodulator and modulator of vascular tone and blood pressure (4, 11), while further studies revealed much broader H_2S functions, such as a role in angiogenesis, glucose metabolism, energy production, nociception, cardioprotection, inflammation, penile erectile function, anticancer effect, and many others (9, 12). Studies from our group and a few others have demonstrated a direct vasorelaxant effect of H_2S on isolated human blood vessels. The discovered mechanisms of action, including interaction with the NO signalling pathway, the activation of ion channels (for K^+ and Ca^{2+}) and the stimulation of cyclooxygenase, indicated a significant role of H_2S in regulating endothelium-dependent signalling events (13-17).

The importance of endothelium was first recognized by its effect on vascular tone, which is regulated through the production of vasoactive substances. Among them, NO has a pivotal role due to the fact that impaired NO bioavailability is the main mechanism leading to endothelial dysfunction, a key predictor of cardiovascular diseases. As a result of endothelial dysfunction, a disorder of key cellular processes and functions, such as vasodilation, platelet aggregation, apoptosis, smooth muscle cell proliferation occurs, as

well as the development of hypertension, atherosclerosis and atherosclerotic vascular diseases (18, 19). However, current literature clearly demonstrated that H_2S has an important role in signalling processes affecting cardiovascular health, either as an independent effector or as an enhancer of the NO system. Cardiovascular effects of H_2S often require preservation of the NO signalling pathway, so the effects may be partially (in the case of vasodilation) or largely (in the case of angiogenesis) diminished in the absence of NO (20).

There are multiple levels of the NO pathway where H_2S has been shown to exert its effects (*reviewed in Szabo, 2017* (21)).

- At the level of biochemical interactions, H_2S and NO (and their metabolites) can react to give biologically active S/N hybrid molecules. Moreover, it has been shown that H_2S can stimulate the release of NO from cellular "depots", such as nitrites, peroxynitrites and nitrosothiols (21).
- Endothelial NO synthase (eNOS). H_2S could stimulate eNOS by acting on the mechanisms that regulate the activity of this enzyme: by increasing the level of intracellular Ca^{2+} (22), by stimulating Akt-dependent phosphorylation of eNOS (20), or by direct sulfhydration of cysteine residues (Cys443), which stimulates NO synthesis (23).
- Guanylate cyclase (GC). It was shown that H_2S could, by reducing iron in the heme of NO-dependent GC, maintain the enzyme in an active form that reacts with NO. The significance of this effect is probably the greatest in states of oxidative stress (20, 21).
- Cyclic guanosine monophosphate (cGMP). H_2S can generate 8-SH-cGMP, which, compared to "regular" cGMP, is more resistant to the action of cGMP-specific phosphodiesterase (PDE) 5, while retaining the ability to activate cGMP-dependent protein kinases (PKG) (24).
- PDE. By inhibiting PDE5 (H_2S can also act on other isoforms, but has the most potent effect on PDE5), H_2S increases the level of intracellular cGMP and thus enhances the vascular effects of NO (20).
- PKG. Polysulfides, generated from H_2S in the cell, could directly activate PKG1α by catalysing the formation of an intramolecular disulfide bond (21).

All of these indicate that interactions between H_2S and NO signalling pathways are substantially involved in cardiovascular protection.

Parallel with investigations of the physiologic roles of H_2S, its role in the pathogenesis of multiple diseases has been demonstrated. Low levels of blood or tissue H_2S have been correlated with disease states triggered by oxidative cell damage, chronic inflammation, immune dysfunction, endoplasmic reticulum stress, dysregulation of mitochondrial bioenergetics, hyperproliferation. These so-called "H_2S-poor" pathological conditions include: ischemia, cardiac hypertrophy, heart failure, hypertension, atherosclerosis, endothelial dysfunction, diabetic complications, liver

disease, preeclampsia, aging, Alzheimer's disease, Huntington's disease. H_2S supplementation could be beneficial in their correction/amelioration. Additionally, there is evidence that H_2S-based intervention could also be useful in conditions not strictly related to low H_2S levels, and support the therapeutic potential of H_2S drugs in cancer, autoimmune pathologies, Duchenne muscular dystrophy/cardiomyopathy, allergic diseases, osteoarthritis, kidney diseases, male subfertility, erectile dysfunction, periodontitis and so on (Figure 1) (25).
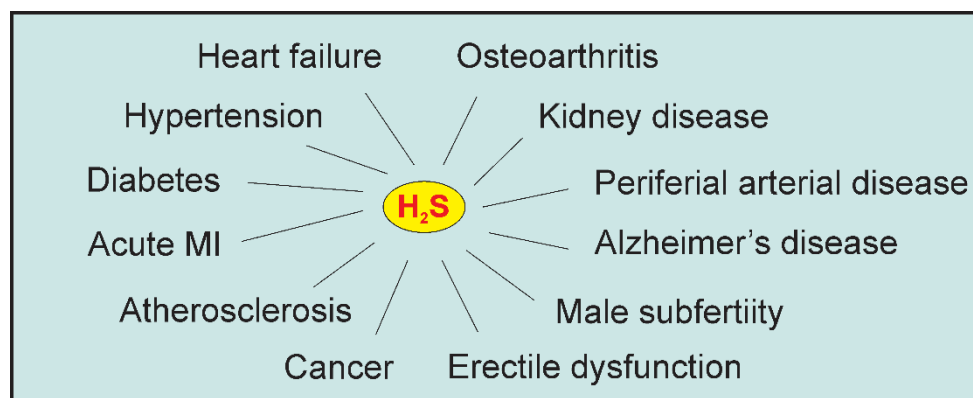
Figure 1. **Therapeutic targets for hydrogen sulfide**
Slika 1. **Terapijski ciljevi vodonik-sulfida**

H_2S and cardiovascular diseases

Cardiovascular diseases are the leading cause of mortality worldwide, causing over 17 million deaths annually. Today, there is a significant number of studies showing that reduced production of H_2S contributes to vascular and cardiac dysfunction in various animal models of cardiovascular pathophysiology. Still, the role of H_2S in clinical cardiovascular diseases is less studied, and some available data follows.

A decrease in H_2S levels has been shown, for example, in the plasma of patients with hypertension (26), diabetes (27) and ischemic heart disease (28), compared to healthy individuals. Furthermore, among patients with ischemic heart disease, lower plasma H_2S levels were reported in patients with occlusion, compared to those with only arterial stenosis (28). A similar finding was also shown in hemodialysis patients, among whom those with advanced atherosclerosis had lower H_2S levels compared to patients with less pronounced vascular disease (29).

Additionally, heart failure patients have marked reductions in circulating H_2S levels compared to age-matched controls (30).

In a study that evaluated the role of H_2S in the etiology of atrial fibrillation, it has been shown that patients with atrial fibrillation had significantly reduced plasma sulfide levels compared to patients without atrial fibrillation. In addition, patients with persistent

atrial fibrillation showed lower plasma free sulfide levels compared to patients with paroxysmal atrial fibrillation. These findings demonstrate the important role of H_2S bioavailability in regulating electrical remodelling and susceptibility to atrial fibrillation (31).

On the other hand, in children with vasovagal (neurocardiogenic) syncope, a significantly higher level of H_2S in plasma was shown compared to the control group (32).

In addition, polymorphism of genes encoding enzymes involved in the H_2S synthesis is associated with various pathophysiological conditions in humans. The polymorphism could potentially affect the enzymatic activity of these proteins and, therefore, the level of H_2S in the tissue. For example, there are estimated 150 mutations of CBS loci, about 20 of which lead to altered enzyme activity. The result is most often homocysteinuria, but certain variants are associated with early ischemic heart disease, essential hypertension and increased risk of stroke. In addition, polymorphism of the CSE gene has been described in patients with increased levels of homocysteine in the plasma, cystathionuria, but it is also associated with preeclampsia and the development of chronic hypertension (10).

H_2S DONORS

The focus of current research is the potential therapeutic application of H_2S donors in order to correct conditions with its deficiency, as well as the mechanisms of their pharmacological effects (9). Evidence on the H_2S role in physiological and pathophysiological conditions indicates that pharmacological interventions aimed at increasing H_2S levels using different donors may be a significant therapeutic option in the prevention and treatment of such conditions. However, the development of an effective therapeutic agent requires comprehensive research and understanding of both the effects of H_2S and the mechanisms underlying them, which helps in identifying the tissues that could be affected and the pathological conditions that respond best to H_2S therapy. Today, the development of H_2S-releasing drugs has reached the level of clinical studies.

Over the last decades, a number of approaches have been used for H_2S investigation, including inhalation of H_2S as a gas, the use of so-called "fast" donors (H_2S salts) or "slow" donors (the prototype of which is GYY4137 (morpholin-4-ium 4 methoxyphenyl phosphinodithioate)). Recent works also include donors with regulated H_2S release, for example, by oxidation, pH change, and esterase. Additionally, one of the approaches involves the addition of H_2S-donating groups to already existing drugs (for example, non-steroidal anti-inflammatory drugs (NSAID)). Some researchers have also used natural H_2S donors, such as garlic containing allicin (diallyl thiosulfonate) that rapidly degrades into diallyl polysulfides acting as H_2S donors in the presence of endogenous thiols (33).

Sulfide salts (sodium hydrosulfide, sodium sulphide, calcium silfide) were the first H_2S donors used in biomedicine. They provided a good base to clarify the roles of H_2S in physiological and pathophysiological processes, but there are significant drawbacks to

these donors as potential therapeutics. Their administration results in rapid and uncontrollable rise and decline of H_2S concentration in circulation or tissue, which is unsuitable for use in chronic conditions, and may result in adverse or toxic effects. On the other hand, the limitations of natural H_2S donors for clinical application include a predisposition to generate numerous by-products unrelated to sulfide release that could lead to unknown biological effects. For instance, diallyl-trisulfide releases H_2S and then transforms into an allyl-perthiol anion, which can bind to cysteine residues and modify protein function. Consequently, there is a need for novel, synthetic H_2S donors with favourable pharmacokinetics and safety (34).

In this article, we described selected H_2S-releasing drugs for which clinical data are available. Drugs such as SG1002, aimed at the treatment of heart failure, and ATB-346, aimed at the treatment of arthritis, have been tested in clinical studies and have shown significant therapeutic potential. Additionally, it has been shown that some already known drugs, such as zofenopril, produce part of their beneficial effects by releasing H_2S, although they were not essentially designed with the aim of delivering H_2S.

SG1002

Heart failure is a clinical syndrome that occurs due to structural and/or functional disorders of the heart, and is manifested by the heart's inability to pump blood at a rate commensurate with the requirements (at rest and during exertion). The causes of heart failure are numerous, but the most common are ischemic heart disease (myocardial infarction) and untreated or inadequately treated hypertension. Despite the advances in therapy, heart failure is still a diagnosis with a poor prognosis and high mortality.

SG1002 (sodium polysulthionate) is a synthetic H_2S donor which is about 99% α-sulfur, with additional traces of ionic substances (sodium sulfate, sodium thiosulfate, and sodium polythionates) that influence its physicochemical properties. The physicochemical and therapeutic profiles of this H_2S systemic prodrug display safety, oral activity, and a unique ability to efficiently generate H_2S in a slow and sustained manner, dose- and enzyme-independently and with no by-products (25).

Preclinical studies conducted in different animal models of heart failure/cardiac dysfunction demonstrated decreased H_2S levels in the setting of heart failure, as well as sulfide levels restoration and cardioprotection by H_2S therapy with SG1002. In these studies, H_2S therapy attenuated cardiac dysfunction via suppression of cardiac endoplasmic reticulum stress (35), upregulation of eNOS and increased NO bioavailability (36) or adenosine monophosphate-activated protein kinase (AMPK) activation (37).

Furthermore, the safety and tolerability of SG1002 were investigated in the Phase I clinical trial (NCT01989208) which included seven healthy and eight heart failure subjects who received placebo or increasing doses of SG1002 (200 mg, 400 mg, 800 mg, twice a day) for 7 days. The study results showed that SG1002 was safe and well tolerated at all doses in both healthy subjects and heart failure patients. Gastrointestinal adverse effects were observed and categorized as "mild", even though not all of them were proven

to be SG1002-induced. Moreover, study data demonstrated an increase in blood H_2S levels and circulating NO bioavailability, as well as attenuation of B-type natriuretic peptide increase in heart failure patients by SG1002 (38). Based on the promising results from the Phase I trial, 800 mg twice-daily dose of SG1002 was chosen for further testing. The randomised, double-blind, placebo-controlled Phase II clinical trial (NCT02278276) was designed to investigate the safety and benefits of SG1002 in heart failure patients, including improvement in levels of circulating H_2S and nitrate and with additional focus on improving clinical endpoints. The current status of this study is unknown (39).

Besides testing for heart failure, SG1002 was tested for men's subfertility treatment. Nowadays, infertility is a global problem, and it is estimated that approximately 50% of cases are associated with male infertility. In a randomized controlled Phase II trial, SG1002 was tested on men presenting with idiopathic oligoasthenozoospermia (alterations in sperm concentration, motility and/or morphology) that represents a major cause of male infertility. The study was performed on 54 subjects divided into three cohorts and administered resveratrol, SG1002 or placebo. The results demonstrated the beneficial effect of SG1002 on idiopathic oligoasthenozoospermia (higher sperm concentration and motility; lower percentage of morphologically abnormal spermatozoa). Furthermore, this study provided additional data on SG1002 safety usage during a period of 75 consecutive days at a dosage of 750 mg/day (40).

Zofenopril

Zofenopril is a sulfhydrylic angiotensin-converting enzyme (ACE) inhibitor, clinically available for the treatment of hypertension and acute myocardial infarction. The positive impact of the cardioprotective effect of zofenopril on clinical outcomes has been extensively documented by the SMILE project, including several clinical trials in patients with different conditions of myocardial ischemia treated with zofenopril (41-45).

This prodrug is unique in producing a long-lasting inhibition of heart tissue ACE, probably determined by the high efficiency with which it is taken by the heart tissue and promptly hydrolyzed by cardiac esterases to the sulfhydryl-containing active metabolite zofenoprilat (46). In both preclinical (47, 48) and clinical (49, 50) studies, zofenopril has been demonstrated to exert cardioprotective and vasculoprotective effects beyond those achieved by ACE inhibition, and independently of the blood pressure lowering effect.

In several studies it has been proposed that zofenopril works as a H_2S donor (51, 52), and that H_2S contributes to its beneficial cardiovascular effects. For example, Donnarumma et al. (53), in *in vivo* murine and swine models of ischemia-reperfusion injury, showed that preconditioning with zofenopril reduced myocardial infarct size and levels of cardiac troponin I. They demonstrated that levels of both H_2S (sulfane sulfur) and NO were elevated in myocardial tissue and plasma, i.e., zofenopril potentiated H_2S and NO bioavailability. They also demonstrated that zofenopril-mediated release of H_2S and NO can scavenge reactive oxygen species (ROS) directly and/or indirectly via upregulation of antioxidant defence. Thus, the authors concluded that ACE inhibition, but also H_2S and an increase in NO (via eNOS activation by H_2S or enhance releasing caused

by increased levels of bradykinin due to ACE inhibition), probably account for the cardioprotective effects of zofenopril.

In a recent study, Makabrey et al. (51) tested the preventive effect of zofenopril on intimal hyperplasia in a mouse model of carotid artery stenosis, as well as in human vein segments, and therefore supported the idea that zofenopril limits the development of intimal hyperplasia via H_2S release, independently of its ACE inhibition activity. They showed that zofenopril was superior to enalapril in reducing intimal hyperplasia in mice (even in the normotensive condition, where other ACE inhibitors have no effect) and in a model of intimal hyperplasia in human vein segments *ex vivo*. The effects of zofenopril were in correlation with a decrease in mitogen activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) pathway activity, followed by reduced vascular smooth muscle cells proliferation and migration.

Sodium thiosulfate

Sodium thiosulfate is a stable H_2S donor with known safety and efficacy in the treatment of cyanide poisoning, calciphylaxis and renal toxicity induced by chemotherapy (54). Furthermore, this compound has potential in treating cardiovascular diseases. In various experimental animal models, H_2S has been shown to protect the heart from ischemia-reperfusion injury (reduced infarct size and apoptosis and improved cardiac function) with an underlying mechanism including the inhibition of leukocyte endothelial cell interactions, mitochondrial preservation, ROS neutralization and the reduction of inflammation and apoptotic signalling (54).

In a Phase I clinical study conducted on 18 patients presenting with acute coronary syndrome, sodium thiosulfate was well tolerated even with concomitant use of antihypertensive drugs (55). Furthermore, the safety and efficacy of sodium thiosulfate were evaluated in a Phase II double-blind, randomized, placebo-controlled, multicenter trial (NCT02899364), which enrolled 380 patients with a first STEMI. However, according to the results presented at the American College of Cardiology's Annual Scientific Session & Expo 2022, sodium thiosulfate showed no benefits in reducing infarct size, although the drug was safe and major adverse cardiovascular events were comparable with placebo. Still, the investigators did not exclude the possibility that the usage of different H_2S donors or administration strategies may have a greater impact, and that it is still early for a conclusion about H_2S being wholly ineffective in ischemia-reperfusion injury (56).

GIC-1001

Trimebutine 3-thiocarbamoylbenzenesulfonate (GIC-1001) is a H_2S-releasing salt of a spasmolytic drug trimebutine, developed to be used as a colon analgesic drug alternatively to parenteral sedation in patients undergoing full colonoscopy (57). Because of the previously demonstrated antinociceptive effects of H_2S (58), it has been proposed that the analgesic effect of trimebutine could be enhanced by *in vivo* H_2S release.

In a mouse model of colorectal distension, it has been shown that orally administered GIC-1001 significantly reduced nociceptive response to all noxious stimuli. The results demonstrated that GIC-1001 antinociceptive properties were increased in comparison with equimolar doses of its parent compound trimebutine (59).

The safety, tolerability and pharmacokinetics of GIC-1001 were evaluated in a Phase I randomized, double-blinded, placebo-controlled, integrated study (NCT01738425). Single and multiple increasing oral doses or placebo were orally administered to 80 healthy subjects. The study results demonstrated that GIC-1001 was safe and well tolerated, with the most frequently reported adverse events related to the nervous and gastrointestinal system (headache, somnolence and nausea) (57).

A Phase IIa randomized, double-blind, placebo-controlled, dose-ranging clinical study (NCT01926444) was conducted to provide clinically and statistically significant evidence of GIC-1001 safety and effectiveness in managing visceral pain in patients undergoing sedation-free, full colonoscopy for preventive purposes. The study included 262 patients who received one of 3 doses (250, 375 or 500 mg, three times a day) of GIC-1001 or its matching placebo for 3 consecutive days prior to colonoscopy (60). During this study, a clinically significant pain reduction (26.6%) was detected after the application of 375 mg GIC-1001 versus placebo ($p = 0.082$). However, it was stated that better statistical significance ($p = 0.061$, N: 213) was observed when rescued patients (those who required sedation in addition to study treatment) were excluded from the analysis, since no pain score was reported after rescue sedation, and this underestimated the overall pain experience of the rescued patients (59). The study results are accessible at *ClinicalTrials.gov* (60), but there are no available publications related to this Phase IIa study.

ATB-346

Nonsteroidal anti-inflammatory drugs, very effective in treating pain, high fever and inflammation, are known for their risk of developing gastrointestinal (GI) ulceration and bleeding. On the other hand, H_2S has been shown to reduce inflammation in the GI tract and accelerate healing of damaged tissue (such as ulcers), while suppression of H_2S production in the GI tract results in impaired healing of tissue injury and exacerbation of inflammation. With that in mind, H_2S-releasing NSAIDs have been developed. Testing in animal studies showed that these drugs are effective in reducing pain/inflammation without causing significant GI damage (61).

ATB-346 is an H_2S-releasing derivative of naproxen, an NSAID widely used in the management of arthritis and other inflammatory and painful conditions. Preclinical testing of ATB-346 revealed more effective inhibition of COX-2 induced by ATB-346 compared to an equimolar dose of naproxen, but with substantially reduced GI toxicity (62). A Phase I clinical trial (NCT03220633) showed the safety and tolerability of single ascending doses of ATB-346 orally administered in healthy subjects. The study results suggested that ATB-346 inhibited COX more potently than naproxen, and for a much longer period of time (61). Further testing was performed in a Phase II clinical trial in

patients with osteoarthritis of the knee taking ATB-346 (250 mg) once daily for 10 days. This daily dose of ATB-346 contains naproxen, which is one-sixth of the naproxen amount in its usual daily dose. The results demonstrated significant pain relief, as well as a decrease in other aspects of the arthritis index (stiffness and difficulty performing daily activities). On the first day of treatment, ATB-346 produced a profound inhibition of whole blood COX activity, which remained consistently and profoundly suppressed throughout the treatment period (63).

An additional Phase II clinical study (NCT03291418) was conducted in order to examine the gastrointestinal safety of ATB-346 compared with naproxen in healthy subjects. Among 244 subjects taking naproxen (550 mg twice daily) or ATB-346 (250 mg once daily), 52% in naproxen group and only 3% in ATB-346 group developed at least one ulcer (≥3-mm diameter). The subjects taking ATB-346 also had a lower incidence of other GI symptoms (dyspepsia, abdominal pain, gastroesophageal reflux, nausea) and significantly higher plasma levels of H_2S. This study demonstrated a significant reduction of GI toxicity of ATB-346, H_2S-releasing NSAID, in comparison to the usual dose of naproxen that produced equivalent COX suppression (61).

Although a reduction in GI toxicity was the primary goal, cardiovascular safety of NSAID-H_2S drugs was also important. Here, naproxen was selected as a "base drug" in ATB-346 because of its relative cardiovascular safety compared to other NSAIDs. During Phase I and Phase II clinical trials in osteoarthritis patients, no significant changes in systolic or diastolic pressure were detected (63).

According to the authors' statement, future studies will be conducted to test the effectiveness of lower GIC-1001 doses in the reduction of pain and inflammation related to osteoarthritis (61).

Conclusion

Research of H_2S-based therapeutics is a rapidly developing field with high potential and with a lot of new compounds reaching preclinical studies. Despite promising data, comprehensive studies are still required. Optimization of H_2S donors, further understanding of H_2S effects and their underlying mechanisms, as well as selection of optimal animal disease models for testing H_2S-releasing drugs could help in the confirmation of drug safety and efficacy and facilitate their translation into clinical settings. Evidence from clinical trials presented in this paper encourages further clinical testing of H_2S-based therapeutics and the possibility of their application in a number of indications.

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Lekovi koji oslobađaju vodonik-sulfid – dokle smo stigli u kliničkim studijama?

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Kratak sadržaj

Vodonik-sulfid (H_2S) je najmlađi član porodice gasovitih medijatora koju čine azot-oksid (NO) i ugljen-monoksid (CO). Ovaj signalni molekul uključen je u regulaciju širokog spektra procesa, kao što su zapaljenje, bol, reparacija tkiva, i ima važnu ulogu u signalnim procesima koji utiču na zdravlje kardiovaskularnog sistema, bilo kao nezavisni efektor ili kao pojačivač NO signalnog puta.

Sa otkrivanjem uloge H_2S-a u patogenezi mnogih bolesti, započeo je razvoj novih farmaceutika koji bi mogli biti od koristi u stanjima sa poremećenim nivoima endogenog H_2S-a. Razvoj lekova koji oslobađaju H_2S danas je dosegao nivo kliničkih studija. Lekovi poput SG1002, za terapiju srčane insuficijencije, i ATB-346, za terapiju artritisa, ispitivani su u Fazi I/II kliničkih studija i pokazali značajan terapijski potencijal. Dodatno, pokazano je da neki već poznati lekovi, poput zofenoprila, deo svojih korisnih efekata ostvaruju upravo oslobađanjem H_2S-a.

Dokazi iz kliničkih studija izneti u ovom radu ohrabruju dalja klinička testiranja terapeutika baziranih na H_2S-u i mogućnost njihove primene u širokom spektru bolesti, poput hipertenzije, dijabetesa i hronične bolesti bubrega.

Ključne reči: vodonik-sulfid, kliničke studije, srčana insuficijencija, NSAIL